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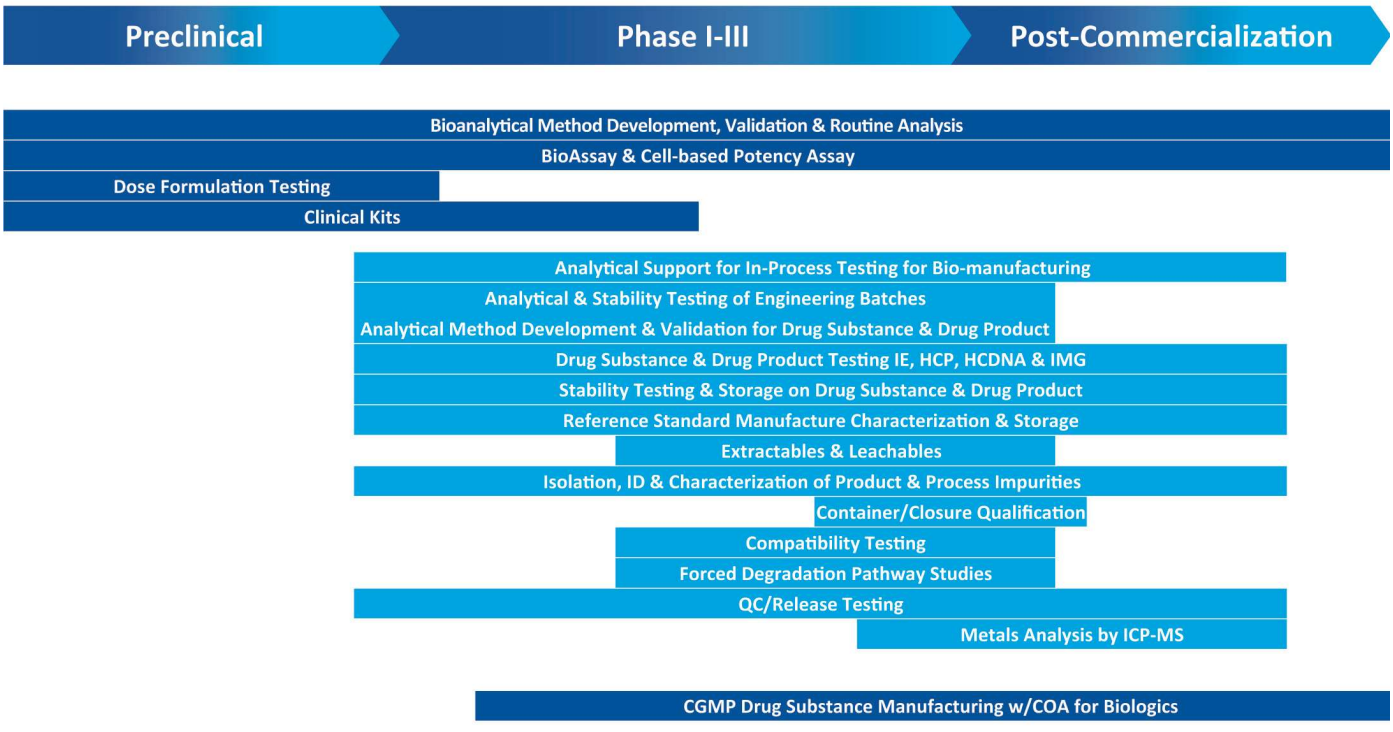

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Finding the Sweet Spot at Biogen Idec

Doug Williams, Ph.D.
EVP of R&D at Biogen Idec **p. 24**

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3 Lessons Pharma Can Learn From ALS Ice Bucket Fever

ROB WRIGHT Chief Editor

Regardless of your opinion of the ALS Ice Bucket Challenge (IBC), which has catapulted the ALS Association's (ALSA's) charitable coffers to feverish heights, there are valuable business lessons from which pharma and biotech executives can learn.

Lesson number one — social media is a very powerful tool. Let's consider some quantitative and qualitative data from the IBC. As of this writing, the ALSA received $106 million in donations from more than three million donors. Pre-IBC, the ALSA.org website averaged close to 8,000 visitors a day. By the end of August, the average number of visitors per day was 630,000 — a 7,775 percent increase in traffic. If you would have told me a few months ago you could use social media to convince Ophra Winfrey, Martha Stewart, and the second wealthiest person in the world, Bill Gates, to pour buckets of ice water over their heads while getting them to give money in the process, I would have told you to go soak your head. What pharma company trying to get people to enroll in clinical trials wouldn't want this level of engagement?

If you want to be able to take advantage of the power of social media, learn how to use it. For example, although part of the IBC's success resides in the fact that people were willing to be narcissistic and post their videos, self-promotion is not the key to success in social media. For example, one of the most important rules of social media success is to tweet, like, and comment more about others than about yourself.

Lesson number two — social media = people. Between June 1 and August 17, more than 28 million people on Facebook posted, commented on, or liked a challenge post. While plenty of companies posted videos of employees participating in the IBC, none come close to those posted by individuals. Thus, while Pfizer on the surface seems to be doing everything right when it comes to social media (i.e., five Facebook pages, eight Twitter accounts, a weibo page [China's version of Twitter], 12 YouTube channels, SlideShare, and LinkedIn), *all* of its accounts include the Pfizer name. While this approach may be great for branding, it flies in the face of what makes social media social — people. Pharma companies need to allow executives to put themselves out there and participate in social media and avoid the temptation to overly police the process. To Pfizer's credit, Ian Read, the company's CEO, does have a limited LinkedIn profile which can be viewed publicly. He is also a member of the LinkedIn Influencers program.

Lesson number three — social media is organic and fun. ALS is a terrible disease. While typical fundraising tactics of guilt can get people to give, the IBC demonstrated that more people will engage if you focus on fun. If pharma wants to get better at engaging with people and improving enrollment in clinical trials, it should try making the process fun. Then, when you find *it*, don't try to trademark it to prevent others from using. Where is the fun in that? L

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Q What was the most valuable leadership experience learned from working under an FDA manufacturing consent decree when you were at Genzyme?

A TO STAY TRUE TO OUR MISSION (delivering products that change lives and provide hope to patients), communication needs to be reinforced constantly on how every action each of us takes helps us to fulfill this objective. During this situation, the team lost confidence in themselves as well as each other. The process of rebuilding confidence in people was the most important leadership challenge. There was no quick or easy solution, and it took time. As a first step, we made it a priority to keep our people and teams connected to our purpose – making medicine for patients depending on our success. When people understand the importance of their work, it translates into an extraordinary level of commitment to your mission. Ultimately, this team came together and achieved much more than many thought possible.

SANDRA E POOLE
Sandra Poole P.Eng, M.A.Sc. ChE is SVP, technical operations at ImmunoGen where she is responsible for the company's process development, manufacturing operations, and global quality organizations. Formerly, she was SVP, biologics manufacturing at Genzyme.

Q Knowing what you know today, having founded a company and taken it public, what insights would you share for folks considering a similar path?

A THE POINT I'D LIKE TO EMPHASIZE is that no organization is going to pursue the best course every time. I've found that a key to success is to review important decisions periodically and systematically and assess as honestly as possible whether they were good calls or not. The good ones are an opportunity to figure out how to replicate what works. The calls with undesired outcomes provide experience for how to modify your own and your organization's approach and ensure that it's done better next time.

RON COHEN
Ron Cohen, M.D. is president, CEO, and founder of Acorda Therapeutics, Inc., a public biotechnology company developing therapies for spinal cord injury, MS, and other nervous system disorders.

Q What was the most valuable experience gained from providing testimony before the U.S. House of Representatives?

A IT IS EASY TO DISMISS THE IMPORTANCE OF TESTIFYING before a congressional committee, given the negative view of Congress which exists today. My experience, however, was quite different. The representatives on the Financial Services Subcommittee were extremely engaged in evaluating the impact of the JOBS Act on Chimerix and on the biotechnology industry in general. I was encouraged by their preparation, by the breadth and depth of their questions, and by their overall interest in the topic. Clearly this bipartisan group of legislators was focused on helping to build our biotech economy. In terms of preparation, my best advice is to be open and honest with the legislators. They were very much interested in my personal experiences as a serial biotech CEO. This type of real-world insight is extremely important to lawmakers in setting legislative policies and agendas.

KENNETH MOCH
Kenneth Moch, former CEO of Chimerix, has 30 years of experience creating, managing, and financing biomedical companies. In addition to Chimerix, Moch has been CEO of several other companies, including Alteon and Biocyte, and he cofounded The Liposome Company (acquired by Elan).

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Small Businesses Left Behind in Obamacare

JOHN McMANUS The McManus Group

The disastrous rollout of Healthcare.com for individuals attempting to purchase health insurance in Obamacare's exchange is well-known, but a similar experience is still ongoing for small businesses. I experienced it myself this past month.

Like many small business owners, I was dismayed by the dramatic cost escalation of providing healthcare coverage for my employees. According to a recent survey by Morgan Stanley, average premiums for the small group market increased 588 percent in Washington, 66 percent in Pennsylvania, 37 percent in California, and 34 percent in Indiana. For my firm, premiums increased 35 percent effective this September for the identical coverage. I didn't know whether to blame the medical device tax, benefit mandates, or other insurance rules that Obamacare has inflicted on the small group market.

Nonetheless, I decided to pursue a better deal through Obamacare's Small Business Health Options Program, better known as the SHOP Exchange, which caters to businesses with 50 or fewer employees. To my surprise, what should have been a simple task — researching coverage and premiums options on the "DC Health Link" website — was ridiculously challenging.

Benefit summaries were readily available, but discovering the premium costs associated with those plans required establishing an online account and providing detailed information on my employees and their families. After nearly finishing the tedious and invasive online account, technical glitches repeatedly prevented its completion, and the site failed to save any of the data entered on previous pages. Large letters blazed across the screen: "Application Error." This song and dance continued for nearly a week, requiring repetitive input of previous information.

After a week of little progress, we decided to call a "navigator" — might as well make use of the $130 million in federal funds doled out to these exchange assistants in the last 18 months. With a navigator's support, the online account process was eventually completed. But once inside the portal, technical problems persisted. Time and time again, after clicking on the "search for plans" icon, the site would freeze. The SHOP exchange is nearly as dysfunctional as Healthcare.com when it was activated last October!

The navigator explained that because of these technical glitches, my firm not only missed the deadline for an October 1 enrollment date, but was dangerously close to missing November's deadline. She noted these problems were system-wide, impacting all of her clients.

But not to worry, she said; we could have my application expedited. "Expedited? Because of the glitches?" No, not that. The navigator confided the administration was happy to expedite the application of one client because he posted his exchange complaints on Twitter. Another unhappy client's application was accelerated because he claimed to have a contact at the *Wall Street Journal*.

I don't have a Twitter account (though my tween kids seem fixated on tracking the number of followers they have on their accounts) and wondered whether informing her of my monthly column in *Life Science Leader* could prompt better service. Fortunately, I didn't have to play that trump card, as the exchange portal eventually worked long enough to obtain a few quotes.

But all that invested time appeared to be wasted when I discovered that plans with similar premiums had significantly inferior benefit packages — gargantuan deductibles and much narrower networks. No plan was substantially cheaper than my current plan. All of the hassle and headache, only to learn my current 35 percent-price-increased-plan may be the best option.

My experience is not unique. In August, the left-leaning Urban Institute issued a scathing analysis of the SHOP exchange experience in eight states, noting that "IT problems were sufficiently serious that they all but prohibited enrollment. … In Maryland and Oregon, major IT problems created tremendous barriers for SHOP enrollment, no online enrollment was available, and SHOP plans could only be obtained via brokers and without employee choice."

In fact, 18 states have postponed its full implementation until 2016. New York's marketplace covers almost one

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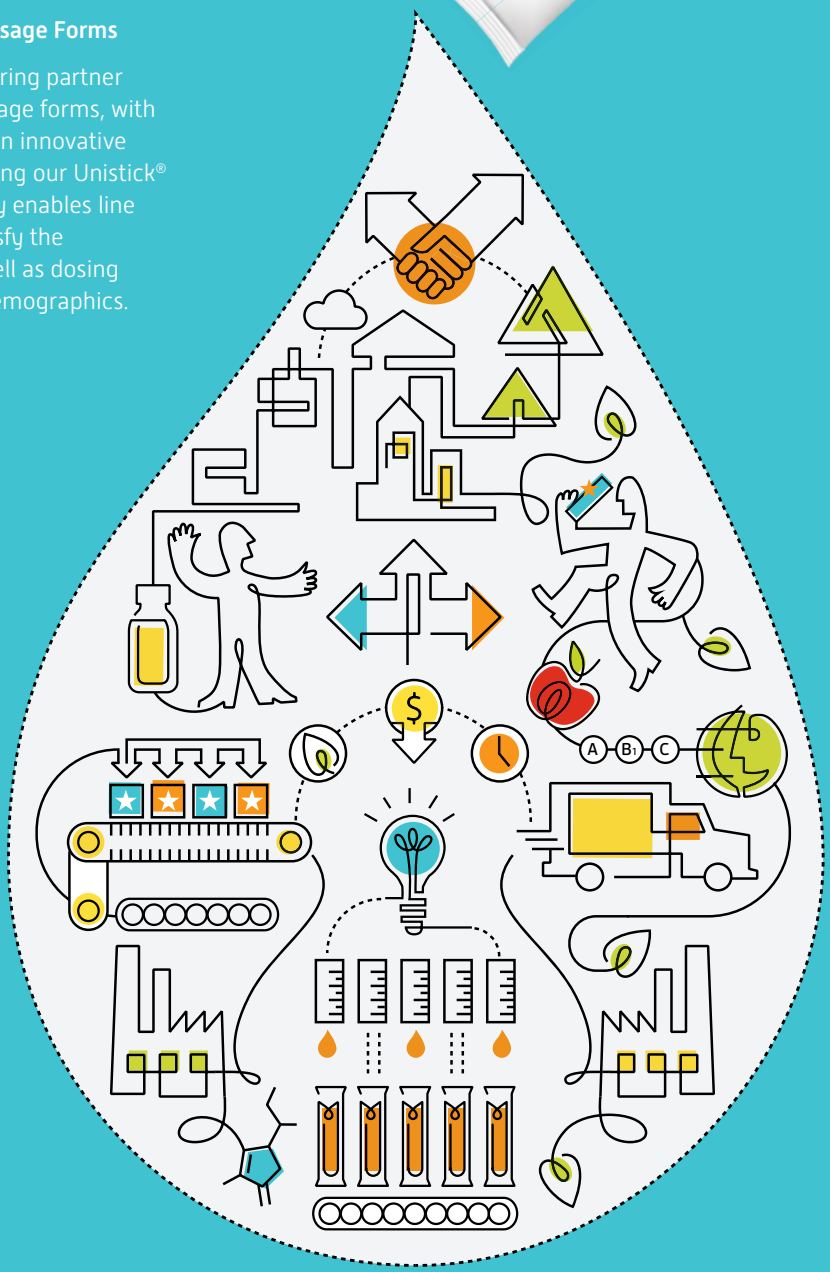

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"After nearly finishing the tedious and invasive online account, technical glitches repeatedly prevented its completion, and the site failed to save any of the data entered on previous pages."

million people, but only 10,000 of those are signed up for small business plans. And in California, a mere 1,200 of the state's 700,000 small businesses have enrolled on the SHOP exchange, covering less than 5,000 people. California began offering online enrollment last November, but after applicants encountered error messages and page-loading delays, the online portal was suspended in February with plans to launch a new portal from scratch this fall.

While Washington policy wonks are aflutter about the healthcare inflation deceleration and modest premium increases in the large group market, and politicians focus on the botched rollout in the individual market, the small group market's turmoil has been all but ignored. Premium escalation is at all-time highs in many states, and Washington's solution — the SHOP Exchange — is totally dysfunctional. The administration has been virtually mum about addressing this crisis but proudly rolled out its breakthrough decision to cover sex-change operations for Medicare's seniors (average age 76), determining them to be "reasonable and necessary."

Fortunately, some new thinking is under way. The Coalition for Affordable Healthcare — composed of business groups, insurers, and providers — is working with several prominent members in Congress on model legislation that could provide some relief. A key provision would overturn a treasury regulation that prohibits employer pretax contributions to employees for the purchase of coverage in the individual or private exchange markets. Another provision would permit the sale of more affordable plans than the current 60 percent actuarial value requirement of the "bronze" plan. A third provision would inform individuals if their plan qualifies for an accompanying health savings account.

Let's hope Congress can move some of these ideas forward and develop other proposals to cut small businesses' health costs. Government solutions clearly are not working. I found out the hard way.

Lindsay Bealor contributed to this article.

FIGURE 1

Small Business Premiums Skyrocket

Percentage Increase in Small Group Market

Washington	588%
Pennsylvania	66%
California	37%
Indiana	34%
Kentucky	30%
Colorado	29%
Michigan	27%
Maryland	25%
Missouri	25%
Nevada	23%

Source: Morgan Stanley survey, April 2014

JOHN MCMANUS is president and founder of The McManus Group, a consulting firm specializing in strategic policy and political counsel and advocacy for healthcare clients with issues before Congress and the administration. Prior to founding his firm, McManus served Chairman Bill Thomas as the staff director of the Ways and Means Health Subcommittee, where he led the policy development, negotiations, and drafting of the Medicare Prescription Drug, Improvement and Modernization Act of 2003. Before working for Chairman Thomas, McManus worked for Eli Lilly & Company as a senior associate and for the Maryland House of Delegates as a research analyst. He earned his Master of Public Policy from Duke University and Bachelor of Arts from Washington and Lee University.

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NORA THERAPEUTICS

This company's novel and lonely development of a new fertility drug belies the industry's current uninterest in the field.

WAYNE KOBERSTEIN Executive Editor

SNAPSHOT

Nora Therapeutics is about the only game in town for development of novel-MOA (mechanism of action) fertility drugs. Its sole product in the current pipeline, a proprietary G-CSF (granulocyte-colony stimulating factor), targets miscarriages in women undergoing in-vitro fertilization (IVF) as well as recurrent miscarriages among other women. Nora's two main Phase 2 trials, THRIVE and RESPONSE, address IVF-related and other miscarriages, respectively.

WHAT'S AT STAKE

Historically, fertility epitomizes areas fit for specialty care drugs, where the problems and solutions are more complex than in diseases treatable with a simple pill. (See "EMD Serono — The Culture of Specialty Care," in this issue.) The usual emphasis in specialty care is on the patient-support programs offering services such as education and reimbursement assistance. But the other side of patient support is answering special unmet needs to expand the therapeutic bounds. Nora Therapeutics may stand alone in completing the circle of treatment for women miscarrying with IVF or suffering repeated, idiopathic miscarriages.

In the words of the company's president and CEO Jeffrey Tong, "We often use the analogy of pregnancy requiring both a good seed (embryo) as well as soil (endometrium). The industry has invested heavily in drugs, diagnostics, and procedures to optimize the seed. We are the only company now researching ways to optimize the soil."

It is a fact that current fertility drugs and almost all R&D in the area since IVF became available in 1978 have concentrated on maximizing the quantity and quality of eggs and fertilized embryos. Nora's drug, NT100, a unique form of G-CSF, is meant to improve a mother's immune tolerance to implantation and maintenance of a fertilized embryo and thereby reduce the chance of miscarriage. Miscarriages among women who have undergone multiple unsuccessful IVF procedures have grown apace with the procedure. Recurrent miscarriages also affect a growing population.

"While many miscarriages are due to early embryonic defects, women who suffer from a history of multiple miscarriages are, in fact, less likely to have embryonic issues, suggesting a potential maternal issue," Tong explains. "In fact, these women have been shown to have an imbalance in maternal-fetal immune tolerance."

Nora appears to have no real competition, either in development or on the market. "Fertility drug pipelines appear to be quite scarce, particularly given the significant unmet need. We don't view any of the existing fertility drugs as competitive. In fact, they would be highly complementary," says Tong.

He calls for more industry attention to infertility and miscarriage. If successful, NT100 would be the first drug in 20 years with a new mechanism of action approved to treat infertility. "We hope that in the future we will see more companies developing drugs for this significant unmet need."

Although infertility may affect as many as one in ten women of childbearing age, or about 6 million in the United States, there are only about 450 IVF clinics in the country. With a specialty care indication, Nora may or may not be a candidate for commercial partnership. Tong gives no sign that it is one, but he does infer the company could, at least initially, go it alone: "Only 250 clinics represent 90 percent of the cycle volume in the United States, and so a targeted, specialty sales force would be ideal to serve the needs of this market."

Nora wisely keeps a narrow focus. Its single-minded concentration on developing one product for two closely related medical needs befits a company of its size and maturity. Nora is a good example of how small companies can identify and occupy an area evidently left abandoned by the pioneers in the field. Just often enough, the most obvious avenues of innovation are the ones most overlooked. L

JEFFREY TONG
CEO

Vital Statistics

8
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Headquarters
Palo Alto, CA

Finances

$53M
raised to date over two rounds (Series A, Series B)

Partnerships

Major investors: Burrill & Co., Novo Ventures, Prospect Venture Partners, Rho Ventures, Vivo Capital

Latest Updates

June 2014: Initiation of Phase 2 RESPONSE study, a randomized, placebo-controlled safety and efficacy trial of NT100 in women with a history of unexplained recurrent miscarriage
April 2014: Close of $18M Series B Financing

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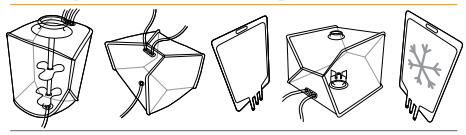

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Is Discounting Services Good For Drug Development?

In the past decade of working in market research, I have witnessed the consumer behaviors of business and personal spending conflate. This has happened for a variety of reasons, the big influencers being the psychology of the sale and later, the economic downturn.

KATE HAMMEKE
Director of Marketing Intelligence
Nice Insight

"When entering a drug development partnership, buyers ... are looking for a discount from the provider for making a long-term commitment."

Many years ago, marketers started using psychological tactics to interest consumers in products they did not need and, since then, have been honing in on new ways to manipulate buyers by playing upon their weaknesses. These methods worked so well in the consumer environment that they have crossed over to selling business-to-business products and services.

However, when the economic crisis hit, it changed the way both consumers and businesses spend, further shrinking the differences in personal and professional behaviors. The charge card — whether personal or corporate — was no longer swiped without scrutiny. Products and services needed to be evaluated for necessity, and if something was identified as a necessity, the search for the best price and provider began. Selling methods had to evolve, and along came the near-constant "sale." This tactic has permeated commerce so thoroughly that in recent years we have been conditioned to shop at any time, but only to buy during a sale. Retail prices start at higher margins than they did a decade ago because so many consumers will not consider purchasing at full price. Business-to-business sellers have also adopted this trick. "List prices" are set at a premium because whether our shopping is personal or professional, we are equally susceptible to the allure of getting a deal based on the nature of our relationship.

When entering a drug development partnership, buyers of outsourced services are looking for a discount from the provider for making a long-term commitment. In reviewing the results from this past year's strategic partnering surveys, the data show that among one-third of respondents, price is considered very influential in partner selection, and 29 percent stated that price is influential. This belief impacts purchase behavior in the form of looking for discounted products or services — aka a "sale." Respondents were asked what percentage of a discount they expected when partnering with a CRO/CMO, and approximately one in four expected a 10 percent discount, which is fair. What was surprising was that the remaining respondents anticipated an even greater price cut, and nearly one in 10 desired a discount greater than 20 percent.

Research shows pricing has a strong influence on partner selection, but it also reveals cost is not the most influential

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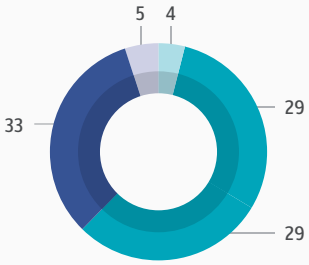
FIGURE 1 Price's Influence On CRO/CMO Selection



Has no influence on selection	4%
Somewhat influential	29%
Influential	29%
Very influential	33%
Is the primary factor in selection	5%

FIGURE 2 Expected Discount On Services When Partnering With A CRO/CMO

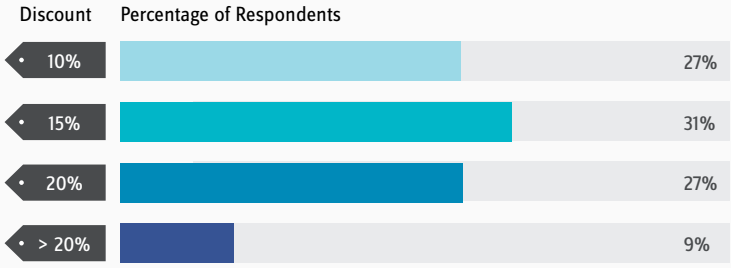


FIGURE 3 2014 Ranked Outsourcing Drivers

Survey Methodology: Nice Insight Strategic Partnering Surveys are deployed on behalf of Nice Insight clients to a targeted group of outsourcing decision-makers. The surveys are comprised of ~40 questions geared toward understanding current outsourcing practices, present and future expectations from outsourcing partners, and which traits contribute to successful partnerships.

element when considered along with quality and reliability. Regulatory and productivity also trumped affordability in the 2014 results, which reminds buyers of the difference between value and price. Value is the combined result of a quality product/service, reliably supplied, and for a price that is in balance with quality and reliability. After all, it doesn't make good sense to compromise quality for price — that's the reason the phrase "buy cheap, buy twice" exists — and if your supplier does not reliably deliver the goods, you may be losing money because of the wait. When a supplier has to compete by offering the lowest price among its competitors, corners may be cut, staff may be underqualified, and the opportunity for error opens wider. These are dangerous possibilities in the drug development industry.

In the final quarter of the year, as plans, budgets, and strategies are identified for 2015, it's important to keep value at the forefront of CRO/CMO partner selection, rather than just price. Let's move away from expected discounts in the short term and look deeper into the future of a partnership, where greater savings can be obtained through utilizing each party's strengths and establishing a win-win relationship. L

N. WALKER

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

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Moving Beyond The Batch

Best practices, opportunities, and challenges in continuous bioprocessing

ERIC LANGER
President and Managing Partner
BioPlan Associates, Inc.

"Already, leading adopters such as Genzyme and Bayer are known to have manufactured a dozen or more marketed recombinant protein products by using perfusion or other continuous bioprocessing technologies."

The traditional approach to upstream and downstream biopharmaceutical processing remains batch processing, but despite ever-increasing yields, technological advances are now making continuous bioprocessing an appealing alternative. What the industry is experiencing is not necessarily a case of old versus new (fiber-based perfusion bioreactors were widely used in the 1980s), but a resurgence in the attractiveness of continuous bioprocessing. New developments, such as the resolution of regulatory barriers (e.g., of how to define lots) and a shift toward QbD (quality by design) and PAT (process analytical technology) with which continuous bioprocessing fits well, are putting the benefits of continuous processing in focus.

In fact, there are several benefits, and a number of emerging technologies complement those of single-use and modular systems (two other current industry trends). The most commonly associated benefits to bioprocessing are:

- Reduced Costs: Continuous processing allows for the use of smaller-scale equipment, reducing up-front capital investments, and generally enabling manufacturers to use smaller facilities and equipment. This doesn't come at the expense of productivity: A smaller volume bioreactor using continuous processing can, over time, match the output of a much larger one operating in fed-batch mode.
- Increased Productivity and Flexibility: By eliminating the need for large transfer/storage vessels, as well as long transfer times and halts between processes, continuous processing runs more smoothly relative to traditional batch-fed processing. This allows manufacturers to attain considerably higher bioreactor cell densities, leading to higher product yield and concentration.
- Better Quality: Biological molecules are produced continuously and naturally. And when comparing continuous culture to batch culture, the former tends to be more controllable and less intense and stressful; it experiences less shear while media nutrient levels keep constant. Product variability (e.g., later culture stage-related loss of cell viability or altered glycosylation) is reduced, with continuous bioprocessing inherently more consistent and robust. And if any problems do occur, only part of the, not the entire, production run will likely need to be rejected.

Other potential benefits associated with continuous bioprocessing include:

- fewer manual interactions
- more automation
- increased use of single-use equipment
- reduced bioprocessing supplies inventory and storage needs
- easier implementation of PAT and up-front bioprocess design using lower staffing levels, presuming adequate automation
- similar equipment and setups being used for manufacture at different scales, up to commercial manufacturing; thus reducing costs and time spent scaling up.

DESPITE POTENTIAL BENEFITS, SIGNIFICANT CONCERNS REMAIN

While there are obvious benefits to continuous bioprocessing, biomanufacturers are faced with several concerns from its use. Not surprisingly, survey respondents to our 11th Annual Report

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*BioPharm International | April 2014

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and Survey of Biopharmaceutical Manufacturers associate far greater concerns with perfusion operations than with time-tested batch-fed operations.

In this year's survey, we identified selected areas where there were differences in the perception of problems and concerns about perfusion vs. batch-fed. Some of the highlights included:

- Process operational complexity (76.8 percent indicating factor is a "much bigger" or "somewhat bigger" concern for perfusion, versus 3.6 percent, indicating it to be a bigger concern for batch-fed processes)
- Process development control challenges (75.9 percent and 3.6 percent, respectively)
- Contamination risks (68.8 percent and 6.3 percent, respectively)
- Ability to scale-up process (58.9 percent and 12.5 percent, respectively)

In many cases, perceptions worsened from last year's survey, an interesting result that doesn't track with trends in the marketplace, with perfusion being increasingly adopted for many new processes and even retrofitting of existing processes. This increase in concern may be the result of increased awareness of the technology as an alternative. Additionally, users and vendors claim that many problem areas have been addressed and that reactions may reflect dated knowledge or experience. In other words, the industry may be behind where it could or should be in terms of adopting perfusion technologies.

WHAT'S TO COME?

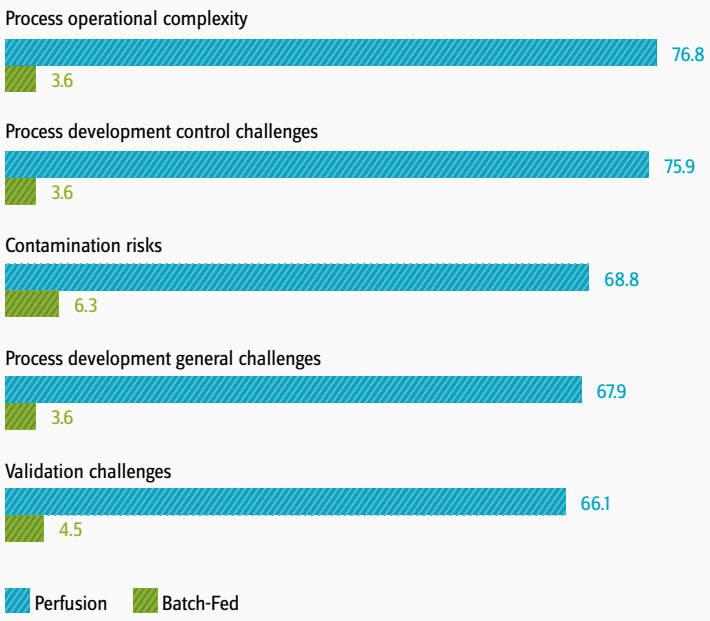
Perceptions and attitudes regarding perfusion will likely change for the better in coming years, as more bioprocessing professionals develop hands-on experience or otherwise become more familiar with perfusion operations and its advantages.

There are signs that adoption of perfusion operations is already on course, despite its perceived challenges. In order to assess potential demand for new technologies at both clinical and commercial manufacturing scales, we presented respondents to our annual study with five bioreactor types and asked, "If you were responsible for specifying a bioreactor type for a new clinical or commercial scale biologics facility two years from now, how likely might you be to implement each of the following?"

While single-use batch-fed bioreactors emerged as the most commonly preferred platform for clinical manufacture and batch-fed stainless steel bioreactors for commercial manufacture, it's instructive (and striking) that slightly more than one-quarter would use a single-use perfusion system for commercial manufacture and close to one-third would use this type for clinical supply manufacture.

Already, leading adopters such as Genzyme and Bayer are known to have manufactured a dozen or more marketed recombinant protein products (but still under 10 percent) by using perfusion or other continuous bioprocessing technologies. BioPlan Associates and others expect increased adoption of continuous bioprocessing at all scales, including commercial manufacture, as the allure of cost savings, flexibility, and increased product entices otherwise skeptical industry segments to explore and adopt continuous bioprocessing.

FIGURE 1 Perfusion Operations Issues: Perfusion vs. Batch-Fed Processes



Source: 11th Annual Report and Survey of Biopharmaceutical Manufacturing, April 2014, www.bioplanassociates.com/11th

Survey Methodology: The 2014 Eleventh Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production yields a composite view and trend analysis from 238 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations (CMOs) in 31 countries. The methodology also included over 173 direct suppliers of materials, services and equipment to this industry. This year's study covers such issues as: new product needs, facility budget changes, current capacity, future capacity constraints, expansions, use of disposables, trends and budgets in disposables, trends in downstream purification, quality management and control, hiring issues, and employment. The quantitative trend analysis provides details and comparisons of production by biotherapeutic developers and CMOs. It also evaluates trends over time and assesses differences in the world's major markets in the U.S. and Europe.

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BIOGEN IDEC'S STRATEGY FOR NEUROLOGY R&D SUCCESS

ROB WRIGHT Chief Editor

WHEN IT COMES TO THE BUSINESS OF NEUROLOGIC DRUG DISCOVERY AND DEVELOPMENT, INVESTORS SEEK INSPIRATION IN RESULTS — WHICH HISTORY HAS SHOWN TO BE A TALL TASK. For example, this past July, researchers at the Cleveland Clinic Lou Ruvo Center for Brain Health concluded that of the 244 drugs tested for Alzheimer's disease (AD) from 2002-2012, only one was a success. This rather sobering statistic doesn't scare the oldest independent biotechnology company in the world, Biogen Idec (NASDAQ: BIIB), from taking on neurological monsters like AD, or even amyotrophic lateral sclerosis (ALS) or Parkinson's disease.

DOUG WILLIAMS, Ph.D. EVP of R&D at Biogen Idec

"It's our view," says Biogen Idec's EVP of R&D, Doug Williams, Ph.D., "the science is starting to reach a tipping point in the area of neurodegenerative diseases." Williams shared with me how the company intends to combine the scientific skills honed in delivering drugs for multiple sclerosis (MS) with the basic principles of prosperous investing (e.g., diversification, risk mitigation) — Biogen Idec's strategy for success in neurology R&D.

IT ALL STARTS WITH PLAYING TO YOUR STRENGTHS

One of the key tenets to evaluating investment opportunities is to seek companies that play to their strengths. Biogen Idec's unquestionable sweet spot lies in developing drugs for MS. "If you look at our current products of Avonex, Tysabri, Tecfidera, and Plegridy, they are all focused on relapsing forms of MS," says Williams. "I think that's really the core strength of our R&D organization." Of this there is no doubt.

Combined 2013 revenues of Avonex, Tysabri, and Tecfidera equaled $5.4 billion worldwide. That represents nearly a 39 percent share of the global MS market. But Biogen Idec's dominance in the United States is even more striking. At the close of 2013, the company held a remarkable 42 percent share of the 400,000 Americans who suffer from MS. And you can expect these market share numbers to increase. Here's why. For starters, because Tecfidera received FDA approval March 27, 2013, it contributed only three quarters of its potential sales revenue for the year. Its combination of efficacy, relative safety, and the convenience of being an oral pill netted the company over $1.2 billion for the first half of 2014, solidifying Tecfidera as Biogen Idec's third MS blockbuster. Add to this the Aug. 15, 2014 FDA approval of Plegridy (Biogen Idec's new interferon therapy given once every two weeks), which analysts anticipate achieving blockbuster status, and the fact that more than half of the world's MS patients reside in Europe, an area where Tecfidera has only recently begun launching, and it is easy to discern Biogen Idec is definitely playing to its strength in MS R&D. "As I think about the way we've divided up the $1.5 billion we roughly spend on R&D every year — which should go up as our revenues increase — probably 70 percent of it is focused on neurology R&D," Williams shares. "Roughly two-thirds of that is probably MS." He adds that this high percentage of resources allocated to MS is a reflection of the company executing a lot of late-stage studies. "Those are the

R-AMP-ing Up Drug Discovery

IN FEBRUARY THE NIH ANNOUNCED THE ACCELERATING MEDICINES PARTNERSHIP (AMP), a public-private partnership venture among the NIH, 10 biopharmaceutical companies, and several nonprofit organizations. Its goal is to increase the number of new diagnostics and therapies for patients, while reducing the time and cost of developing them. The $230 million AMP initiative will begin with three- to five-year pilot projects in three areas — Alzheimer's disease (AD), type 2 diabetes, and autoimmune disorders of rheumatoid arthritis (RA) and systemic lupus erythematosus (lupus).

If you look at the list of companies involved, you will see a number of traditional Big Pharmas (e.g., J&J, Lilly, Merck, and Pfizer). But you will also see Biogen Idec. While securely in the top 50, the company is by far the smallest to get invited to the NIH AMP party. This doesn't bother Biogen Idec's EVP of R&D, Doug Williams, Ph.D., who shares how the company got asked to participate. "It was actually a direct contact from Francis Cuss [EVP and CSO], who runs R&D at Bristol-Meyers [Squibb] and called me to tell me about the program and see if we were interested in participating," he divulges. But why was Biogen Idec selected? Williams believes it was partially because of the company's visible interest in developing drugs for AD, but also a function of its demonstrated willingness to participate in public-private consortia (e.g., the ALS Research Consortium, spearheaded by Biogen Idec's CSO, Spyro Artavanis-Tsakonas, Ph.D.).
Although Williams believes it was logical for Biogen Idec to be approached to participate in AMP, he felt it made even more sense for the company to get involved. "These diseases are bigger than any one company," he says. "It's going to require a public-private partnership with a significant focus for us to succeed in the development of drugs in this space. We became interested in AMP because of our growing interest in Alzheimer's disease." But the reason Biogen Idec decided to get involved is because "it [AMP] focused on two things important to us." One is coming up with new biomarkers so researchers will know whether a drug is working earlier in the process, rather than having an expensive Phase 3 failure. "The second was the realization almost everyone who's in Alzheimer's disease today is focusing on the Beta-Amyloid (Aß) pathway," he explains. "We need to move beyond this to find even better targets and broaden the approach to treating Alzheimer's beyond just the Beta-Amyloid (Aß) hypothesis." In addition, Williams believes the mechanisms that perpetuate and potentiate neurodegenerative syndromes may have commonalities. As such, there's a possibility that a drug developed for something like Alzheimer's could treat multiple neurodegenerative diseases.

According to Williams, there are plenty of considerations to take into account when becoming involved in public-private partnerships like AMP (e.g., how it's structured, how intellectual property flows). His advice is not to let these types of potential roadblocks be reasons for not participating. "We've come to the conclusion that the real competition comes when you're developing the drug candidate, not when defining new pathways and targets."

expensive ones to carry out," he reminds.

Biogen Idec plans to build upon its strengths by extending its MS franchise. "We're moving into therapies that do more than just slow down the progression of the disease; we're trying to develop drugs that can reverse some of the damage by remylinating the CNS," Williams shares. For example, Anti-LINGO-1 is Biogen Idec's investigational monoclonal antibody currently in Phase 2 clinical development. It targets LINGO-1, a protein expressed selectively in the CNS known to negatively regulate axonal myelination and axonal regeneration. "We're also moving into secondary progressive multiple sclerosis [SPMS], which is a slightly different form of MS." Although Tysabri is already approved for relapsing forms of MS, the company is involved in a Phase 3 clinical trial for SPMS, anticipating results sometime in 2015. The other area where Biogen Idec intends to build upon its

AMP Partners

GOVERNMENT	INDUSTRY	NONPROFIT ORGANIZATIONS
FDA	Abbvie	Alzheimer's Association
NIH	Biogen Idec	Alzheimer's Drug Discovery Foundation
	Bristol-Myers Squibb	American Diabetes Association
	GlaxoSmithKline	Arthritis Foundations
	Johnson & Johnson	Foundation for the NIH
	Lilly	Geoffrey Beene Foundation
	Merck	Juvenile Diabetes Research Foundation
	Pfizer	Lupus Foundation of America
	Sanofi	Lupus Research Institute/Alliance for Lupus Research
	Takeda	PhRMA
		Rheumatology Research Foundation
		USAgainstAlzheimer's

strength is what Williams refers to as the concept of logical adjacencies, starting with MS.

APPLYING THE BASIC PRINCIPLES OF SUCCESSFUL INVESTING TO R&D

Biogen Idec seems to be following the old adage of "Invest in what you know" when it comes to R&D — much to the delight of analysts and shareholders. (The company is forecasting 38 to 41 percent sales growth for 2014 and non-GAAP EPS of around $13 as of its second quarter earnings call.) Unlike investors, who seek broad diversification into nonhighly correlated assets in order to reduce risk (i.e., fast food, technology, pharmaceutical companies, manufacturing, etc.), Biogen Idec is looking to diversify its R&D portfolio by expanding into highly correlated opportunities — the logical adjacencies to which Williams refers. This is a risk-reducing behavior as the company is building upon its R&D expertise in diseases which manifest themselves similarly. "We're not moving into the area of neuropsychiatric diseases at the moment," he asserts. "We don't feel like that's really our sweet spot. Our belief is the maturity of the science is best in the areas of neurodegeneration, for example AD, Parkinson's disease, and ALS." Makes sense, right? To be sure, all of the diseases Williams mentions represent a huge unmet medical need. But the statistics don't lie. Most companies have tried and failed when it comes to developing drugs for AD. The most commonly prescribed treatment for Parkinson's, levodopa (also called L-dopa), is a 45-year-old medication. When it comes to ALS, no currently available treatment halts or even slows its progression. My question to Biogen Idec's head of R&D was, "Imagine I am a shareholder. Convince me why this is a good idea and how you are going to do it." He replied, "This is just one aspect of a balanced portfolio of spending across R&D."

Just as investors seek to have a balanced investment portfolio, Biogen Idec is seeking to have a diverse portfolio of products in its pipeline by investing not just in what they know, but what they know works. For example, this past March the FDA approved the company's hemophilia B drug, Alprolix, and in June, Biogen Idec was granted FDA approval of its hemophilia A drug, Eloctate. While analysts don't anticipate these to have the impact of Tecfidera, these two hemophilia drugs help diversify the company's revenues away from MS and could eventually generate hundreds of millions in annual sales. "You could look at our hemophilia programs and see those are somewhat less risky in the sense that these drugs will address unmet medical needs, but the risk profile is different," says Williams. "They're basically extending the half-life of the molecules, but we know the molecules themselves actually work."

In addition to achieving balance and building on competencies, Williams also discussed the importance of learning from the failures of others. In particular, he explained why Alzheimer's is number two in terms of relative R&D spend in the Biogen Idec neurology portfolio. "Yes, there have been a number of failures

Taking The ALS Ice Bucket Plunge – Before It Was Cool To Do So.

UNLESS YOU HAVE BEEN LIVING UNDER A ROCK, you have most likely heard of the social media philanthropy craze – The Ice Bucket Challenge. When I began writing this article, the phenomenon had netted the ALS Association $41+ million in donations, a significant increase over the $2.1 million netted over the same period last year. Before I completed writing the article, donations surpassed the $100 million mark. However, you have to be impressed by people and companies which do the right thing before it is cool (no pun intended) to do so.

Back in 2012, Biogen Idec created the ALS Research Consortium. The brainchild of Spyro Artavanis-Tsakonas, Ph.D., the company's chief scientific officer, the partnership brought together a group of handpicked investigators working on the various processes and pathways important in the pathogenesis of ALS. Each participating lab, which included researchers from Yale, Harvard, Columbia, and The Rockefeller University, was to undertake a three-year project. In addition, members would meet on a regular basis to provide updates and share information and insights emerging from their research. The initiative was an extension of a previous collaboration forged in July 2012, also championed by Biogen Idec, which brought together Duke University and the HudsonAlpha Institute for Biotechnology with an objective of sequencing the genomes of approximately 500 patients living with ALS within the first two years and ultimately, sequencing 1,000 ALS genomes within five years. While all of this sounds very impressive, what stunned me about Biogen Idec and Artavanis-Tsakonas, who is also a professor of cell biology at Harvard Medical School, is how the company was willing to go ahead with founding the ALS research consortium (announced Dec. 20, 2012) and commit more than $10 million over three years to fund research projects of its members, despite only two weeks later (Jan. 3, 2013) publicizing the Phase 3 failure of the only ALS compound in its pipeline, dexpramipexole — a candidate licensed from Knopp Biosciences for $80 million in up-front payments and up to $265 million in milestones. The founding of the ALS research consortium is another example of what makes for a prosperous investor, as well as a successful drug development researcher — not panicking during failures. Many people, when the price of a stock they own begins to drop, look to sell. However, this might be the best time to buy more. When it comes to creating thought leadership in drug R&D, don't run from failures. Instead, seek to be more like Biogen Idec and invest in understanding why.

in Alzheimer's," he concedes referencing J&J's Bapineuzumab and Lilly's Solanezumab — both failing in Phase 3 studies. "But we've learned a lot from those failures. I think the current generation of studies we're conducting — and particularly those focused on the Beta-Amyloid (Aß) pathway, which is the dominant area of focus today for new Alzheimer's therapies, are much more intelligently designed as a result." There is another advantage to taking the approach of being a fast follower (i.e., entered early but not first) into a market, as opposed to being a first mover (i.e., first to sell the product). Research has shown companies first to sell a product have nearly a 47 percent failure rate. Fast followers on the other hand, have only an 8 percent rate of failure. If you have a low tolerance for risk and limited resources, you would be wise to follow Biogen Idec's example of studying the failures of others and then applying lessons learned before deciding to enter.

A basic principle of investing is to be realistic about your tolerance for risk. "If you look at the way studies are being run now," Williams states, "they're much more intelligently designed and have better end points. Furthermore, we're much more careful about the patients we're enrolling." He says Biogen Idec confirms patients actually have the target for their drug before being treated. The company decided to apply advanced imaging technologies to confirm patients being enrolled in Alzheimer's studies were appropriate targets. "Everybody going into our studies is now imaged with an imaging reagent, Florbetapir (trade name Amyvid), which was approved for imaging Beta-Amyloid (Aß) in the brain," he affirms. Good thing. As it turns out, imaging has revealed nearly 40 percent of the patients Biogen Idec has imaged with clinical signs and symptoms of AD don't actually have the Beta-Amyloid (Aß) target for their drug. "This has enriched our study populations by including only those who have the target."

Another way to reduce risk in developing drugs for these neurological diseases is to partner and collaborate while also spearheading thought leadership. For example, in March, Biogen Idec announced a partnership to develop and commercialize two of Eisai's clinical Alzheimer's candidates, E2609 and BAN2401. As part of the partnership, Eisai has an option to jointly develop and commercialize two of Biogen Idec's AD candidates, BIIB037 and an antitau monoclonal antibody. Regarding collaboration, Biogen Idec is participating in the Accelerating Medicines Partnership (AMP) — a venture among the NIH, 10 biopharmaceutical companies, and several nonprofit organizations. (For more about AMP check out the sidebar — *R-AMP-ing Up Drug Discovery*.) As for thought leadership, the company spearheaded the creation of the ALS Research Consortium long before the recent ALS Ice Bucket Challenge swept the globe. Ultimately, when it comes to investing in a drug R&D program, Williams would probably ascribe to focusing on and identifying diversification, balance, and risk. "We try to balance the portfolio across different diseases, different types of therapies, and different risk profiles." Sounds like a pretty good R&D investment strategy to me.

> "The science is starting to reach a tipping point in the area of neurodegenerative diseases."

DOUG WILLIAMS, Ph.D.
EVP of R&D at Biogen Idec

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EMD SERONO - THE CULTURE OF SPECIALTY CARE

WAYNE KOBERSTEIN Executive Editor

KNOWN AS MERCK SERONO OUTSIDE OF NORTH AMERICA, EMD SERONO BRINGS ITS HISTORICAL IDENTITY AS A SPECIALTY CARE DRUG COMPANY TO THE CORPORATE BIOPHARMA DIVISION.

PARIS PANAYIOTOPOULOS, President and Managing Director of EMD Serono

During the past eight years, since its acquisition by Merck KGaA, Darmstadt, Germany, EMD Serono has quietly expanded in the shadows of the pharma/biopharma giants and its German parent. EMD Serono is the North American face of Merck Serono, which was featured in our April 2014 issue. EMD Serono/Merck Serono is the biopharmaceutical division of Merck KGaA — a 30 percent public, 70 percent family-owned corporate entity descended from the old, original German Merck, also called E. Merck. Like J&J, the Merck Group has a public stock listing, on the Frankfurt Stock Exchange, but its separate businesses do not.

"Outside of the U.S., the biopharmaceutical division operates as Merck Serono, but the organization is one global team," explains Paris Panayiotopoulos, president and managing director of EMD Serono. "In 2013, Merck Serono generated 56 percent of Merck Group sales, of which 21 percent comes from EMD Serono in North America." The umbrella biopharma unit shares four main R&D centers, in Billerica, Massachusetts; Darmstadt, Germany; Beijing; and Tokyo. Reflecting the long-standing Serono heritage, the company says it stands among "the top five U.S. biopharmaceutical companies exclusively focused on specialty care."

Specialty care is subtly distinct from the simplest concept of so-called specialty pharma; the word "care" implies much more than reformulation and drug-delivery. Consistent with its long focus on the patient-centric area of fertility, EMD Serono supplies a variety of patient support tools with nearly all of its products. All are injectables or infusion drugs that require extensive patient care, and the company offers services such as hotlines and educational materials to ensure proper use and compliance. "Specialty care is defined by smaller patient populations with high unmet needs," Panayiotopoulos says. A company publication also cites these criteria: "high cost, difficult medication delivery, and/or complex treatment maintenance."

EMD Serono's current products on the market are in the areas of multiple sclerosis, metabolic endocrinology, and fertility — all areas where specialty care products fill particular medical needs. But the company's current R&D pipeline contains a different mix, with candidates in oncology, immuno-oncology, multiple sclerosis, and immunology, signaling changes and new directions in its future portfolio. Still, according to Panayiotopoulos, all pipeline products in the new areas will match the specialty care model, allowing his company to maintain its traditional focus. (See "Plowing Fertile Ground.")

PLOWING FERTILE GROUND

SOME SAY HISTORY IS ONLY USEFUL IN BUSINESS when it is well-related to present or potentially developing circumstances. What does it matter that the company name began as Ares Serono, then a lonely pioneer in reproductive medicine? Has some vestige of the company's original culture and tradition somehow survived to imbue the new entity, even after its merger with E. Merck? Actually, yes it has.

Geneva-based Serono was fiercely independent and virtually without competition in the fertility field when I met then-CEO Fabio Bertarelli, toward the end of his long stewardship, in 1993. The old man gave this American innocent abroad a bemused but hospitable, and forever memorable, reception. He carried a certain cynicism born of a long struggle in a tough business, but he showed almost affectionate forbearance for my New World naiveté. When I returned to meet Fabio's son and successor, Ernesto, in 1996, the company had a completely different feel of accelerated modernism. In another few years, it would be shopping around for a buyer in what turned out to be a long and frustrating exercise, but the quest finally ended with the $13.3 billion purchase of Serono by E. Merck in 2006. Ernesto Bertarelli went on to win the America's Cup for a second time, then turned some of his enormous wealth to buying back the old, shuttered Serono headquarters in Geneva to house a biotech research center.

EMD Serono, descended from a company with a 40-year history in the United States, was E. Merck's biopharma beachhead in North America, where the German company has been contractually barred from doing business under the Merck name since the end of The Great War (WWI). Merck claims to be the world's oldest pharmaceutical and chemical company, tracing its roots to 1668, when the family patriarch purchased a pharmacy in Darmstadt, Germany, still its headquarters. The acronym EMD applies to all Merck Group divisions and stands for "Emmanuel Merck, Darmstadt." (Emmanuel initiated "industrial production" at the company in the early 1800s.) Worldwide, Merck KGaA is also known for its hugely lucrative invention of liquid crystal displays in addition to its pharmaceuticals.

Relative youngster Serono goes back to 1906, when its patriarch founded a "pharmacological institute" in Rome. But a new era began in 1949 when a chemist at the company discovered an industrial way to produce gonadotropin as a fertility treatment. Forty years later, Serono entered the biotech sector with its first rDNA-based products, Gonal-F (gonadotropin) and Saizen (somatropin) for AIDS wasting. From the beginning, the company saw its new rDNA drugs as specialty care products, effectively establishing the model Serono still employs today.

SIDE-BY-SIDE DEVELOPMENT

Globally, Merck Serono's commercial portfolio now contains nearly all of the products EMD Serono sells in the North American market, but it also includes oncology products. Together, EMD Serono/Merck Serono hopes to emerge as a strong player in the oncology space. EMD Serono currently has no oncology products, whereas Merck Serono had previous oncology experience with Erbitux (cetuximab) but not immuno-oncology. The two share a nearly identical, global pipeline of products in development, which indicates a long-term strategic alignment, starting with several cancer drugs in Phase 3 trials.

Merck KGaA's chairman, Karl-Ludwig Kley, in the 2013 annual report, suggested specialty care will remain the focus of the biopharma unit's long-term global franchise: "The aim is to establish Merck Serono globally as a preferred biopharmaceutical partner that offers innovative specialty medicines, leading brands, and high-value solutions." In former times, "leading brands" might have been synonymous with primary-care blockbusters. But based on today's premium-pricing model, specialty care indications can also support leading brands, even in a revenue sense.

Specialty care is more than a marketing term; managed care organizations often have specific rules regarding coverage, cost share, and/or benefit management for specialty care drugs. Dealing with the complexity of treatment for the targeted diseases requires simplifying administration with appropriate technology such as autoinjectors or special formulations, educating patients, and managing supportive care efficiently and effectively. Almost in a class by itself is the imperative of helping patients, providers, and payers work through insurance coverage and reimbursement issues. "As a specialty care company, we have always focused on three areas: innovative products, devices, and patient support services," Panayiotopoulos says.

He points to a growing industry trend favoring specialty care. In 2008, the FDA approval rate of specialty care drugs was about 30 percent; in 2013, seven out of every 10 FDA-approved drugs were specialty care. "We've been strategically well-placed in that space with our drug products, devices, and support services, and given that our pipeline is all specialty, that is where we intend to move forward."

Typically, the company must create its support services in parallel with the product — planning for, implement-

ing, and constantly improving them from the early stages on, throughout the product's entire life cycle. As it develops the drug, the company also builds a technical and informational infrastructure to support its use in patients. Whatever the larger corporate context or even the product portfolio, that is the culture, the particular set of capabilities, EMD Serono brings to the business.

"We have a deep expertise in specialty care including a proven track record of success commercializing biologic and specialty pharmaceuticals in fertility, endocrinology, and neurology," says Panayiotopoulos. "We have worked to develop patient support programs that serve our unique patient populations effectively. We take our responsibility in this space seriously, and our organization is galvanized around the patients we serve."

EMD Serono has four rDNA-based products on the market: Rebif (interferon beta-1a) for multiple sclerosis, Gonal-F (follitropin alfa) for female infertility, Saizen (somatropin) for growth-hormone deficiency, and Serostim (somatropin) for HIV-associated wasting. Support services for patients include MS LifeLines, Fertility Lifelines, Connections for Growth, and The AXIS Center. The MS LifeLines program support center answers calls 24/7. MS LifeLines includes a nationwide nurse network providing in-home training on product usage and reimbursement specialists to help patients understand their insurance benefits and "assist eligible patients in getting affordable access to Rebif," including through a zero co-pay program. In fertility, the company has also created financial assistance programs for patients: Compassionate Care, the Co-Pay Program, the Go Direct to Savings Program, and its recently announced Compassionate Corps program offering financial assistance to qualifying veterans.

Panayiotopoulos gives a more detailed example of how the company develops patient support tools for an innovative product, in this case, Rebif. "Last year, we launched Rebidose, a prefilled, disposable auto-injector to help patients with the self-injections. We have a 24/7 call center with many nurses around the country who are certified by The International Organization of Multiple Sclerosis Nurses. They help patients on the difficult journey of chronic MS, from the beginning throughout their use of the product. Recently, with more pressures on the reimbursement side, we set up specialists who help patients get access, either through our zero-dollar

CATCHING UP IN CANCER?

EMD Serono and its German counterpart in the Merck KGaA biopharma division place big hopes on expanding into cancer, where the North American company has no current presence and its global group has only one main product, Erbitux (cetuximab). We challenged the company's CEO, Paris Panayiotopoulos, on the details of the expansion in the hot new field of cancer immunotherapy.

How does EMD Serono expect to compete with the leaders in the field of PD-1/PD-L1 inhibition who are now going on to Phase 3 trials with exceptional Phase 2 results already behind them?

EMD Serono has strong confidence in its immuno-oncology research and early development platform. For nearly seven years, our company has been actively building our iONC platform by recruiting preeminent talent, creating a world-class immuno-oncology medical consortium, and building a portfolio of novel cancer immunotherapies.

We will compete through our unique strategy that differentiates our efforts — from our science to our business to our focus on patients — and our robust pipeline centered on three Innovation Clusters: therapeutic cancer vaccines, cancer stem cells, and tumor immunotolerance. Our biomarker strategy is also well ahead of the competition with a biomarker program associated with each of our assets in our iONC portfolio.

Our iONC platform has also accomplished a number of firsts in the industry. Two years ago, we established an autonomous immuno-oncology innovation platform integrating research, early development, and biomarker strategies — making us the only company to separate immuno-oncology R&D from the oncology platform. We also established the industry's first fully dedicated immuno-oncology postdoctoral and clinical fellowship programs.

What are your main oncology drugs under development?

TH-302 is an investigational hypoxia-activated prodrug in Phase 3 trials for both soft-tissue sarcoma and pancreatic cancer. It is licensed and codeveloped with Threshold Pharmaceuticals. Sarcomas are a group of aggressive cancers of connective tissues of the body for which there are currently limited treatment options. Soft tissue sarcomas are treated with surgery, chemotherapy, and radiation. An estimated 36,000 new cases of soft-tissue sarcomas were diagnosed in 2013 in the U.S. and Europe.

MSB0010718C is an investigational, fully human monoclonal antibody that targets a protein known as programmed death ligand-1 (PD-L1). It is currently under active investigation in a Phase 1/1b clinical trial designed to assess tolerability as the primary outcome, with pharmacokinetics, pharmacodynamics, and efficacy measured as secondary outcomes, in a range of cancers. In addition, we recently initiated a proof-of-concept Phase 2 study in subjects with Merkel cell carcinoma (MCC).

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co-pay program for those patients who are insured or our patient assistance programs for the uninsured. If we were operating in the primary care area with millions of patients across the country, all that would be much harder to do."

Of the 30 compounds in development by the biopharma unit, Panayiotopoulos says four are in Phase 3 and nine in Phase 2 trials. In one new area, oncology, the company and partner, Threshold Pharmaceuticals, are developing TH-302, an investigational hypoxia-activated prodrug in Phase 3 development for soft-tissue sarcoma — an indication with only about 36,000 patients diagnosed in the United States and Europe in 2013 and thus a specialty care area. The partners have the same compound in a Phase 3 trial for pancreatic cancer. (See "Catching Up in Cancer?")

NORTH TO GLOBAL

Panayiotopoulos describes how the global R&D function is organized to integrate the development programs from which EMD Serono and Merck Serono will draw future products. "Our global R&D efforts are structured along four translational innovation platforms [TIPs], which correspond to the key research areas: oncology, immuno-oncology, and immunology/neurodegenerative diseases, as well as global health, which addresses neglected diseases such as schistosomiasis and malaria. The TIPs define the strategies for respective platforms and projects until proof-of-concept and articulate the strategies in business plans that span three years. An external independent advisory board approves the TIP business plans and reviews them on a biannual basis. TIPs also largely drive decision making and portfolio prioritization — including which R&D center will run a particular program — until proof-of-concept. It is important to have a global R&D organization because the end output, launching the drug, will be serving a number of markets globally," Panayiotopoulos explains. "Of course the U.S. market is a very important consideration in the portfolio decision-making process."

EMD Serono and its corporate twin on the other side of the Atlantic stake the future on specialty care — a heritage brought to the biopharmaceutical unit and the corporation by the namesake they both share. An interesting union of two family and corporate histories, the original Merck and the old Serono, the company should continue to be a strong, global contender in the billowing specialty care field. L

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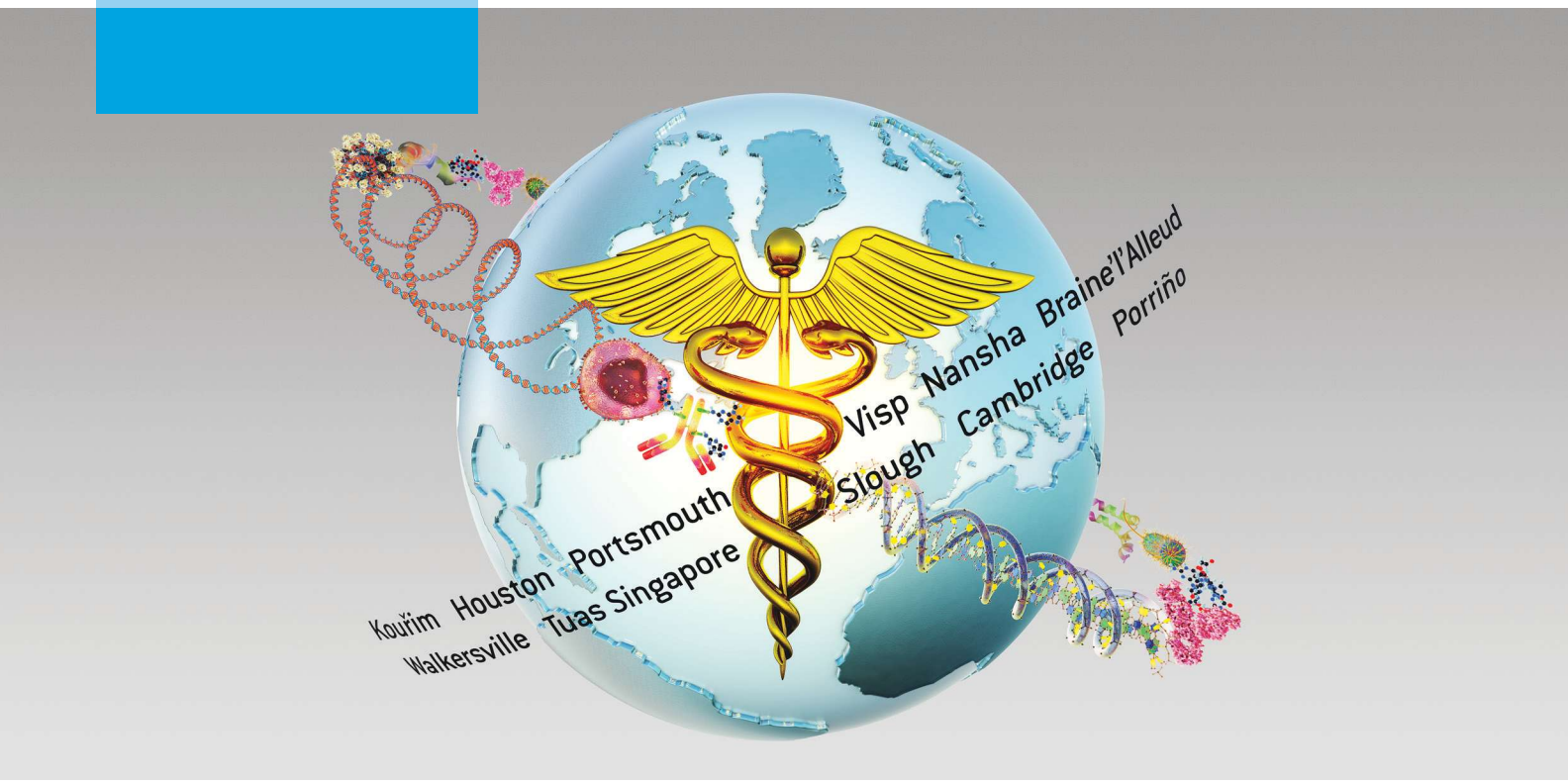

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COMBINATION CANCER IMMUNOTHERAPY — A VIRTUAL ROUNDTABLE

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

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

Drugs that target the immune system, not the tumor, may have entered the long war on cancer at last. Although some still dispute the validity of cancer immunotherapy, others are charging ahead. Results of large Phase 2 trials showing durable responses from a new class of drugs called checkpoint inhibitors, along with progress on the vaccine/immunostimulator front, have fired up supporters and attracted new interest from former doubters.

Our virtual roundtable, a compilation of responses to questions from key experts and players in the field, considers the ramifications of a growing consensus that using cancer immunotherapies in combination, rather than as single agents, will be essential to have maximal effect for patients. In a matter of years, many cancer immunotherapies will be available, many combinations will be possible, and the choice of combinations will be quite challenging from a clinical, regulatory, and reimbursement perspective. Biomarkers and companion diagnostics may also play a big role in guiding the way, as will a deepening understanding of immunotherapy mechanisms and cancer response. But who should decide how combinations are tailored and delivered to individual patients, and on what grounds should they base those decisions?

PART TWO: Key Opinion Leaders Benchmark the Science

MORE QUESTIONS TO ANSWER

Whether by written or in-person response, our panelists all tackle the same set of issues in combination cancer immunotherapy — in this second part, the deeper issues involved in therapeutic choices — by physicians, payors, and regulators. Their answers to our questions, along with further queries and interjections by the moderator, follow.

QUESTION: What are the essential constituents of any cancer immunotherapy combination?

KELTNER (Moderator): Even as this discussion goes on, new targets for immunotherapies continue to proliferate — from new checkpoint inhibitors, to immunostimulators, to entirely new classes. Thus, the discussion of the emerging alternatives and their respective roles is bound to show both agreement and divergence among the panelists.

SZNOL: We don't yet have the answers to this question. In animal models, you see strong activity when you combine two checkpoint inhibitors, such as PD-1 and TIM3, PD-1 and LAG3, or PD-1 and CTLA-4, and very impressive data with blockade of one checkpoint, such as PD-1, together with one co-stimulatory agent, such as CD-137 or OX-40. Even if we developed biomarkers, we might still have to make guesses in the clinic. A given patient, based on a biopsy, might need two checkpoint inhibitors, and if the patient does not respond, we might add another agent.

Inhibiting checkpoints is not always necessary. Interleuken-2 works without inhibiting any checkpoints in a subset of patients. Why does it work at all? We don't know, but it does not require PD-1 or CTLA-4 blockade or anything else. How does CTLA-4 work without blocking PD-1 when the T cells that infiltrate the tumor upregulate PD-1 or are subject to PD-1/PD-L1 suppression? Why does cell therapy work? When you give the engineered cells back, they upregulate PD-1. It is an analog, not a digital, system, and if you drive your system enough, you may overcome checkpoint immunosuppression.

URBA: Combinations one day will be developed based on a personalized approach addressing tumor and host characteristics. Generically, I would include an antigen-priming or boosting step. This would most likely be a vaccine, although it could be an intratumoral injection of a lytic virus, cytokine, bacteria, chemotherapy, or radiotherapy administration. One would want to ensure the proper local milieu, so some form of adjuvant tickling the appropriate receptors might be included. Future combinations are likely to include a checkpoint inhibitor and perhaps also an immunostimulatory component. I could see inclusion of specific strategies to alter potential inhibitory processes such as elimination of T regs, neutralizing negative factors (IDO, arginase, TGF-beta), and modification of macrophages.

GRETEN: Vaccines are a bit more complicated because it's very difficult to develop one to be used off the shelf, rather than an individualized vaccine for every single person, as in prostate cancer with the Provenge vaccine, which requires a very costly, time-intensive, and difficult procedure. My basic idea is, why not just use treatments that you do anyhow, such as chemotherapy or ablation, optimize them, and use them as a kind of vaccine to induce a response, then combine them with immunotherapy to achieve better responses?

WOLCHOK: There will be a very broad list of different combinations — combinations of immunotherapies with other immunotherapies; with regional therapies such as oncolytic viruses; locally destructive techniques such as radio frequency ablation, cryosurgery, and radiation therapy; and oncogenic-pathway targeted therapies. It will still require a lot of investigation, but we have already established a firm foothold for immunotherapy in producing a durable response for patients with multiple kinds of malignancies.

SZNOL: This is not a war between immune therapy and targeted therapy or chemotherapy. We can figure out a way to use all those approaches to treat patients more effectively. In melanoma, we treated patients who failed to respond to immune therapy with dabrafenib or trametinib and got a substantial clinical benefit.

⊕QUESTION: Do you believe PD-1/PD-L1 therapy, or some other approach, will be the "backbone" of cancer immunotherapy combinations? Or will consensus on a hierarchy of therapies evolve along with the growth of scientific understanding and use of biomarkers?

KELTNER: The exploration of overall safety profiles in combination immunotherapies may be just as important as the overall efficacy of combinations, favoring immunotherapy mechanisms with inherently low toxicity — such as newer-generation, off-the-shelf cancer vaccines — in selection of combinations.

FONG: With other immunotherapies coming down the pipe, it will be important to see their clinical activity, but just as important, their toxicities. If you have a relatively nontoxic treatment, it really makes it that much easier to layer things on top of it, whereas if something already has a lot of side effects, we must try to navigate around them in any combination. Even if the

PANELISTS

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President and CEO, Epistat

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C James Allison, Ph.D.
Executive Director, Immunotherapy Platform and Chair, Immunology, The University of Texas MD Anderson Cancer Center

D Lawrence Fong, M.D.
Professor, Department of Medicine (Hematology/Oncology), UCSF

E Mario Sznol, M.D.
Professor of Medicine (Medical Oncology); Clinical Research Program Leader, Melanoma Program, Yale Cancer Center

F Alan Venook, M.D.
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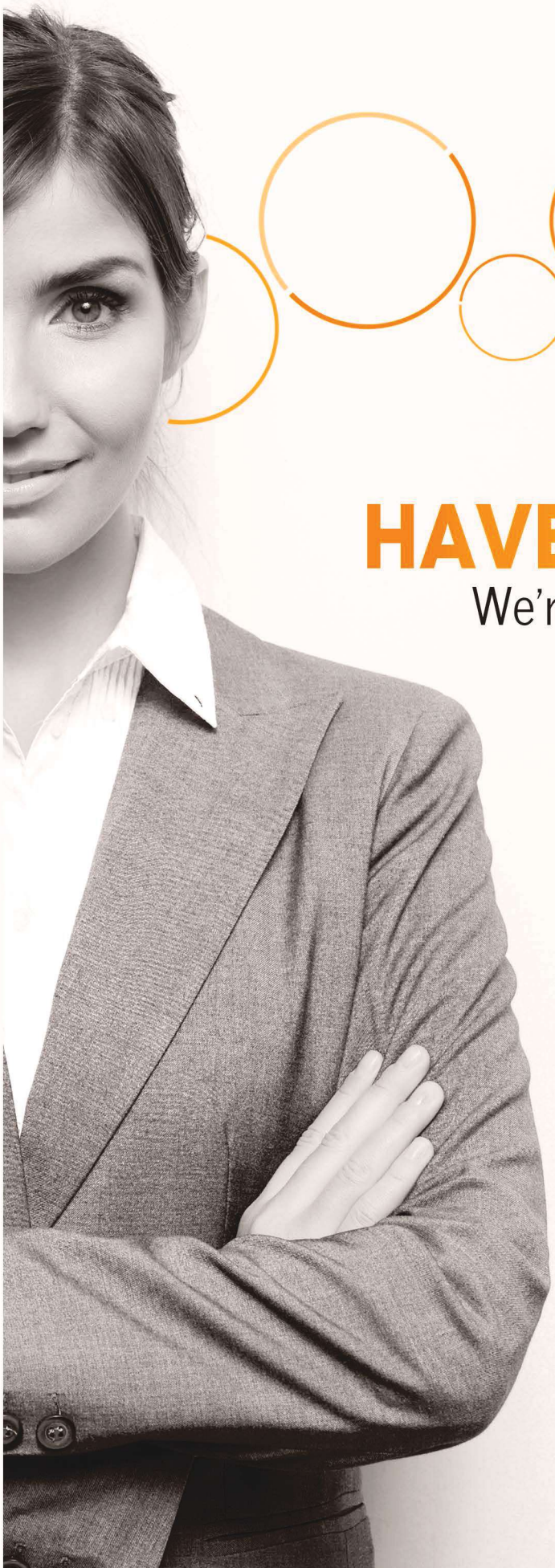
I Neil Berinstein, M.D.
Director, Translational Research, Ontario Institute for Cancer Research (OICR)

J Jedd Wolchok
Chief, Melanoma and Immunotherapeutics Service, Memorial Sloan-Kettering



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immunotherapy only had the same efficacy as chemotherapy regimens, but had no toxicity, it could become the backbone of cancer treatment.

Other approaches are very complementary — for example, a cancer vaccine such as Provenge or another prostate cancer vaccine called PROSTVAC-VF, which is a recombinant viral vaccine. These could stimulate immune responses in a patient.

WOLCHOK: Safety profiles definitely have to be considered, on an agent-by-agent basis. There are some situations where we're going to need to use therapies that target the tumor to release antigens and alter the microenvironment, and in fact some of them may even have immunomodulatory effects as well.

SZNOL: At least, with immunotherapies, you may have a different return for the adverse effects — a better chance of being able to live the rest of your life without having to take a drug chronically and going back to a fairly normal quality of life. But these drugs can produce permanent side effects: Some people lose their pituitary and have to take a prednisone or thyroid pill for the rest of their life; and if they get sick without a pituitary, they need to get replacement hormone therapy. So patients don't go back completely to normal in some cases, but it's pretty close to normal.

ALLISON: When CTLA-4 was new, there were a lot of lessons learned; it was a whole new concept, a new way of treating cancer, and it was terra incognita from the moment the field opened. The adverse events were not expected. There had been no toxicity in mice, no toxicity in monkeys, so they first popped up in humans. It took awhile to get a handle on it, but now there is a dosing algorithm, so when PD-1 came along, everybody was ready. Immunotherapy probably is inherently less toxic than chemo, but it can have severe toxicities. People died before we had the algorithm. There is also an indication that some people who only receive anti-PD-1 recur more often than people who just get anti-CTLA-4, so the backbone will probably be those two in combination along with a third one — not anti-PD-1 by itself.

SHARMA: Anti-PD-1 is also administered for a much longer period of time as compared to anti-CTLA-4. Anti-PD-1 is given for a period of two years of therapy in the current clinical trials, while anti-CTLA-4 was FDA-approved to be given over a period of about three months as four doses of the antibody, with each dose being given three weeks apart, and then you're finished with the treatment. Anti-PD-1 may become a backbone where other treatments can be given during the two-year period of anti-PD-1 therapy.

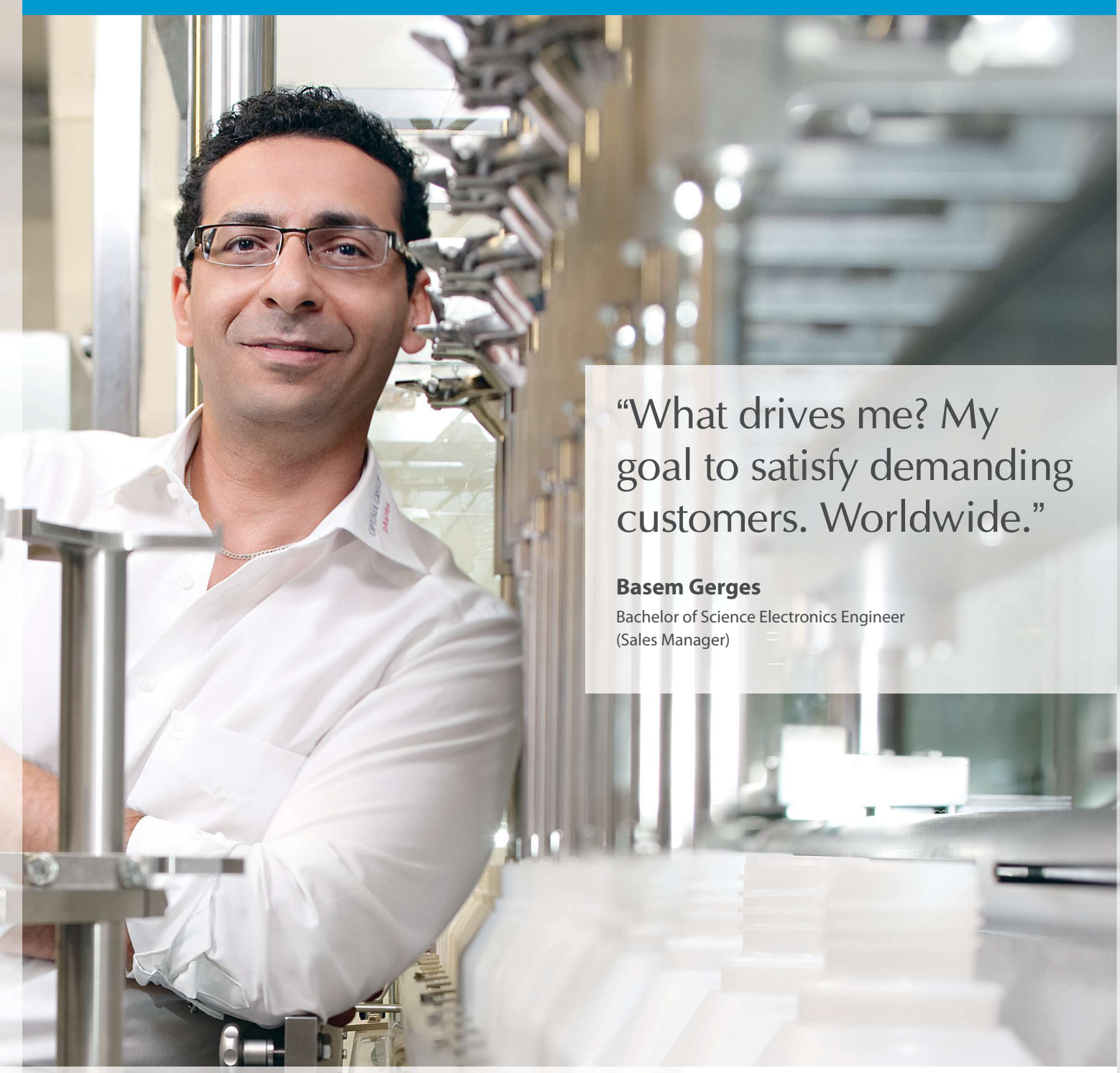
ALLISON: And 20 percent of those people treated with anti-CTLA-4 are still alive after a decade or more. With anti-PD-1, survival data is still early and patients are still under observation.

BERINSTEIN: As is the trend in cancer therapy, there is a push to make cancer immunotherapy more personalized. Anti-PD-1 or PD-L1 therapies only have activity in a subset of patients, which may be disease-specific. It is likely that other immune inhibitory pathways are more dominant in the nonresponders. In the future, it may be possible to identify more dominant pathways by interrogating each patient's tumor individually. In this way, immune modulation can be prescribed for each patient in a more logical and patient-specific fashion. However, in the immediate/short term, it is likely that the hierarchies of appropriate combination treatments will develop based on well-designed and controlled pivotal clinical trials, and these will inform the best combination therapies moving forward for a variety of cancer types. It is also possible that a complex combination therapy that will likely include the PD-1/PD-L1 pathway will be able to provide a safe and effective approach to treating cancer without seeking a personalized approach. The field is not there yet.

KELTNER: Proof that "we're not there yet" already exists in data from the ASCO presentation given by Pam Sharma entitled "PD-1/PD-L1 Inhibition: Identifying Relevant Biomarkers," as she discussed ASCO abstract 5012 composed of an anti-PD-1 clinical trial and abstract 5011 composed of an anti-PD-L1 clinical trial. The trial targeted patients whose tumors expressed the PD-L1 antigen, and the responses in those patients were dramatic. But some PD-L1-negative patients also responded, casting doubt on the usefulness of PD-L1 as a biomarker for patient-treatment selection. The field of prostate cancer biopsies has clearly demonstrated the danger of making negative determinations based on single biopsies, just as the presence of a target on some cells in a tumor, at a fixed point in time, cannot guarantee all of the tumor cells will respond well to a targeted drug. Such challenges do not bode well for biomarkers to guide patient-by-patient selection of immunotherapies.

In the genomic era, we all got caught up in the idea that you look for the mutation, then you look for the drug to target the mutation. But that only addresses the static state — the mutated gene itself is static, but the immune system is dynamic. If a patient's tumor biopsy is PD-L1-negative today, it could be PD-L1-positive tomorrow. You might think the PD-L1-negative patient will not respond to PD-L1 or PD-1 therapy, but that is not true. Some of them do respond, and the reason may be not that the target is absent, but that the target is dynamic and changes over time based on the presence of other immunologic factors such as IFN-gamma, and you cannot label "positive" or "negative" on a single biopsy.

ALLISON: T cell infiltration produces gamma interferon, which upregulates PD-L1 in the tumor, and if you biopsy the wrong portion of the tumor where there is not an effective immune response, the tumor is not going to express PD-L1. As a matter of fact, if there really is no PD-L1, it means the immune system is quiescent in the patient, so that ought to be reflected in low T cell counts and all the immune factors. Instead, people just jump to one biomarker. When you give anti-CTLA-4,



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Professor, Department of Medicine (Hematology/Oncology), UCSF

you are going to see a lot of PD-L1-negative patients get these ICOS-positive cells that make gamma interferon; they're going to make the tumor cells and other cells in the microenvironment express PD-L1, which provides the perfect opportunity to give anti-PD-1 or anti-PD-L1 therapy. But you couldn't have known that the tumor cells would express PD-L1 based on the initial biopsy.

WOLCHOK: We would love to have a perfect predictive biomarker for these treatments. But the truth is, we don't. The PD-L1 tumor expression has been considered very carefully over the past few years since the initial data began to emerge, and it did seem to identify patients who are more likely to respond to PD-1 blockade, but that is really the limit of the association. It is not a binary indicator. It is an inducible dynamic biomarker unlike a BRAF mutation, a static biomarker. PD-L1 is expressed on normal endothelial cells and antigen-presenting cells, and by interrupting that pathway, you may augment immunity even if you are not directly affecting the interaction between PD-L1 on the tumor cell and the T cell. This pathway has a role in immune regulation outside of the tumor microenvironment as well. In my opinion, as it stands now, we should not use PD-L1 as a biomarker to restrict access to these medicines, which can provide long-term disease control.

SZNOL: It is going a bit too far to rule out PD-L1 as a biomarker because there is unquestionably an association between PD-L1 expression and response. It is not a perfect predictive biomarker, but it certainly does stratify groups into those with relatively higher response rates and relatively low response rates. If it were so dynamic, there would be no correlation, but in fact there is a fairly strong correlation in several different diseases. I believe PD-L1 to be very useful as a biomarker for PD-1-based therapies, and with combinations, for stratifying groups by probability of response to PD-1 alone. Phase 2 trials should target activity for the combination of different antigens in those two groups. If you treat 100 patients with PD-L1-low tumors, your response rate might be 15 percent. With a combination, you may increase the response rate from 15 to 40 percent. Patients with PD-L1-high tumors may have an expected response rate of 35 to 40 percent, so with a combination, you have to target a higher response rate.

What I'm hoping is we'll have enough information over the next few years to combine patient characteristics and some relatively simple information from the tumor biopsy to make a good guess on the right treatment approach for any individual patient. Because immunotherapy has produced long, durable remissions in a subset of patients, it will change patients' expectations. Now, when someone comes in with cancer, they won't want their doctor to say, "You're going to live four more months, you will have to take this pill, and you will have to deal with side effects during the whole time." Patients want to say, "I'm willing to give you three or four months of my life. I'm willing to accept some side effects, but at the end of those four months, I want my cancer gone, I want my life back, and I don't want to think about this anymore." That's what they want. If we develop therapies that give them that, those are the therapies patients will choose and the doctors will want to give.

KELTNER: Still, in the real world of cancer therapy — outside of clinical trials and academic institutions — reliable tumor biopsies are available in only a minority of cases. The situation suggests a major goal for industry should be developing set combinations with high response rates across most patients and tumor types.

⊕QUESTION: By what criteria will physicians select specific immunotherapy combinations for individual patients or patient groups? Or will regulatory and reimbursement realities dictate the combinations?

KELTNER: The history of drug therapy in cancer is one of development, approval, and sale of single agents, with very recent ventures into approval and sale of agents in combination. For the foreseeable future, approvals of single or dual agents with single labels will continue to determine reimbursement for expensive cancer immunotherapies. If a combination does not get reimbursed, few clinicians will have the luxury of prescribing it on a "personalized" basis, even with good disease/biomarker data to support it.

FONG: Those realities, regulation and reimbursement, will dictate the combinations. Unfortunately, treatments such as anti-CTLA-4 and Provenge are already very expensive. We're really constrained in using these drugs by what is reimbursed, and that unfortunate reality will dictate the usage of these different drugs, especially in combination. More often than not, drugs are approved as single agents and insurers may not be willing to have the doctor prescribe more than one at the same time. But that is where we will need trials that show the combinations actually work. Unless there's a change in the cost and access to these drugs, it's not going to be like chemotherapy where we oncologists can prescribe different drugs and be able to tailor a treatment "on the fly."

I do not see all the different immuno-therapies as being mutually exclusive. If anything, it is great that we're hitting different elements of the immune system. Once we know where the fundamental blocks are and can identify those within a patient, we might figure out in advance,

rather than empirically, which of the combinations would be good for them.

KELTNER: Paying for combination immunotherapies might be less of an issue than paying for drugs with a less substantial therapeutic payoff — that is, if the new therapies have the impact on safety and survival the current data suggests.

WOLCHOK: Whether a drug is approved in a given disease affects whether it is reimbursed. It seems to be less of a problem with the numerous PD-1 pathway-blocking medicines being explored in a wide variety of diseases. We are entering a new era in the tools we will have at our disposal to treat cancer. Immunotherapy is now a standard approach to cancer treatment, and we will see it integrated into treatment programs, not just for one or two diseases, but for a wide variety.

URBA: Regulatory and reimbursement issues always affect how patients are treated. Except in clinical trials, physicians can only use agents that have been approved for clinical use. Current economics now dictates a value assessment for new therapies that was not required before. Value will certainly depend on price, and there will be ways to price oneself out of the market and make combinations financially impossible for individual patients or their insurance/health plans. The big plus for immunotherapy is the durable nature of responses compared to far shorter remissions for patients with solid tumors receiving chemotherapy or targeted therapy. This is the true value — the benefit to the patient — and this is where it should, and I believe will, eventually be judged.

I believe physicians will select on the basis of what is best for their patient and in the future this will be based on characteristics of the tumor and the patient's immune status. In the future there will be an immunoscore for patients at diagnosis that will help their doctor know which immunotherapy or combination will be required. This will assess both the type and extent of immune response in the tumor and the general health of the cancer patient's immune system.

SZNOL: We already pay a great deal of money for treatments that are really suboptimum. We are developing new treatments that may be expensive, but would be returning people to fulltime jobs in three or four months, without continuing their treatments indefinitely until they die. Maybe society will consider that a worthwhile cost.

SHARMA: Insurance companies tend to pay for treatments that are approved

by the FDA, and most physicians tend to prescribe treatments along these same lines. But again, we need to make sure we're not selecting for treatment on a single biomarker such as PD-L1. If a patient has a tumor that is deemed to be PD-L1-negative, this should not exclude patients from treatment and they should still be considered for treatment with anti-PD-1 or anti-PD-L1. I consider it an ethical issue. The response rate is lower if a patient's tumor is PD-L1-negative, but it is not zero. For patients with no other treatment options or for whom there are limited treatment options that may only provide a few weeks to months of life, it's worrisome that these patients would be denied the opportunity to have access to an immunotherapeutic agent with the potential to provide long-term survival.

QUESTION: Will the most effective immunotherapy combinations be specific to traditional cancer indications (NSCLC, HCC, etc.) or tend to have general effectiveness against all or a wide range of cancers?

KELTNER: Although panelists have already hinted at immunotherapy's potential to treat a multitude of cancers, the effects of having highly safe and effective agents (in combination) that were also widely applicable would be unprecedented and profound. At the same time, panelists may have different reasons for, and place different limitations on, those effects.

SHARMA: It will depend on the number of patients who respond in all tumor types. We don't know that number yet. Initially, all the protocols were focused on melanoma, then skin cancers, now lung cancer, but we are now conducting trials with patients in small-cell lung cancer, gastric cancer, pancreatic cancer, triple-negative breast cancer, bladder cancer — all those tumor types on one protocol — and already seeing a few responders in those patients. It will be interesting to see what happens as more and more data comes in from the studies of other tumor types with new clinical trial protocols, where I believe we will see responses as well.

ALLISON: Some tumor types will probably be more responsive than others. You can get the immune system primed, and when you know it's primed, you know exactly when to treat. But I believe eventually we will see immunotherapy used for every kind of cancer.

FONG: Immunotherapy has taught us we can't predict which cancers are going to actually respond. The big surprise was anti-PD1 and anti-PD-L1 antibodies working in lung cancer, because we have seen so many therapies fail in that disease. We need to try immunotherapies in many different cancers just because they may work.

GRETEN: There is no reason to believe that immunotherapy would work in only one disease and not in others. The whole field was surprised to see the data on using checkpoint inhibitors in non-small-cell lung cancer, and there is a lot of debate about why these patients actually show responses, but none of the hypotheses have proven correct. It is the same with targeted therapies; we have no biomarkers, and biomarkers would not only help us select patients that would respond, but also to understand why and how a therapy works or not. In general, even with the best treatment for solid tumors, we never get more than 50 percent of the patients to benefit. That means the majority of the patients do not benefit. One good approach is to understand why we have such good data in non-small-cell lung cancer but not in all the other diseases. What happens to those patients where the drug doesn't show a response?

WOLCHOK: There's a lot of talk about the importance of antigen expression, and a lot of interest focused on the so-called neo-antigens formed from the mutations that arise during carcinogenesis. It is probably not a surprise that the diseases where immunotherapy has shown significant benefit have cancers with an abundance of mutations — melanoma, tobacco-related cancers, now bladder cancer, head and neck cancer — which, because of their association with environmental exposure, have numerous mutations. There now are very important trials going on looking at the activity of immunotherapy in patients who have familial syndromes involving mismatched repair defects and "microsatellite instability" and are over-represented with passenger mutations because of the defects that lead to the cancer.

> "The T cell therapy, like CAR-T, may work, but it is mostly wishful thinking right now. Even if it turns out to be doable, it will be ridiculously expensive."
>
> **ALAN VENOOK, M.D.**
> Professor, Department of Medicine (Hematology/Oncology), UCSF.

QUESTION: Do you see limits on the practice model for cancer immuno-therapies, i.e., will cell-based approaches remain restricted to a small number of patients in intensive care or salvage settings?

KELTNER: Most of our panelists work on the side of "off-the-shelf" immunotherapeutic agents, but they may acknowledge some plausible technological solutions and see a defined role for cell-based therapies.

ALLISON: If you had asked me about cell-based therapies two or three years ago, I would have said they tell us what the immune system can do, yet I doubt they are exploitable. But with the new techniques, such as the chimeric antigen receptor approach and the T cell receptor constructs, they now seem more practical. The new techniques allow physicians to take the patients' own blood and redirect their T cells' specificity, making them more useful. However, although cell-based

therapy looks impressive in leukemia, because leukemia has antigens that are simply not found on other tumor cells, it is not the same with solid cancers. It is possible to do antigen spreading and combine checkpoint blockade with adoptive cell therapy, but I do not believe it will ever be front-line therapy.

SZNOL: I am on a scientific advisory board of one of the companies developing cell-based therapies, and I do believe they will work. There will be ways to do relatively rapid isolation of cells from tumors that are tumor-antigen specific, and relatively simple ways to do rapid expansion and reinfusion. So far, the data suggests if you progress on checkpoint inhibitors, you can still respond to the cell therapies, though they may not become front-line treatments. They could become commercially available as a process where you take a piece of tumor, put it in a bag, ship it overnight, and three weeks later get back a bag of cells to infuse — then someday become a blood-bank procedure.

URBA: Widely applicable, off-the-shelf combinations would be ideal, and there will likely be examples of them for specific disease types and perhaps even shared among a few different types of cancer. However, based on what we are learning of the genetic complexity of tumor cells and the plethora of immunological states within a tumor microenvironment, it looks like there will be significant personalization for some time. Cell-based therapy is one example. In some instances, it appears that once certain principles are understood, anti-CD19 CAR-T (Chimeric Antigen Receptor Therapy) could be more widely available. But picking individual T cell receptors, as is happening in some of the solid tumor work, is not likely to be broadly available any time soon.

FONG: Dendreon has shown you can apply cellular therapies to a broad population. Whether that is a viable or sustainable business model, I defer to the business folks. The model of moving cells to a centralized production facility from apheresis centers, which are widely available, is possible today. But any treatments, such as some adoptive T cell therapies that could cause patients to get significant side effects and end up in the intensive care unit, may not be appropriate in a typical community setting. It would be preferable to have an off-the-shelf therapy, and one of the hopes with the patient-specific therapies is we could learn how they work and potentially transform them into an off-the-shelf type of therapy.

GRETEN: I do not think that these highly individualized therapies, where you have to produce the drug for every single patient, will be something feasible long term. The incidence of leukemia in patients who actually require such treatments is so much lower than patients with solid tumors. It would be a significant challenge for the healthcare system to provide cell-based therapies for solid cancer.

BERINSTEIN: There are pros and cons for both approaches. Clearly, using patient-tumor-specific therapies should be able to provide a level of specificity and memory which may not be possible in all patients using the off-the-shelf therapies. Using patient-derived immune cells that are engineered and reinfused can also be effective (CAR therapy). However, the antigens being targeted must be selected carefully to avoid serious toxicities. Unfortunately, these personalized treatments require higher levels of infrastructure and cost. But the considerable redundancy in immunosuppressive pathways requires off-the-shelf immunomodulators be combined to achieve suitable efficacy, and the most effective combinations will likely need to also incorporate strategies to enrich tumor-specific T cells. We need to identify the appropriate combination of therapies, effective and safe, that will provide a clinical benefit in a majority of patients and eliminate the need to resort to patient-specific approaches.

> "Because immunotherapy has produced long, durable remissions in a subset of patients, it will change patients' expectations."

MARIO SZNOL, M.D.
Professor of Medicine (Medical Oncology); Clinical Research Program Leader, Melanoma Program, Yale Cancer Center

QUESTION: Is it premature for companies to jump in and start developing immunotherapies?

KELTNER: In point of fact, and unlike other fields where the KOLs are exclusively academic, scientists/opinion leaders are leading much of the commercial development in the cancer-immunotherapy sector. On the other hand, skepticism remains in the KOL community.

VENOOK: It's fine for companies to do, but most agents are not ready for Phase 3. Again, I just think they're building expectations excessively. The T cell therapy, like CAR-T, may work, but it is mostly wishful thinking right now. Even if it turns out to be doable, it will be ridiculously expensive. Look at Provenge and ipilimumab — is either one enough of an advance for the cost? I believe they are on the margin.

KELTNER: Is it still too early to do late-stage trials with immunotherapies, single or combination, on the scientific and regulatory fronts? Or do immunotherapies, which may be more effective in earlier-stage disease, defy the old paradigm of conducting new-drug clinical trials only in late-stage patients?

SHARMA: We have always had the paradigm in oncology of starting out with Stage 4 metastatic-disease patients for whom nothing else has worked, and then moving it earlier into a clinical trial setting where patients with earlier-stage disease receive treatment before surgery. I believe we'll see the same paradigm with immunotherapy.

FONG: This is a really important question. As an example, if the FDA continues to mandate survival as an endpoint, it will get increasingly difficult for us to move immunotherapy into early-stage disease — especially in prostate cancer, one of the areas we focus on. If the FDA wants to support faster development of drugs, it will need to change the approvable endpoints in these cases.

ALLISON: Earlier may be better, but it can be too early. All this works by getting the T cells primed, and you have to have tumor-cell death to get the information to the immune cells, so if you have just a tiny tumor mass, that's too early — unless you have a genomically targeted drug that just kills all the tumor cells, or at least enough of them to cause inflammation.

GRETEN: The biggest fear I personally have is that, instead of doing small, very careful studies, companies face too much pressure to immediately start large randomized Phase 3 studies, which in the end may fail. That is always a problem with a new movement in any disease. Obviously, there is huge competition among the companies, small and large, but it may lead to making mistakes that in the end will harm the field.

A lot of the rules that we have in oncology all of a sudden don't apply any more, especially with early drug development. We like to look at progression free survival [PFS], or response rates, but now we may not even see dramatic changes in PFS. We have to come up with new, immune-related response criteria, but at the same time, some patients show really extended overall survival that is not mirrored by an early signal.

Let's say checkpoint inhibitor XY does not work in colon cancer — does that mean it will work if you combine it with something else or give it earlier in the disease progression? We should slow down development and initiation of huge Phase 3 studies until we really understand the mechanisms. If not, what are we going to do with all the negative studies?

Ending this part of this series with a provocative question primes the discussion for the highly interested industry participants in Part Three, "Combination Cancer Immunotherapy — Companies at Stake," coming next month. Meanwhile, please join the discussion on Twitter at #CCIRLSL.

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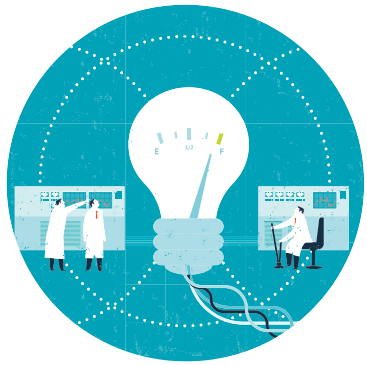
Bayer HealthCare's CoLaborator On Mission (Bay)

LOUIS GARGUILO Executive Editor @Louis_Garguilo

The next suspense novel based on a new or imagined biotechnology breakthrough might consider borrowing its title from Bayer HealthCare's incubator: "The CoLaborator." More likely, pharma companies in the process of discerning ways to interact with life sciences start-ups would do well to study Bayer's innovative model for collaboration.



The model is one of immersion and access. Bayer has thoroughly ensconced itself within the tight-knit and thriving biocluster that is Mission Bay, San Francisco. It also has opened its labs to an unprecedented degree. Bayer's specific candidates for collaboration are early-stage start-ups with exciting technologies that need a hand in hypothesis validation and business plan development. The payoff for Bayer may or may not be an augmentation of their pipeline, but Bayer thinks the benefits will come.

"When we moved our U.S. research presence here to Mission Bay in 2011," says Christopher Haskell, Ph.D., head of U.S. Science Hub, Global External Innovation and Alliances and the CoLaborator, "we were placed right in the middle of a rapidly evolving ecosystem where start-up companies are being created at an amazing rate." Haskell says Bayer recognized the opportunity to be exposed to "an enormous number of interesting ideas, technologies, drug platforms, and concepts for therapeutics."

Bayer joined a nurturing ecosystem throughout northern California that for years has hatched start-ups through support programs from the campuses of the University of California San Francisco (UCSF) and the university's initiatives such as the UCSF Entrepreneurship Program, the original QB3 Garage, and newer QB3 incubators (QB3 is the acronym for California Institute for Quantitative Biosciences), and other academic settings and organizations. How would Bayer fit in?

ENTERING THE ECOSYSTEM: LESSONS IN LOCATION AND COHABITATION

Enter the CoLaborator, Bayer's incubator solution, and a part of the company's overall strategy for reaching outside for internal drug discovery and development enhancement. "What we wanted to do for our part," explains Haskell, "was create methods by which we could stay in early contact with new companies to assist and see how things evolved. It was important to find ways to do shared risk-reward partnerships to help validate their technologies for them, and test within Bayer whether these drug platforms had legs to live up to the initial promise. We were looking for a hands-on way to help the whole community."

Why Bayer moved to Mission Bay has a relatively easy explanation; some of it we've mentioned. How it established itself as a contributing neighbor who at the same time can take advantage of what the region has to offer is worthy of a study on biocluster integration strategy.

First, more on the why. With its merger in 2006, Schering bought Bayer a research group located in Richmond, CA, 20 miles north of San Francisco. It had a nice campus and facilities, but felt geographically isolated. Some at Bayer, including Haskell, sought alternative locations to combine its North American drug discovery operations. Areas considered included Fremont and Alameda, CA, as well as Mission Bay. Haskell takes it from here: "As soon as our head of global drug discovery, Dr. Andreas Busch, toured the region and met with some of its leaders, including Regis Kelly (director, QB3; managing partner, Mission Bay Capital; general partner, QB3 Incubator Partners), he was convinced it made perfect sense to locate us in the middle of this growing innovation center."

This resulted in the consolidation and location in Mission Bay of Bayer Healthcare's U.S. research headquarters,

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now known as the Bayer HealthCare U.S. Innovation Center. About 70 scientists are devoted to research for Bayer — and also to interacting with CoLaborator tenants three floors below them (more on the tenants soon).

How did the proverbial 800-pound gorilla go about establishing itself in the entrepreneurial neighborhood? According to Haskell, Dr. Busch instructed the Bayer group: "Go out and have coffee. Go meet people. Find out what other people are doing. Talk science to them. Take Bayer and immerse us in this innovation culture."

Bayer scientists might not have actually knocked on doors and offered cookies as the new neighbors, but they did quickly set up a Master Research Agreement with UCSF. "We weren't sure what we wanted to do yet, but we knew we wanted to work with UCSF," says Haskell. "We started with an agreement that nailed down the key issues of IP and publication. Under that we are able to write task orders for individual projects, so entrepreneurs can quickly move ideas forward. Today we have a number of ongoing projects." Bayer also entered an agreement directly with QB3, which operates at UC campuses in San Francisco, Santa Cruz, and Berkeley, and serves as a primary point for start-ups.

"Obviously, you don't want to give away IP at this stage, but Bayer has garnered a lot of trust at the CoLaborator."

BRIAN FETH
CEO of Xcell Biosciences

Brian Feth, CEO of Xcell Biosciences, a biotech that got its start in QB3 and became one of the first tenants at the CoLaborator, agrees Bayer has worked well with the other players in the area. "We initially spun out of the Berkeley ecosystem at the QB3 incubator in the East Bay [the other side of San Francisco from Mission Bay]. We met Chris [Haskell], who came to the QB3 network lunches to talk about how start-ups could engage with Bayer. We spoke over the next two months with Chris [Haskell] and Rick Harkins [principal scientist of global external innovation and alliances at Bayer] on ways we might work together scientifically, and about the CoLaborator." Xcell then established a pilot research study with Bayer on pancreatic cancer cells, focused primarily on proving that Xcell's technology can capture and grow pancreatic tumor cells from various patient blood samples. "As we flushed out the ideas for the pilot study with a separate research group within Bayer, we also naturally shifted into the CoLaborator space. This then allowed others to enter the QB3 incubator and is a win for all parties."

THE NUTS AND BOLTS – AND STRATEGY – OF AN INCUBATOR

The CoLaborator opened in September 2012 and occupies most of the first floor of Bayer's U.S. drug discovery headquarters. It comprises 6,000 square feet of lab space, in an open layout, divided among six tenants appropriate to the needs of each company. The facility is full, and Bayer doesn't plan to expand at this time. "We provide a great lab space equipped with expensive equipment it would not make sense to buy for a start-up," says Haskell. He mentions modern hoods, minus-80-degree freezers, liquid nitrogen services, core items such as basic CO2 incubators, centrifuges, water baths, microscopes, and the requisite various facilities support and licenses, including for biohazardous waste pick-up and chemical disposal. Feth of Xcell particularly mentioned utilizing tissue culture hoods and a qPCR (thermocycler for precise temperature control and changes to conduct polymerase chain reactions) as important to his company.

Bayer makes no bones that it brings in companies with technologies within its areas of interest. "We want companies doing things we are extremely excited about," says Haskell, "and where there is at least the potential for working with Bayer. For example, there was an exciting company working in neuroscience that didn't make sense to put in here because we are just not in that area."

Haskell then offers a key insight into Bayer's drug discovery strategy and worldview. "Bayer is always seeking to engage with innovators to stay on the forefront of drug discovery research. Our company is in a good position so we are taking our core skillsets and finding others who can complement them as we move into new therapeutic areas. You may see other pharma companies really flashing internal programs, and then essentially trying to backfill that with external assets. I would say Bayer is not doing that. We also look externally for inspiration and are motivated by the entrepreneurial spirit from the Mission Bay ecosystem to achieve this type of combining of technologies for breakthrough drug innovation with greater patient impacts. There are so many great ideas out there."

Regarding the structure of relationships, Haskell says, "The CoLaborator lease is separate from any other type of partnering agreement. There is no equity or licensing as a part of being a tenant. Although we are interested in the programs at these companies," he continues, "we know it is important to give start-ups independence from Bayer so they can grow without reach-through from our side. Potential partnerships might be farther down the road because they have a certain critical path to solve in their business plan that does not necessarily involve us, and that is fine."

Despite this degree of autonomy Bayer provides tenants, Feth and others we talked to for this article all confirm it is the close interactions and mentoring received from the scientists at Bayer that adds the greatest benefit to the

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"We would have moved forward with the pilot study with Bayer even if we hadn't gone into the CoLaborator," explains Feth. "At the same time, it is hard to quantify the value of seeing Chris and Rick [Harkins] on a regular basis. We were always amazed to find that Rick is completely up to speed on our project on a daily basis."

Haskell says each company at the CoLaborator has unique circumstances. "With three of the companies, we have ongoing projects that cover a variety of different models. With some, we simply lead them in understanding how best to think about applying their technology. Just giving them feedback on what we would find valuable at Bayer often proves beneficial, to both sides. With many companies we help design benchmarks on how their approach is performing compared to everywhere else in the world, and provide feedback on research proposals and business ideas and models. We put them in touch with toxicology or regulatory experts as well as our bench scientists and others."

Feth says, "The partnership aspect is really important. Partnerships suggest early revenues, providing the ability to validate and also bring credibility to a young organization such as ours. The external validation we receive from being in this space is significant."

Regarding this last comment, while some early-stage companies would rather fly under the radar, Feth enjoys basking in the aura of a big-company endorsement such as Bayer's. "Certainly it is part of marketing for us. For example, a VC sees we can form important industry relationships. We are gaining from valuable feedback on our business model and product development before investing a lot of time and money. And you can't be shy about talking to customers and potential competitors, which Bayer can help us with," he says. Then echoing a sentiment also clearly espoused by Haskell when I asked him about reservations entrepreneurs might have opening up to Bayer, Feth comments: "Obviously, you don't want to give away IP at this stage, but Bayer has garnered a lot of trust at the CoLaborator. Mutual trust is a most important factor, if not the most important."

GOOD FOR THE BAY, GOOD FOR BERLIN

Imitation is the best form of flattery. Dr. Stefan Jaroch, head of external innovation technologies, among others at Bayer HealthCare AG's global headquarters in Berlin, Germany, liked the concept so much they established their own CoLaborator.

Thousands of miles away from Mission Bay, Berlin also has gained notice as a burgeoning biotech cluster with excellent research and medical centers, and according to Jaroch, "with a lively start-up company scene." He says, "There is the same entrepreneurial spirit here. A similar, exciting collaborative environment is now being created in Europe with the aim of fostering early innovation. Berlin is not only Bayer's global pharmaceutical headquarters, but is also our largest site for research and development. This allows for expanded opportunities for close interaction between entrepreneurs and an array of Bayer scientists. We believe the CoLaborator fits perfectly into this landscape and community."

I asked Jaroch what has been exciting or even surprising about the CoLaborator and made the efforts at an already busy headquarters campus worthwhile. "The first three tenants have already moved into the CoLaborator premises in Berlin. Calico GmbH is involved in the development of monoclonal antibodies and biomarkers. DexLeChem GmbH engages in research and development in the field of homogeneous chiral catalysis. Provitro AG operates in the fields of tissue microarrays, immuno-histochemical analyses, and cell-culture technology. We were aiming to create something beyond the traditional incubator, and I have been very pleased to see how well the CoLaborator is received in the life sciences start-up scene in Berlin."

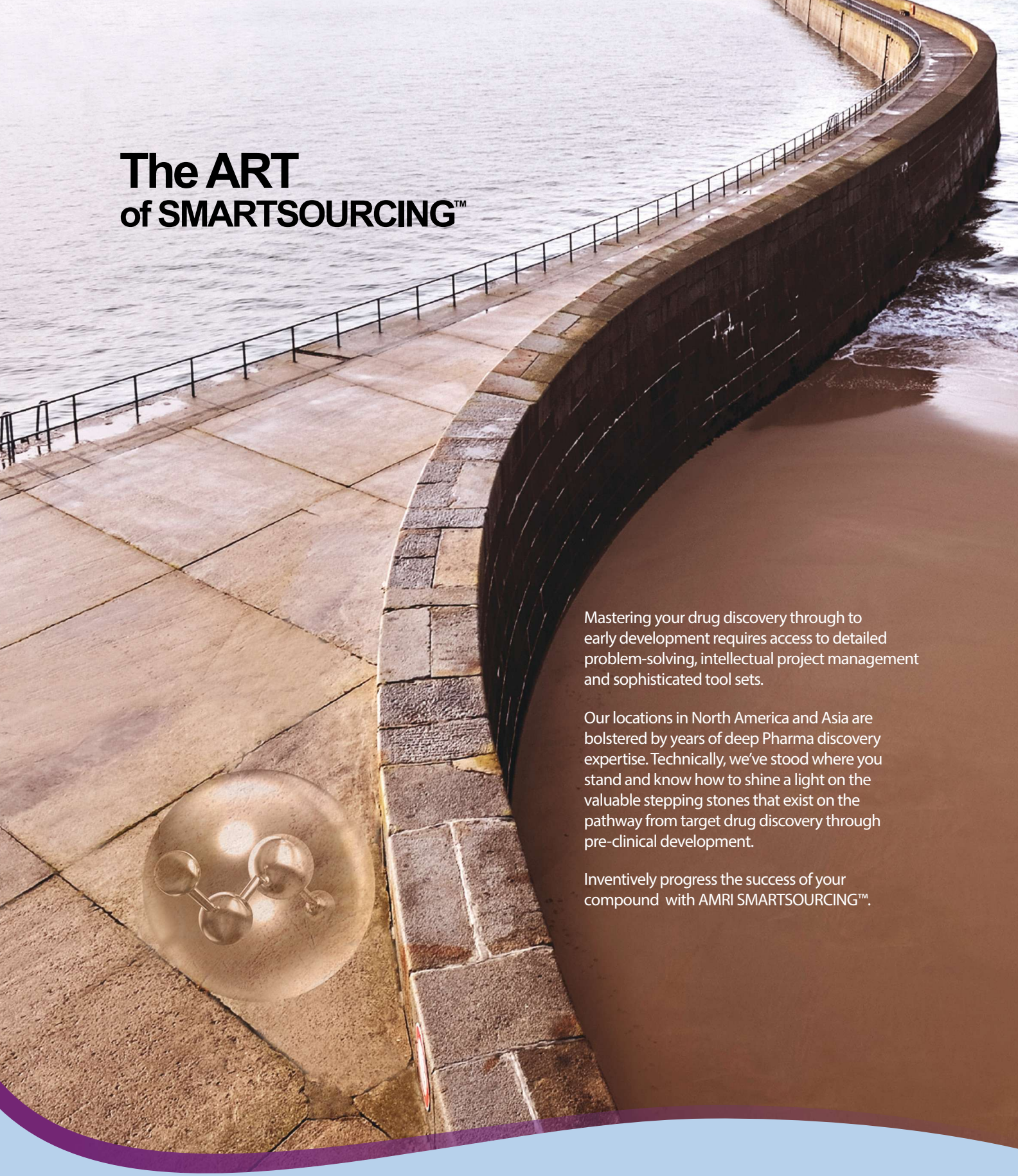
(As a quick aside, and by way of serendipitous corroboration, while recently talking with a former colleague who resides in Berlin and invests in biotechs, he enthusiastically explained to me that he and his scientists had utilized advice and space at the Berlin CoLaborator.)

"Although we are interested in the programs at these companies, we know it is important to give start-ups independence from Bayer."

CHRISTOPHER HASKELL, Ph.D.
Head of U.S. Science Hub, Global External Innovation and Alliances and the CoLaborator

What is different between the two locations is that Bayer moved into its San Francisco neighborhood, while the company has been a long-term presence and community leader in Berlin. This may bring different challenges, but the concept of immersion into the local start-up community and culture, willingness to open labs to provide assistance from its own scientists and facilities, partnering with other stakeholders, and relationships built on both legal agreements but more importantly mutual trust, are all common attributes of the two CoLaborators.

"Our interactions and relationships are really proximity driven," says Haskell. "We don't foresee the CoLaborator strategy as a nationwide model. We feel the unique location and opportunities offered in Mission Bay make this work well for us here. If I want to work with someone in Utah or Colorado or Texas, the CoLaborator model obviously is not the right tool." But innovation does not stop at the water's edge, so to speak. "We are, though, looking at other ways to do that, too," says Haskell.



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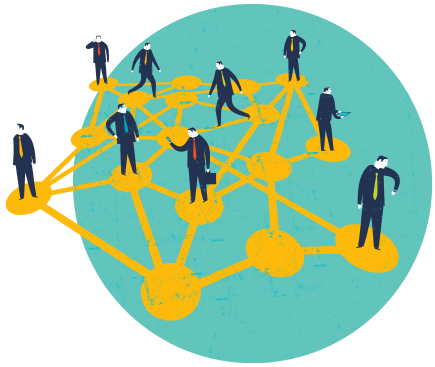
As The Pharma Landscape Changes, So Should Your Partnering Approach

ED MISETA Executive Editor @OutsourcedPharm



The landscape for drug development is constantly changing. A technique or practice that was commonly accepted a few years ago may today be outdated and obsolete. This is true regarding all aspects of your business, including emerging markets, regulatory developments, and certainly partner relationships.

At the 2014 ISPE CMO Executive Workshop, Courtney Billington, VP, Global Janssen Supply Chain at Johnson & Johnson, provided the Big Pharma perspective on these topics, and what needs to change in the relationship between pharma and CMOs.

Billington began his discussion by noting that as pharma companies continue to meet the needs of customers and patients around the globe, and as the industry continues to innovate to address unmet medical needs, the overriding goal is to tackle every disease we have no cure for.

Regulators are working alongside pharma to speed patient access to medicines through accelerated regulatory pathways, but these changes have also created increased complexity and an environment that is fundamentally different from what it was just 10 years ago. "When you think about the supply chain, for example, we were never on the critical path," says Billington. "We would spend 18 months, perhaps years, waiting on regulatory approval. Pre-approval inspections would take place well in advance of when we expected to launch products. Today those things are happening in parallel. Many steps, such as finalizing files and working with CMOs to ensure inspections are ready, are happening at the same time. That environment is dramatically different from what we have seen and experienced in the past."

In addition to the regulatory changes, pharma is also exploring more opportunities in emerging markets, especially locations outside the BRIC (Brazil, Russia, India, and China) countries. One large focus is on central and western Africa, where Billington notes pharma is looking to create new opportunities. Although many of these areas are fertile for growth, getting into these countries will be a challenge. These new areas will also place pharma under the scrutiny of additional (and different) regulatory requirements.

MORE DISCOVERIES OUTSIDE THE WALLS OF PHARMA

As pharma companies look for ways to accelerate the growth of drug pipelines, many are doing more work with external partners. "Pharma companies are always looking to add new medicines to their pipelines, and we know our internal laboratories are not going to be the only new sources of innovation," says Billington. "Some of our new relationships will be with very small biopharmaceutical companies. They may have started their initial discovery and development efforts with CMOs, but will then partner with, or be acquired by, a pharma company looking to forge new pipeline relationships."

These new relationships, along with other consolidation activities taking place in the industry, add to the complexity of the current environment. Today it is not unusual to see two companies that once had been competitors now working together.

Data shows approximately 30 percent of global manufacturing is currently done internally, with the other 70 percent coming through CMOs. Clearly, discovery and development could not be done without these partnering relationships, and much of it is done to gain access to new markets.

Billington realizes this changing environment will force pharma to change as well. "This constantly evolving landscape means pharma will need to partner in a very different way. There is still a place in this industry for transactional relationships, but more and more we really find ourselves having to look for true strategic partners. When you have CMOs producing 70 percent of your portfolio, you cannot handle those companies in a transactional manner. Companies need to have strong programs and processes in place to make sure those relationships continue to work and grow. There needs

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to be strong linkages in place between the organizations, and the needs of both organizations must be met. When working with regulators, it is important for both the sponsor and the CMO to come across as one unit on a unified front, not as factions of different companies."

This approach will entail finding different ways to work together. Billington believes one of the first steps is ensuring there is a balanced relationship in place, not one that is skewed in one direction or another. In the past, both sides have verbally stressed the need for a win/win relationship, while at the same time doing everything they could to get a larger slice of the pie. This only can be achieved by each side providing greater transparency to the other.

EXPECTATIONS FOR CMOs ARE RIDING HIGH

Sponsors looking to establish more strategic partnering agreements will go in with high expectations for their CMOs. Increased transparency, sustainability, and systems integration are issues that will need to be further resolved.

Traditionally, the negotiation process revolved around three factors: quality, scheduling, and cost. While all of these factors are still important, Billington believes the industry needs to transition away from that mentality and begin to better manage and deal with the complexities of partnering arrangements. This is the best way for firms to provide true transparency in offerings, which will ultimately transition into the marketplace. Regulators want to see pharma managing supply chains in a way that shows it is looking at the complete offering, and not just at various pieces of the supply chain. Strategic partnerships are a definite move in that direction, but that will happen only when there is increased transparency between partners.

Sustainability is another area that will be around for the long term. Billington believes everyone in the life sciences agrees we have a responsibility to protect the environment in which we live and work, and this topic is one that will continue to grow in importance. He notes good green chemistry should be a goal of both pharma and CMOs, and that more and more customers, especially downstream, are demanding it. Not only that, they are asking for statistics or some other proof that efforts are being made.

"Lastly, as part of our need to come together seamlessly as one complete entity, we need to do a better job of linking our systems together," he adds. "With the technology available today, there are a lot of things that can help us to do that. We need better signals to help us in forecasting demand, and we need to share capabilities better than we have in the past."

Ten years ago, Billington notes 10 percent of innovation was coming from outside the company. Today that figure is closer to 50 percent. The dynamics are changing quickly, and will require companies to change quickly as well. "We have to respond faster and better to these dynamics," says Billington. "The future of this industry will no longer be about who has the biggest pocketbook or who has the most people. It will be about who can best manage that myriad of strategic and transactional partners."

CHANGE THE MINDSET AND CLEARLY DEFINE ROLES

In order to succeed in the future and continue to meet customer expectations with affordable and high-quality medicines, pharma and CMOs will need to move beyond the competing mindset that has existed in the past. Billington used to be in charge of manufacturing for many years. During that time he would often see peers in the contract manufacturing group openly competing with his plants, and vice-versa.

"My plants were constantly trying to figure out how to do things we did not have the competency to do in-house," he states. "In many cases it would have been much easier to simply give that project away to a CMO who had better knowledge and capabilities in that area. We need to move away from that competing mindset and identify the strengths and weaknesses of both sides, and design a strategy around how to best maximize the benefits of both."

Expectations of roles and responsibilities also have to be made very clear, especially when it comes to quality agreements and supply agreements. Billington believes pharma needs to be more mindful of the fact that a CMO might be working with 50 other companies, and they all want things done their own way. "We need to be very clear about our expectations," he says. "But we also need to be more open to accepting their processes and expertise. The best way to do that is to have processes in place to enable discussions between both parties and properly communicate the ultimate outcomes that we want to have occur. Whether it's in-person meetings, teleconferences, or phone discussions, communication is the best way to keep everyone engaged and on the same page."

One important aspect of this process is making sure both sides are clear as to the status of the relationship. Making certain CMO relationships more long-term is a goal of many sponsors, but transactional relationships still have their place as well. The key is to make sure each side is clear and transparent on how it views the relationship.

Billington was recently sitting in a room with representatives of a CMO helping to bring a new product through the pipeline. J&J had not worked extensively with the company. "Suddenly, they are talking strategic partnership and strategic this and strategic that," states Billington. "I finally said, look, we are not really there yet. You haven't done much for us other than a little development work. I don't want you to misconstrue this relationship. We have three levels for our suppliers, ranging from a purely transactional relationship up to what we refer to as a strategic partner. Many suppliers still need to get through those first two levels before we get to what we refer to as a true strategic relationship."

Since it is easy for misunderstandings such as this to occur, being clear and straightforward from the start can avoid confusion and resentment later on in the process. In the end, it is proper management of these relationships that will enable pharma to take care of the most important stakeholder in the process: the patient.

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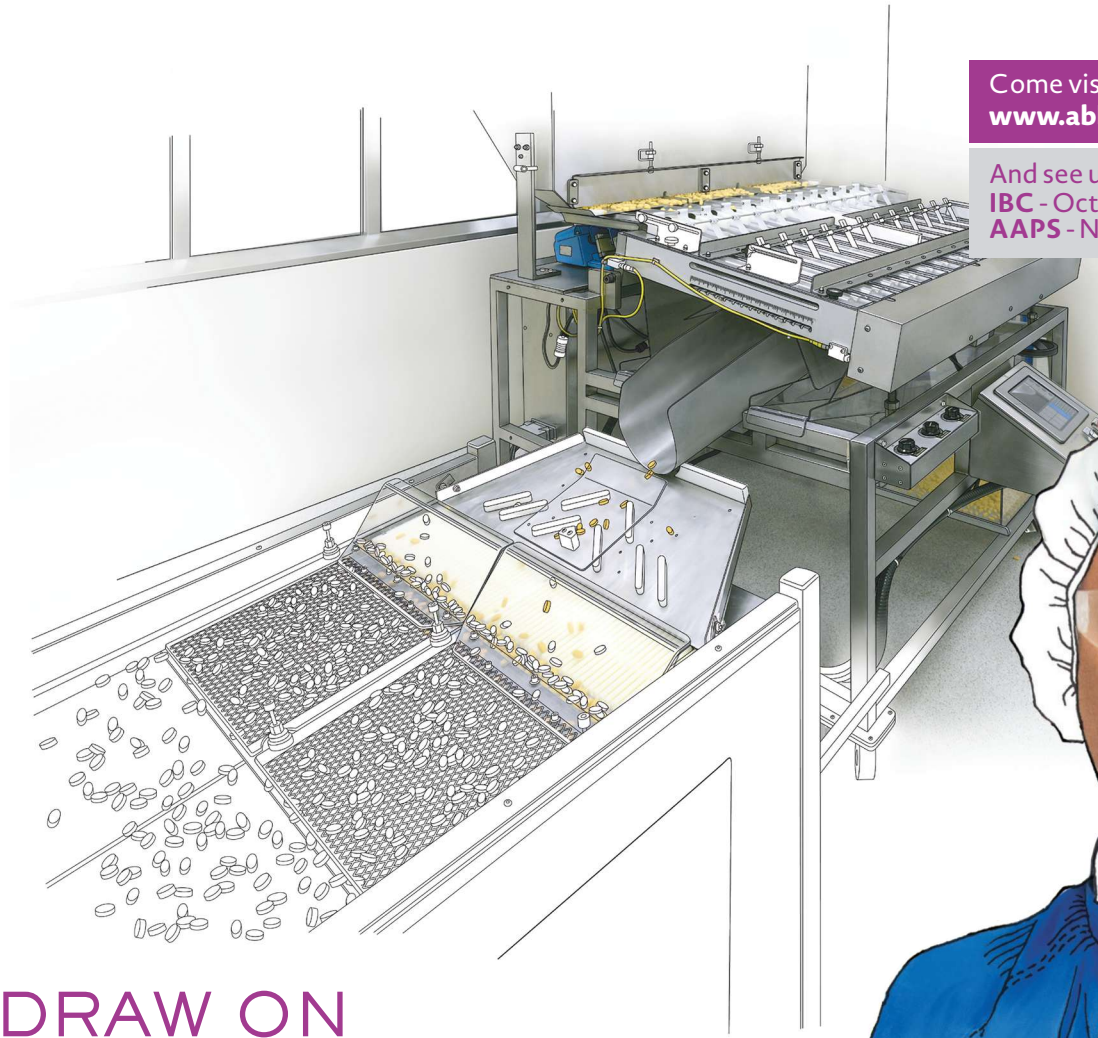

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From Outsourcing To Partnersourcing: Pfizer Puts CMOs To The Test

ED MISETA Executive Editor @OutsourcedPharm

If you have a molecule in production and are ready to outsource it, how do you know which CMO will be best qualified to handle it? How can you definitively know the strengths and weaknesses of a handful of CMOs under consideration? And more importantly, how can you tell which CMO will most closely align with your own organization's culture and principles?

Site visits, audits, and RFPs will provide you with some of the information you require (cost, for example), but may still not tell you everything you need to know. Is one CMO better than another when it comes to large versus small batches? What about quality and timeliness? What is their track record when it comes to reliability? Unfortunately, if a sponsor has different teams performing the reviews, that could also inject variability into the process.

When Pfizer decided to move from a functional outsourcing model to a partnering model, company executives realized they needed a way to evaluate the culture and capabilities of a list of CMOs. To accomplish this, Pfizer undertook a multimillion dollar exercise that included sending one monoclonal antibody project to different vendors. The case study was co-presented by Pfizer and Cook Pharmica in a session titled *Moving from Outsourcing to Partnersourcing* at the 2014 Biopharmaceutical Development & Production conference in San Diego.

ALIGN YOUR PRIORITIES AND PRINCIPLES

At Pfizer, there are six guiding principles that have been adopted internally to guide the everyday behavior of all company employees. In selecting the CMOs to participate in the study, Pfizer set out to identify firms exhibiting these same principles. Pfizer keeps these principles in mind when evaluating a CMO, and each one carries a different rating.

"The first principle, which is always at the top of our list, is quality," says Dr. Sonia Kansal, senior manager of biotherapeutics and vaccines outsourcing at Pfizer. "If quality is the key component for everything that we do, we obviously attempted to make sure the CMOs we selected had a solid history of quality. In evaluating this tenet, it helped if the CMO had been inspected by the FDA and had a positive regulatory outcome. However, we did not make that a requirement. This is an area where we had to give companies a little leeway. Regulatory inspections can be an issue for some firms, since they may want to get audited but can't because they don't manufacture a commercial product."

Confidentiality is the second principle, and Pfizer prefers to work with CMOs that view it with equal importance. Discussing the company's projects with another client would be considered a severe breach of trust. Kansal notes the possibility of leaked information is a risk companies take on every time they outsource a project. While it's difficult to measure how confidential a CMO might be, there are ways of determining how willing a potential partner might be to share information. "If we visit a CMO and they start discussing an early-phase product they are manufacturing for another client, that would send up an immediate red flag," she says. "Having a regulatory strategy in place is also a plus for us."

Spending the company's money in a cost-effective manner is another important principle, although Kansal is quick to note that in the pre-commercial space, this factor is not as critical as the others. The company simply wants to make sure it is being charged a fair price for the work performed. Pfizer will often request a quote from several companies and receive figures that are two or three times higher than what other companies are asking. For that reason alone it always needs to be a consideration when choosing a CMO.

Perhaps the only principle that rivals quality in terms of importance is timeliness. The old adage "time is money" holds true in pharma, so minimizing the time to proof of concept as much as possible is

critical. This will also lead to Pfizer being able to maximize the number of proof of concepts being completed per year.

Flexibility and adaptability are the two final factors to look for, and Kansal tends to group the two together. She notes many things can change after the start of a project with a CMO, especially planned timelines. She views flexibility as the ability of the CMO to respond to scheduling changes imposed by the sponsor, as well as having the resources and technology platforms in place to meet Pfizer's needs. Adaptability is the CMO's ability to meet shifting environment and project needs.

"There is one additional principle that is also important to us, and that is location," she says. "We would prefer to not work with too many CMOs that are located where it would take us a full day (or more) to get there. We also tend to shy away from a CMO that had five different locations, for example, that we need to work with. Even if each location has the same quality system in place, a different culture often exists in each location, which can make for a more difficult partnership. We have all heard stories of companies with a top-notch quality system that will get an FDA warning letter for a subsidiary in a different location."

WHICH MODEL IS MOST APPROPRIATE?

When outsourcing to CMOs, Kansal believes there are two basic models, each with its own pros and cons. There is the functional model where various functions are outsourced to companies with a specialty in certain areas, such as analytical, drug substance, or drug product. When using this approach Pfizer seeks CMOs with a good history of working with a specific drug substance. With this type of relationship, sponsors are able to take advantage of the specialization that each CMO can bring to the table. "You can get quotes from 10 different vendors and see if one of them is offering a lower price, better or additional services, or more timely delivery. There is also a good amount of flexibility there to leverage the relationship in ways that will most benefit the sponsor."

The biggest negative to this type of relationship is it can create a longer and more complex supply chain. If using three different CMOs, a sponsor will have to manage three different vendors, have three times the travel time, three times the qualification effort, etc. This also will add time to the entire life cycle and delay the important proof of concept.

Alternatively, when utilizing a single vendor location, that vendor will provide all necessary services. In this case the pros

are a strategic partnership where a company is working with just one quality system, one executive leadership team, and one set of project managers. "This model allows a firm to gain cost and time efficiencies, which will get product to clinics much faster. "The downside for the company is placing a lot of risk in the hands of a single provider," warns Kansal.

The study performed by Pfizer was intended to determine whether this type of strategic partnership could actually work. All the vendors selected were not single-location companies, and in some cases, there were different companies within the same location.

To make sure Pfizer was always comparing apples to apples, key project attributes were put in place. First, each CMO under evaluation had to have a global presence. To minimize variability in the evaluation process, the same technical team was used to evaluate all of the vendors, albeit with different project managers. Extensive milestone tracking systems were used internally to keep a close eye on what was occurring. Kansal notes not all of the tracking information was shared with each vendor.

"We also made sure we were able to have a separate budget set up for each CMO participating in this experiment," says Kansal. "We wanted to determine the true cost of outsourcing for each of the CMOs involved. You can only do that if there is a way to keep the budgets completely separate." Kansal notes travel costs were also included, since they can add up quickly if a vendor is located 6,000 miles away.

IMPORTANT LESSONS LEARNED

There were numerous lessons Pfizer learned from conducting this exercise in CMO "speed dating." The company wanted to ensure subject-matter experts were engaged with each other from the very start. This involved literally taking a bus load of experts to the CMO site for the initial technical evaluation. "This was an incredibly critical step," says Kansal. "We had our subject-matter experts talking to each other, forming close relationships from the very beginning. That led to better partnering and communication throughout the entire project. When it came time to form sub teams, the team members already knew each other and were able to immediately start discussing the project specifics."

Also closely related to the communications effort were numerous meetings with each CMO to keep everything on track. Meetings were held weekly, but even more often when necessary. Kansal says Pfizer personnel traveled to the CMO locations as much as possible, noting in these partnering relationships that nothing beats the value gained from face-to-face meetings.

Perhaps one of the biggest lessons learned was the importance of trust in partnersourcing. Kansal believes this is one facet of the relationship that cannot be compromised. "You don't meet people and immediately trust them," she says. "True trust can only be built over time, and this effort enabled us to work with all five companies for an extended period."

A final lesson learned was the importance of project responsibility. While ultimate responsibility for a project lies with the sponsor, Kansal noticed some CMOs seemed to take a lot of pride in co-owning the project. "They didn't have to, but we saw it as making the effort to go above and beyond," she says. "Some simply saw it as their own project. That is always nice for the sponsor. We saw that as a sure-fire way for a CMO to build our trust, and that is also how you build a strategic partnership that will help in all future relationships."

Pfizer certainly gained a lot of vendor insight as well. Each CMO had expertise in different areas. Some were stronger upstream and others downstream. In the future, when faced with an actual project, the company will know where to turn for needed capabilities. L

Collaborative Approach Helps CMO Meet Project Goals

When delivery dates are a concern, developing a process from scratch can be tricky, since timelines can add pressure to make quick decisions that may not serve the best long-term interests of the project. For this exercise, Cook Pharmica was asked to develop a process and platform approach that would yield the best end result: a well-defined process that could be used to support a broad pipeline of projects. "Generally, when a large pharmaceutical company comes to you with a proposal, they will dictate the terms of the project and how to develop the process," says Frank Marchesani, business development executive at Cook and a co-presenter (along with Pfizer) of the *Moving from Outsourcing to Partnersourcing* session at the 2014 Biopharmaceutical Development & Production conference. "In this case, we were able to develop the process from the ground up, presenting us with the chance to impress the client with our capabilities."

Unlike the standard practice of outsourcing a molecule, where there is a strict emphasis on keeping costs down and timelines tight, the partnersourcing model enabled a more collective effort between Pfizer and Cook. "For us, the partnering model is consistent with the collaborative culture and approach we take with all our clients and their projects," adds Marchesani. The development of close working relationships between subject-matter experts from both organizations, ensuring better understanding and alignment, was just one of several benefits of the model. As the project progressed, it became clear that not only was there a good cultural fit between the two teams, but the collaborative nature of the project enabled Pfizer to leverage some of the development expertise at Cook Pharmica to improve the process.

Ultimately, Cook was able to deliver on the challenge and provide a quality product that met all the project requirements. Equally important, both parties learned from each other, developing a relationship of trust to apply to future opportunities, and proving that the partnersourcing approach works.

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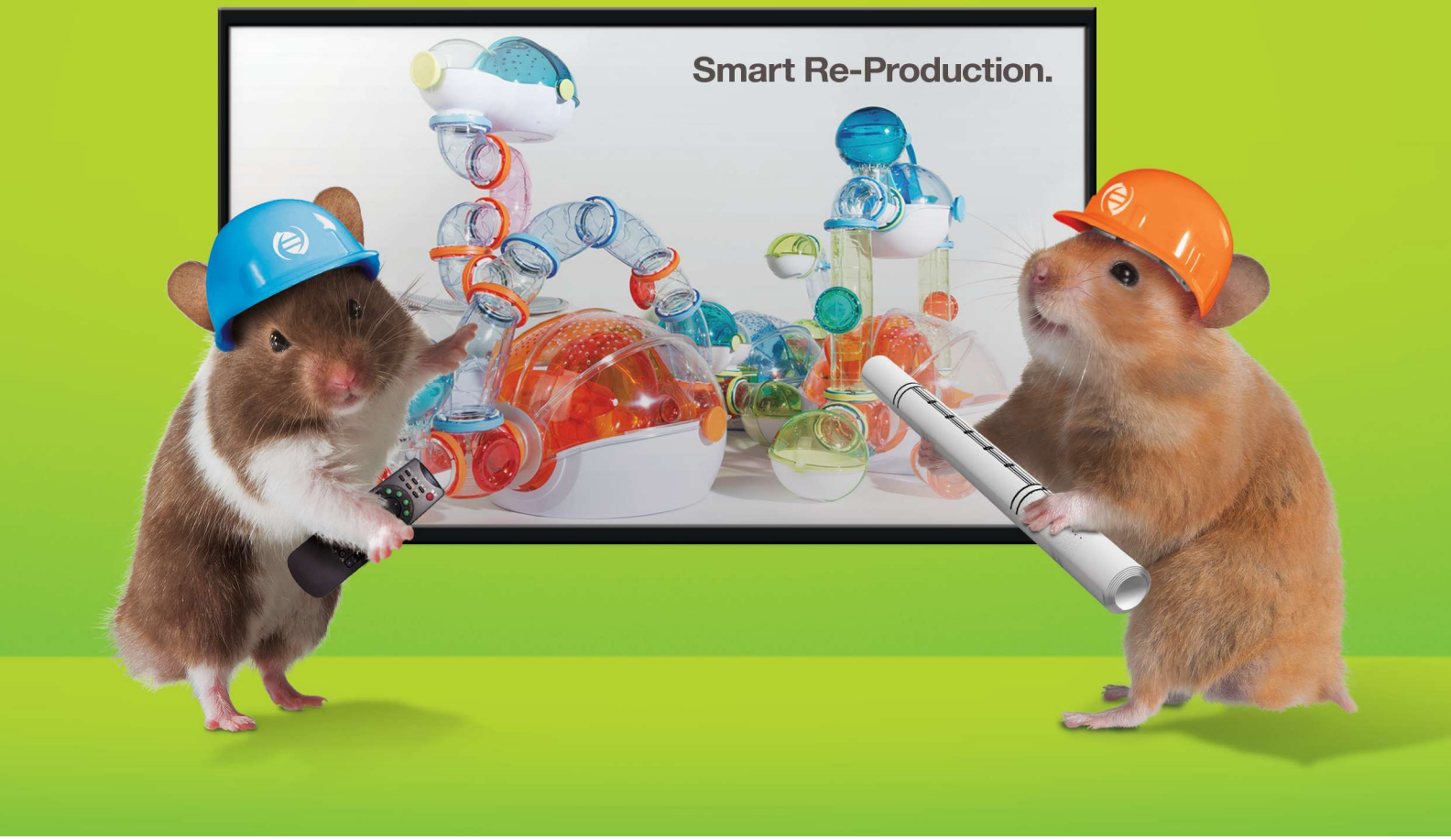

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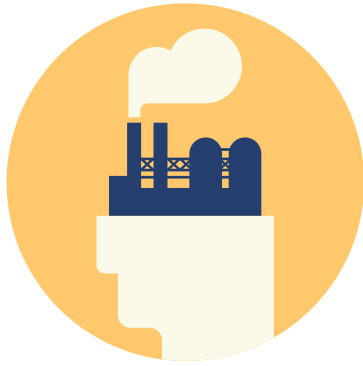
Aging Facilities:
Retrofit Or Build New?

GAIL DUTTON Contributing Editor @GailLDutton



When BD Rx introduced prefilled syringes to flush IV lines in 2005, it converted an existing facility to produce these integrated devices. Later, when the prefilled format was extended to four generic injectable drugs, BD designed a new manufacturing facility to meet the more stringent manufacturing and regulatory concerns.

The new facility integrated everything from drug formulation through manufacturing into a single plant. "Although vertical integration enabled us to do things never before done with sterile products, it also brought new challenges," says Mark Sebree, president, BD Rx.

While the specifics of the plant and processes are proprietary, Sebree explained that about half of the products must be sterilized with pressure and heat, and the others manufactured aseptically. The ability to move the products in a no-touch environment required the company to build handling processes that had never been seen before. Automating the plant so thoroughly that the syringes are handled without any human contact helps BD meet increasingly stringent regulatory requirements and also improves efficiency.

Sebree says similar efficiency would have been unlikely in a retrofitted environment. "The problem with retrofitting an existing building is the point of contact between the old and new environments," he says. Retrofitting to meet current air handling requirements is an obvious issue, but temperature and humidity control also can be challenging in older buildings or in facilities designed for other uses, he says. "Temperature and humidity are hard to control to today's standards in a building that's 30 to 50 years old."

Specific challenges vary according to the type of pharmaceutical product being made. "For sterile products, err on the side of building new facilities to avoid the point-of-contact issues," Sebree advises. "But, if you're making solid dosages, you wouldn't have the same need."

AGING FACILITIES CONTRIBUTE TO DRUG SHORTAGES

According to Maik Jornitz, co-chair of the PDA Aging Facilities Task Force, "Most of the facilities are product-dedicated. Therefore, the age of manufacturing facilities probably correlates closely with the age of the pharmaceuticals being produced."

In fact, many of the recent drug shortages are caused by quality issues in manufacturing facilities rather than shortages in APIs. Sebree says, "As drug shortages grow, alternative ways of manufacturing must be applied, and the FDA must work with manufacturers more closely on infrastructure."

The drug shortage is one of the reasons the PDA formed the Task Force on Aging Facilities. U.S. regulators and lawmakers recognize the correlation between aging facilities and the drug shortage, and Jornitz says this isn't just a North American phenomenon; it's a global issue.

"Aging facilities may run perfectly with trained staff and the right processes and systems in place when staff really understands the processes and owns them," Jornitz says. "However, these staffers also are aging. As they retire, companies lose their expertise. Then, facilities experience more outliers and citations, and processes no longer run as they should."

To put this in perspective, many pharmaceutical manufacturing facilities have expanded several times during multiple decades, cobbling on additional space for new processes. Eventually, once-streamlined workflows become convoluted and inefficient for materials management as well as human processes.

REGULATION STYMIES INNOVATION

The inability of companies to improve product lines without revalidation poses an additional barrier. Kevin O'Laughlin, a principal of KPMG's Advisory Practice, says that after scale-up, regulations virtually lock a company into a process and into a facility. "It's very costly to change manufacturing processes because you have to reopen the NDA (new drug application) and revalidate systems, which allows the FDA to challenge the formulation and other aspects of the drug." Therefore, companies carefully evaluate which NDAs may be reopened when considering the pros and cons of modernizing or moving production lines or entire manufacturing facilities.

Political considerations may impact these decisions, too. "Especially in Europe, national health services may link registration in a national market to maintaining a production facility in

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that country. That's often a reason aging plants remain in a company's network," O'Laughlin says.

TASK FORCE ADDRESSES ISSUES

The PDA task force aims to be a platform for regulators, industry, and vendors to create solutions for aging facilities. "Technology has outpaced the regulations," Jornitz says. "The life sciences industry needs to be able to optimize processes using state-of-the-art technology." Doing so requires reducing the regulatory burden to make optimization economically feasible.

Part of that process involves encouraging regulators to examine their own requirements with an eye to outcomes rather than processes or technologies. The goal would be to develop outcomes-based strategies to meet regulatory requirements and allow new technologies to be added.

Additionally, Jornitz says, "Regulators must ask themselves why such levels of scrutiny are needed when companies are motivated to improve their processes. Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, agrees we need a better way to allow industry to improve processes." The ability to apply more effective technology to drug development is one of the reasons the generics industry is so successful. In addition to getting drugs off patent, newer technology helps companies further lower their prices, Jornitz maintains.

Bipartisan discussions are under way with Congress to support the rapid development of the life sciences industry in the U.S., but more education and discussion is needed as regulators rethink current regulations.

In addition to Congress, the PDA task force itself is looking at regulations and technologies. The subgroup for analytics, for example, is assessing new quality-control technology, including sensors, sample analysis, and assay validation. The facilities subgroup is addressing infrastructure, focusing on utilities and cleanroom standards. Air changing systems also are being evaluated in terms of reducing particulate load rather than rate of air change.

RETROFITS REQUIRE GUTS

As pharmaceutical manufacturers look outside the suburbs to locations within cities, "Old spaces with high ceilings are perfect for retrofits," says Carol Patterson, senior partner at Zetlin & DeChiara LLP, a law firm that specializes in construction law. There are many examples of small molecule manufacturers gutting and using existing manufacturing facilities.

"These are ideal assets," Jornitz says, "because they already have much of the infrastructure — power, utilities, chillers, water purification, compressed air, etc." However, "You can't convert from one to the other." Cleanrooms, for example, have issues with drywall, epoxy coatings, mold, and cleaning regimens. Instead, companies must take a smart approach and be able to gut the building to its shell and add a new cleanroom structure. "It can't be a gradual changeover because small molecule manufacturers usually can't use the same equipment as large molecule manufacturers."

Challenges extend beyond equipment to include process flow and, potentially, decontamination. New, high-efficiency biotech process designs may not fit architecture designed for a different process flow. "Plants were mothballed because they were designed for specific products," Jornitz points out. So the costs of gutting, cleaning, and retrofitting often don't make economic sense.

From a product flow standpoint, single use technology can overcome those challenges. "There's increasing interest in modular components, which are making projects more efficient and opening spaces that otherwise wouldn't be considered workable," Patterson says.

But, Jornitz adds that single-use systems require a different mindset than steel systems. "They are also a bit more risky," and can be less productive. For example, recent research reports the cytotoxic compound bisphosphate leaches from some single-use bags, reducing cell growth. Steel systems don't have this challenge.

Another alternative, Jornitz says, is to install drop-in, premanufactured cleanroom pods inside an existing building. With this method, bioprocesses can be up and running in about 12 months, compared to the two to four years required to permit and build a traditional building.

GREENFIELDS AND COLLABORATION

In mature markets like the U.S., Canada, and EU, building new is somewhat unusual for pharmaceutical firms, but less so for biotech. "Biotechs are managed differently from pharma, and they have different systems and processes," O'Laughlin points out, so there's little incentive for those companies to retrofit existing manufacturing facilities. Instead, they tend to build from the ground up.

O'Laughlin says a quick look at KPMG data shows a 100,000-square-foot biologics plant may cost $80 to $120 million. "Biologics plants are much more complex and expensive to build and outfit. It is not unusual for plants to cost $150 million to $500 million, depending on size and the complexity of the production process." A typical cost to build the same size secondary packaging facility for traditional pharmaceuticals ranges between $35 million and $65 million, excluding the cost of the land, "although I'm certain there are new plants outside this range," he says.

For new builds, Patterson strongly recommends taking a collaborative design approach as a smart way to save money and increase overall project efficiency. "In an integrated development approach, the contractor is part of the design team from day one. The advantage is that construction difficulties can be resolved early at the most cost-effective phase."

The environment that has suppressed technological innovation in existing product manufacturing lines is finally being challenged.Regulators and industry leaders are rethinking processes to enable life sciences companies to integrate state-of-the-art technologies into existing processes. The result will provide companies with reasons to look more broadly at their own infrastructure as they determine the relative merits of retrofitting or building new manufacturing facilities. L


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GEORGE BRUNNER

The following is part two of a three-part series depicting the personal journey of a fictional CEO as he develops a strategy, using the data his company generates and consumes, to shorten his drug development timeline and predict and prevent problems before they occur.

As you may recall from last month, Cabot Harrington, CEO of a midsize pharmaceutical company called Helioarc, decided to leverage his data more effectively. This month, Harrington went to visit some of his pharma colleagues to see specific examples of how data analytics were being used.

His first visit was to a pharma company similar in size to Helioarc; he heard about their efforts to develop a modern data repository. This pharmaceutical firm began a project in 2012 with the goal of uncovering ways to design better clinical studies and learn from the past, get earlier results in the hands of principal investigators, and access data more efficiently.

VIEW STUDIES ACROSS CROs

Their new data repository allowed them to view discovery and clinical studies across all their CROs, in addition to their own organization. When data streams in from external CROs, it is often incompatible. "Rarely," said the CTO, "do CROs have the same applications as we do, and many are unaccustomed to delivering data in the form required by us."

VIEW STUDIES FROM THE PAST

Another focus of the project was to improve the pharma company's efficiency on clinical studies by giving them access to the rich historical, often forgotten, data from older studies. Companies are missing opportunities; if you have the ability to re-execute studies, searching by compound or compound type, to find connections between studies, it can result in fresh insights.

His colleagues spoke about a scenario (part of a study done a few years ago) where extensive information existed on how one particular molecule had reacted and performed. That data ended up as invaluable to a researcher considering the molecule for another application, so he did not need to begin from scratch.

They showed Harrington the solution that had been architected, which allowed cross-study analysis of subjects, compounds, and compared results of older study results with current study goals. It was very visual and easy to navigate.

CHALLENGES OF DATA INTEGRATION

But getting to the current state wasn't so easy. Harrington learned that the first few months of this data analytics project had been difficult. To set up the new data repository, data from four different systems — toxicology, hematology, pathology, and electronic lab notebooks — had to be accessed. The employees involved rarely shared systems and were now being asked to submit their data — current and future — to a central data repository.

Harrington's colleagues emphasized the importance of talking to every member of the team and including them in developing the data analytics project goals. One SVP said that he knew it would finally be OK when he emphasized to the teams that one of the key goals of the project was that their work would "never be lost." The concept of hard work being kept alive for future possibilities definitely resonated with his teams.

LEGACY SYSTEM PROVIDERS: NEUTRAL ENOUGH?

The pharmaceutical company executives also told Harrington the value of hiring an objective data analytics partner to help envision, and then implement, the new system. Legacy service providers, even those who claim an expertise in life sciences,

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KEEP EXPLORING

"If a study is exceeding expectations, that is critical information to have at the earliest stage possible, given today's landscape of accelerated approval status, fast track, etc."

may not have the ability to neutrally evaluate the options, simply because they are tied to their own system solution.

REAL-TIME ACCESS ON CLINICAL STUDIES

Another key part of the project was to gain real-time access to ongoing clinical studies. Why wait until a study is complete or, indeed, wait for even interim reports if data can be accessed in real time, and potentially indicate early positive or negative outcomes? If a study is exceeding expectations, that is critical information to have at the earliest stage possible, given today's landscape of accelerated approval status, fast track, etc.

PUSH, NOT PULL

One other important goal for the study was to implement "push" technology. Data interactions between a pharma company and its CRO should be designed so that the pharma teams no longer have to "pull" the data from the CRO or wait for written reports. Data should be "pushed" from the CRO directly into the hands of the clinical research team, in real time, ready for viewing at any time.

It was clear that, after a year of effort, the company was able to analyze and achieve actionable insights from this information.

- Scientists designing new studies now have the ability to review information from older studies for possible re-use of data or insights and potentially predict future success more accurately.
- Access to study results is accessible in real time; there is no longer a need to wait until after the study is completed.
- There is a single repository for standardized study data and integration for faster insight.
- Data quality and availability has improved significantly.
- Data is more easily and consistently integrated across multiple CROs.
- The speed and quality of data received from CROs was improved.

Over the next few weeks, Harrington visited and spoke to other colleagues in the industry to find out more about how he should structure his Big Data initiative.

COMPLIANCE DATA: DIFFERENT DATA, SAME SOLUTION

One compliance-related story resonated strongly, because it solved one of Helioarc's biggest problems — wasting time locating information for regulatory agencies such as the FDA, EPA, and USDA.

Harrington's colleague shared that his experience had been initiated when a chemical spill incident focused (negative) attention on the fact that his organization could not "put its hands on the information required" to quickly assess the spill situation. From this, the company began to review all compliance-driven inventories, data flows, controls, and processes. The company ended up focusing on cross-site chemical inventory, because it had seen just how risky not having full visibility to this information could be.

The solution suggested by its IT partner, a data analytics company hired after the chemical spill, was to develop an integrated data repository designed for maximum analytical performance. As the CIO explained, that data repository gave employees/users one access point and much greater accuracy when

looking to identify a potential solution for a compliance-driven problem.

Various data sources fed into the chemicals inventory, including vendor data, chemical ordering databases, bidding documents, accounting and financial info, laboratory chemical process records, and R&D request forms. Harrington was beginning to realize that data could be viewed as an asset, and that data repositories were the new "online banking" for those assets.

The IT partner helped scrub the data, which was a time-consuming process, but achieving clean and concise data is critical. It meant interaction with each of the data "owners" over many months, including the procurement department, clinical discovery staff, and principal investigative staff, to clearly map the current process for all data tied to the chemicals' life cycle.

Compliance has improved in the chemical tracking. With a new single data repository, plus processes in place to input more accurate data, reporting and analysis have been simplified and compliance procedures improved. And there is now a "single version of truth" regarding the chemicals inventory data. L

For over 25 years George Brunner, CTO at Acumen Analytics, has been lending his vision and leadership driving technological innovation in pharmaceutical, biotechnology, medical devices, and other life sciences sectors.

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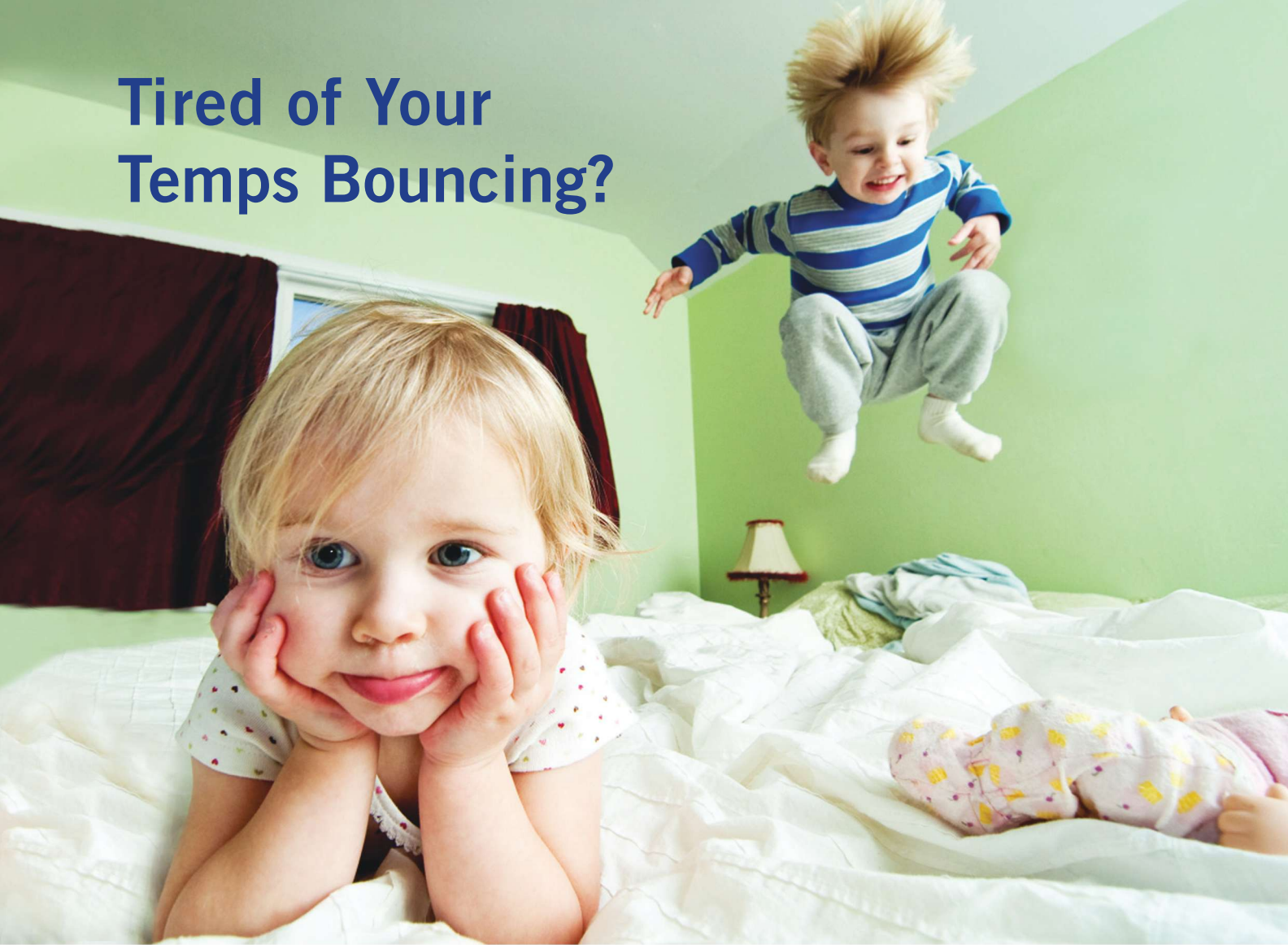

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What Industry Trends In Biotherapeutic Manufacturing Tell Us About The Next 10 Years

TRISHA GLADD Executive Editor @pharmaonline

When considering the topic he would present at the 11th Annual BioProcess International Conference & Exhibition, Ralph Lambalot, VP of biologics development at AbbVie, thought this year's event would be a good milestone to look back at how far the industry has come in the past 10 years and what we can infer from the decade's trends about where innovation will go in the next 10 years.

In his presentation, titled *Delivering Innovation in Biotherapeutic Manufacturing: From Continuous Improvement to Disruptive Innovation, What Can Current Industry Trends Tell Us About the Next 10 Years?*, Lambalot references a quote by science-fiction writer William Gibson, "The future is already here — it's just not very evenly distributed." In pharma, Lambalot believes there are pockets of innovation that exist today that can provide insight into what the future may hold for the bioprocess professional.

"There's been a lot of great work done with different industries for innovation models, and there are many concepts people are familiar with, like 'continuous improvement' and such being a source of incremental innovation. There's also the concept of 'breakthrough technologies,' which can lead to some discontinuity in the marketplace," says Lambalot. "Those sorts of innovations are hard to pick out in advance, but if the future is here right now, where are we seeing those pockets of innovation that may be pointing to what we, as bioprocess professionals, really want to keep an eye on? Then we can look at how it's going to affect how we do our work."

DOES THE INNOVATION S-CURVE APPLY TO PHARMA?

According to the book, *Diffusion of Innovation*, by Dr. Everett Rogers, adoption of an innovation follows an S-curve when plotted over time. Innovators are the first adopters, followed by early adopters, early majority, late majority, and then laggards, who are the last to adopt, usually because they have the most aversion to change. It is when the laggards begin to adopt that the innovation has typically hit its plateau. However, Lambalot says this isn't always the case in pharma. While an innovation may have hit its plateau for adoption, companies should explore opportunities to drive that curve further and create more value for their product, their company, and the industry. He references monoclonal antibodies as an example.

Monoclonal antibodies (mAbs) have been in development since the late '80s. Once they were in clinical development, a lot of companies began pursuing monoclonal antibodies as a mode of therapy, and over the past 10+ years, there has been a growing number of mAbs out on the market. If mAbs are following the S-curve, then this may indicate the platform is maturing and running toward the end of its plateau for innovation. Lambalot argues the opposite. "The monoclonal antibody field is still very ripe for innovation. As biologists and clinicians, we are just now beginning to understand the mechanistic properties of our molecules. As process engineers, we are just now beginning to learn different ways of controlling the productivity of our cell lines as well as the actual molecular attributes of the antibodies as they are expressed," he explains. "I think we are beginning to see an inflection in our ability to control those attributes, and even more importantly, we want to have an understanding of their relevance. Does it give us a superior efficacy profile, or does it give us a superior profile for formulation in stability?" It is these types of innovation that go

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beyond the typical, continuous improvement programs that focus on speed, cost, and quality. While those areas are important, Lambalot says it is likely other areas, like multispecific IgGs (immunoglobulin G) and antibody drug conjugates (ADCs), that will provide the most opportunity for true innovation.

THE EFFECT OF DEMAND ON INNOVATION

The pharmaceutical industry is under constant pressure to come up with new, life-saving medications. However, these breakthroughs in science often take time and money, and with the pressure to produce something quickly using the most cost-effective processes, scientists and engineers are often restricted in their ability to innovate. To keep up with the industry Joneses, companies can sometimes be hesitant to focus on an area that may not appear to have an immediate payoff but could potentially lead to success down the road. Lambalot says innovators need to be given the opportunity to push the limits of their field in order to come up with the next big thing.

"Truly disruptive innovation happens when there is an outlier," explains Lambalot, who references a concept written in Malcolm Gladwell's *Outliers: The Story of Success*. He continues, "Somebody has taken a completely different tack on things, and those of us who may be aligned with the current model may look at that other technology as a real high-flier. Well, that high-flier could actually be the inception of a new platform that in, who knows, five or 10 years, the rest of us may be adopting. Then the next thing we know, we're all conforming to that new technology." Lambalot adds that while the high level of conformity driven by regulatory authorities also impacts innovation, organizations like the FDA are typically supportive of innovation as long as a company has a robust data package to support it.

Lambalot adds that the types of innovators a company employs are also vital to the fostering of innovation, as explained in the article "The Three Critical Innovation Roles," written by Henry Doss on Forbes.com. According to Doss, there is the broker, the role model, and the risk-taker. The broker is the one breaking down silos and sharing information across functions, in order to make connections between the people with the ideas. Then there's the role model who understands the importance of risk-taking and nurtures an environment that supports risk-taking. Finally, you have the actual risk-taker — the person who is willing to go out and take a chance, even if it means failing. "You want that whole mix, because if you had the risk-taker alone, they may be pushing against bureaucracy or resistance, so you need the risk-taker with the role model providing the support," explains Lambalot. "The broker is sort of a catalyst. If they can make connections between like-minded risk-takers, they can really make something happen."

THE FLEXIBLE FUTURE

So what do the next 10 years look like for biotherapeutic manufacturing? According to Lambalot, they look highly flexible — as in flexible factories. In his opinion, the age of the large-volume, single-product manufacturing facility has passed. "I've visited many facilities that were built by design for single products but have already been retooled for multiproduct manufacturing," he says. "I think we've evolved our capacity thinking more from a tailor-made design to flexibility. Disposables are certainly helping with our ability to be flexible on the manufacturing floor."

Disposables are also an area where he believes industry will need to work together to advance innovation. "We're all jumping in line and adopting disposables, but I think as with anything in our industry, we are expecting our vendors to keep a keen focus on their assurance of supply and their ability to deliver on the quality and integrity of their products," explains Lambalot. "The challenges for vendors of disposable products are going to be pretty high, and I think we, as an industry, really need to work together there."

"The challenges for vendors of disposable products are going to be pretty high, and I think we, as an industry, really need to work together there."

RALPH LAMBALOT
VP of Biologics Development at AbbVie

While some groups argue for harmonization of this technology, there are others who argue that it's important to be differentiated in order to have some competitive advantage. In the case of disposables, Lambalot argues that harmonization, commoditization, and redundancy of supply is what will drive competitiveness. "Biologics manufacturers need interchangeability of different disposable products to assure their own supply chains. I believe the vendors who achieve this will have a competitive edge in the marketplace." In addition, he believes one of the biggest areas of innovation for single-use is the ability to drive continuous processing. "We see a lot of batch processing of monoclonals, and it's certainly served us well over the years," notes Lambalot. "But we might be at an inflection where engineers can look at the process economics of a disposable manufacturing line and really drive the productivity of those lines to levels that we haven't been able to achieve with fixed stainless. I'm not sure we've necessarily seen that yet."

Innovation drives the future of any industry, and pharma has some of the world's most brilliant minds at the wheel. Collaboration and communication will be key in determining where we go from here. Most importantly though, success won't come from pushing the mind to its limits; it will come from pushing it beyond.

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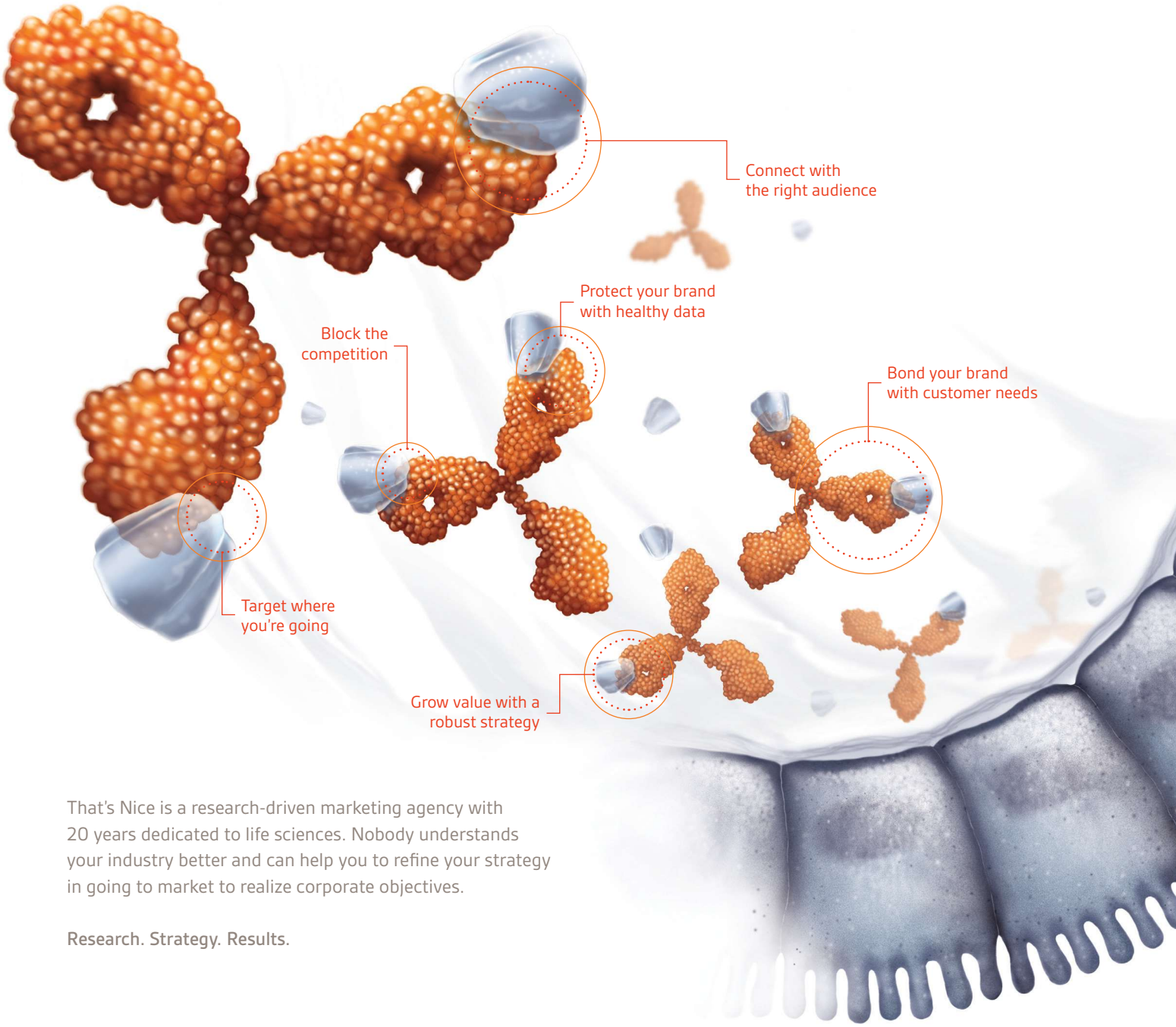

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Uncertainty: The Leadership Challenge Of Today

LAURA BUTLER

One of the greatest challenges leaders face is uncertainty. In today's knowledge-based organizations, four areas are affected by uncertainty — talent engagement, change, diversity and inclusion, and work/life integration. Uncertainty in these four areas arises from the following:

1 TECHNOLOGICAL UNCERTAINTY

We face it every time we turn on a computer and wrestle with new software. Information technology is so vital in supporting the increasing demands of healthcare innovation and is driving the need for very different skills.

2 POLITICAL UNCERTAINTY

Inside healthcare organizations, a new sense of accountability has driven leadership change. The 2012 Towers Watson study presents the evolving leadership model and includes accessibility, global and cultural acumen, transparency, authenticity, and interpersonal agility as competencies that will be required in leaders of the future.

3 FINANCIAL UNCERTAINTY

Things like pension plans, stock options, market volatility, and dot com bubbles are a few examples of what leaders face today when trying to forecast financials. Being ready is the only security.

4 STRATEGIC UNCERTAINTY

A five-year plan has become an impossible dream, yet we yearn for a vision — a sense of direction and destination to give meaning and value to the activities and struggles of the day.

An effective leader replaces uncertainty, fear, and doubt with purpose, courage, and trust. Purpose is the energetic "magnet" that pulls people together and points them in a similar direction. Courage provides strength and commitment in the face of fear. Trusting a person's purpose overcomes doubt.

Laura Butler is the CEO of WorkLife Performance Consulting, an enterprise focusing on executive coaching, team facilitation, and the creation of customized performance management programs for both profit and nonprofit clients.

The problem is that we have taught managers and leaders how to plan, organize, and lead organizations based on workplace practices and programs from the 20th century. The 21st century presents us with new demands. Leaders at every level need to formulate and implement different strategies for survival in this new world and new economy, even more so with new uncertainties.

The question is: How can leaders lead during these times of uncertainty?

ARTICULATE A GUIDING VISION.

The leader has to be clear about what they want to do, professionally and personally and must be able to tell a compelling story that allows others to see their role in the attainment of that vision.

COMMUNICATE PASSION.

The leader who communicates passion gives hope and inspiration to other people to follow their own passion in alignment with the guiding vision.

LEAD WITH INTEGRITY.

It is the basis of trust. You can't have trust without integrity, and it cannot be acquired, but must be earned. Doing the right thing as compared to doing things right sets the tone for expectations throughout the enterprise.

To succeed and be ready, companies have to adapt to change. Leadership, then, has become about learning how to cope with rapid change and ongoing uncertainty. How ready are you to lead in a world of uncertainty? Certainly, uncertainty is here to stay in spite of our efforts to dispel it.

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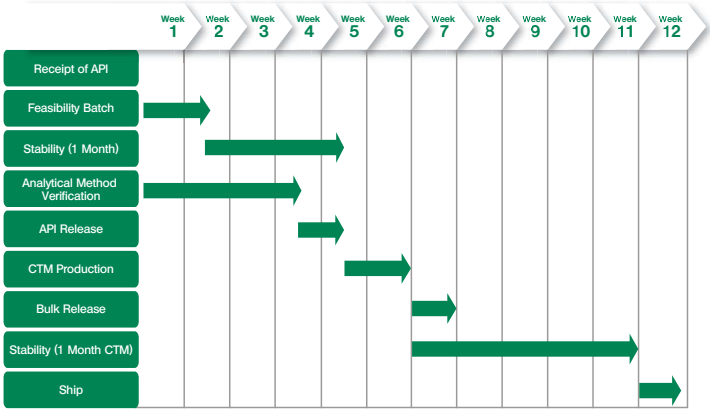

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