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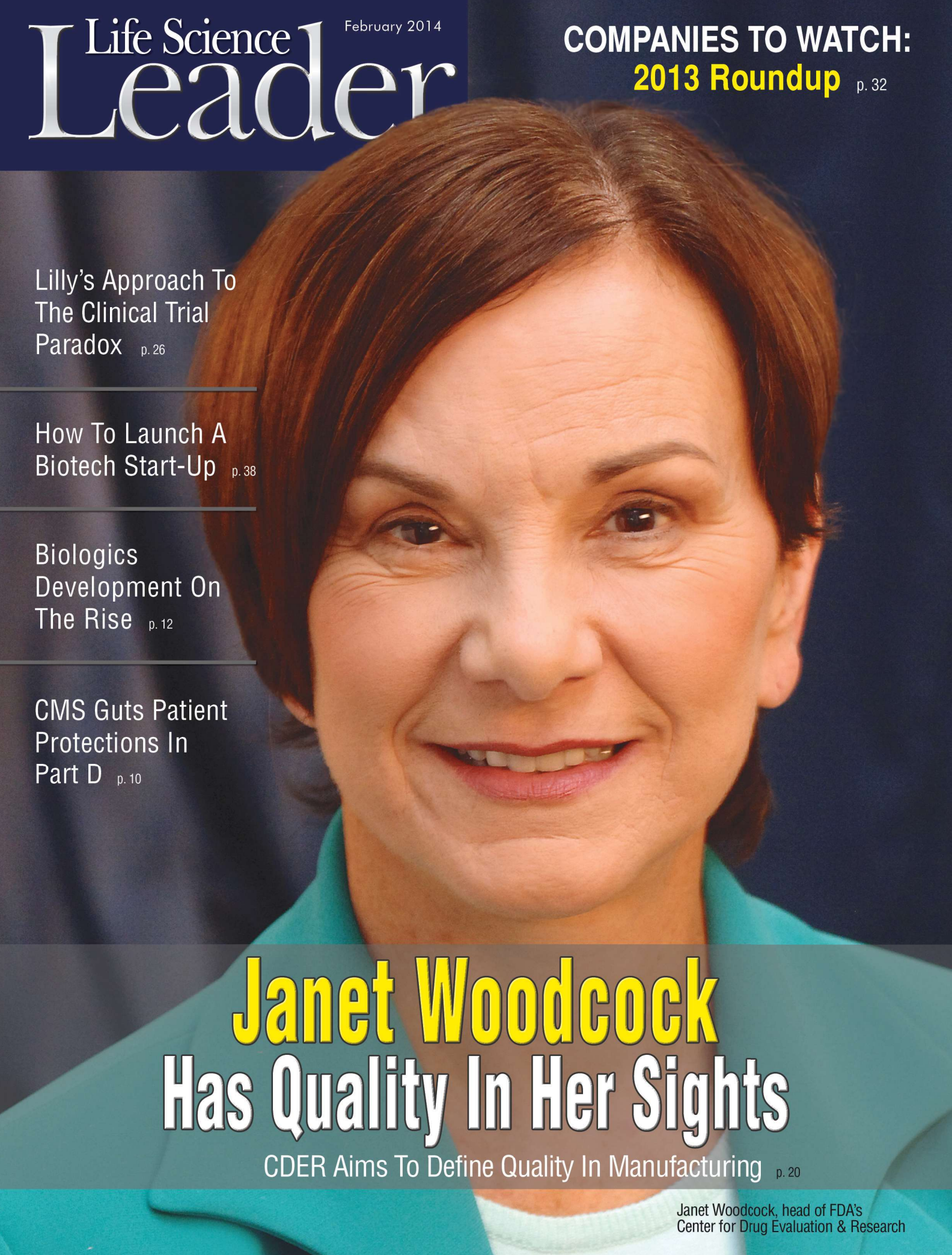

Janet Woodcock, head of FDA's Center for Drug Evaluation & Research

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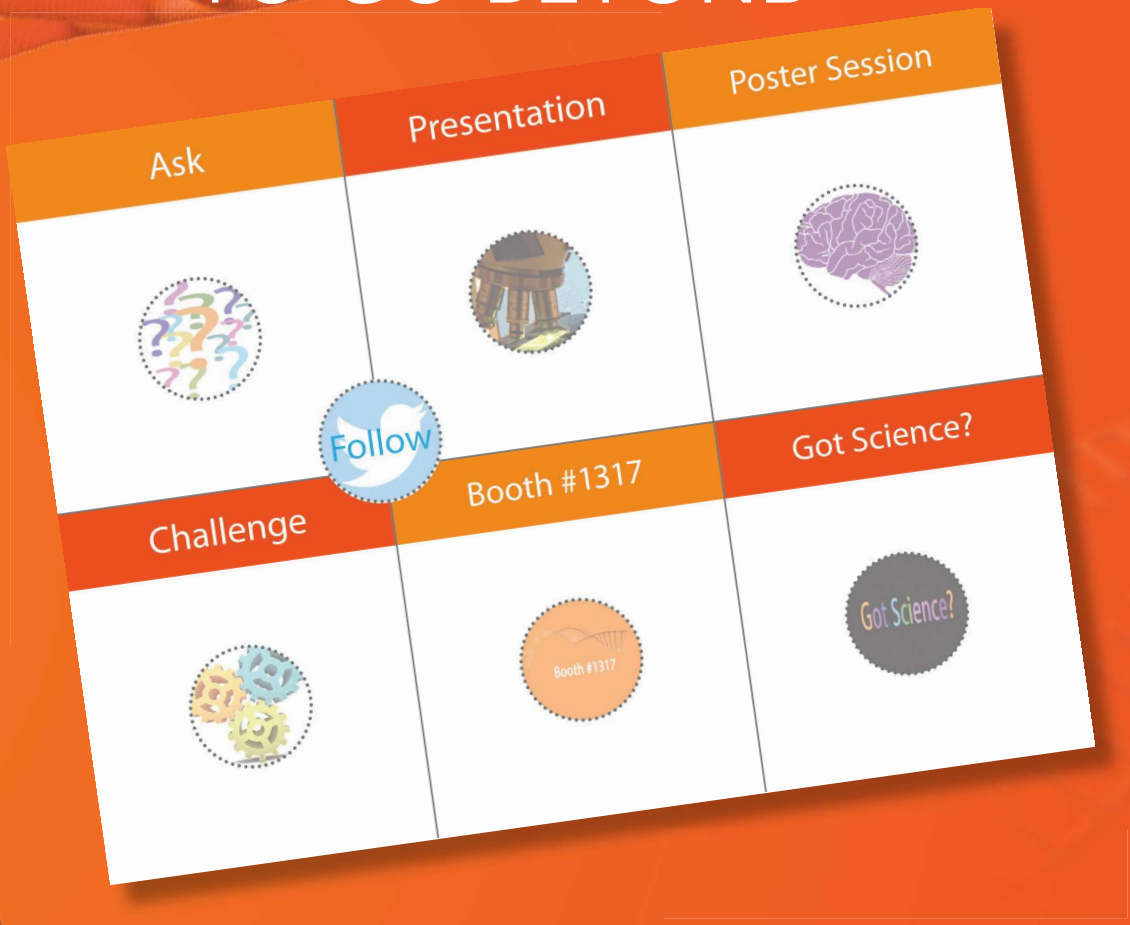

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20 FEATURE: FDA

Janet Woodcock, director of the Center for Drug Evaluation and Research (CDER) at the FDA, talks about new mandates, user fees, and uncertainties that will occupy the FDA's drug center in 2014.

February 2014

DEPARTMENTS

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EDITOR'S NOTE

Reports Of U.S. Biomedical R&D Demise — A Great Exaggeration

Prior to heading out to the 32nd Annual J.P. Morgan Healthcare Conference in San Francisco last month, I stumbled across several article headlines indicating the United States' domination of global biomedical R&D was fading. What metric was used to determine this? R&D spend. According to "new" research from the University of Michigan Health System, the U.S. share of the global biomedical R&D business declined from 51 percent to a mere 45 percent from 2007 to 2012. And while Europe remained unchanged at 29 percent, Asia rose from 18 to 24 percent. According to Dr. Reshma Jagsi, associate professor of radiation oncology at the University of Michigan Health System and author of the study, "The United States has long been a world leader in driving research and development in biomedical science." I would argue it still is, and this six-percentage-points slip isn't the doomsday scenario some would have you believe.

For starters, the majority of the Asian increase came from Japan ($9 billion), while China added $6.4 billion. You should also take into account that the time period referenced just so happens to also encompass "The Great Recession" (December 2007 to June 2009), as well as the $250 billion pharmaceutical industry patent cliff (2011 to 2015). Numerically, the biomedical R&D geographical spend translates as follows: U.S. $119 billion, EU $76 billion, and Asia $63 billion. The United States still holds a commanding lead, which is even more apparent when you factor in some other metrics. For example, the population of Asia is estimated to be 4.3 billion. At 733 million, Europe makes up about 11 percent of the world's population. The United States' population of 317 million is less than half that of Europe, and a mere 7.3 percent of Asia. This translates to a U.S. R&D biomedical spend of $375 per resident — more than three times Europe's $103 per person and 25 times that of Asia's $15 per person. The 2013 Legatum Prosperity Index, which takes into account both income and well-being in its prosperity ranking of 142 countries, provides additional insight.

Of the top 10 most prosperous countries, 7 are in Europe: Norway (1), Switzerland (2), Sweden (4), Denmark (6), Finland (8), Netherlands (9), and Luxembourg (10). The three outliers are Canada (3), New Zealand (5), and Australia (7). The United States (11) ranks second on the health metric behind Luxembourg — a country with a population less than Albuquerque, NM. Where do the two countries highlighted as leading the Asian biomedical R&D surge fall? Japan sits at 21 and China at 51, with respective health rankings of 6 and 68. The only BRIC (Brazil, Russia, India, China) country in the top 50 is Brazil (46). At an overall prosperity ranking of 106, India has demonstrated a blatant disregard for foreign IP protection under the guise of providing its impoverished with access to medicines. Though Cipla's billionaire chairman, Y.K. Hamied, has called for "automatic license" of foreign patents to local Indian champions, he should be advocating greater national investment in biomedical R&D in order to truly reap the rewards of job creation and other long-term, downstream national economic benefits. Currently, India devotes a measly 1.25 percent of GDP to healthcare — a level below that of Haiti. For years, the United States has been bearing a disproportionate share of the world's biomedical innovation, and this little correction, in my opinion, is long overdue. So too is a correction in India's approach to solving its healthcare infrastructure problems.

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Q: Which life sciences industry shipping guidance should executives be familiar with?

PDA Technical Report No. 58 *"Risk Management for Temperature-Controlled Distribution"* was published in 2012 by a team of global authors and contributors from pharmaceutical and biopharmaceutical manufacturers, their supply chain partners, and service providers. It is meant to assist stakeholders in the supply chain to preserve the quality, safety, and efficacy of these medicinal products during distribution. This guidance document complements the information provided in ICH Q9 "Quality Risk Management" by assessing, controlling, and reviewing risks with equipment, processes, people, and external factors, such as weather and natural disasters, during distribution.

As the pharm industry continues its global expansion, temperature-controlled distribution risk management becomes a dynamic and interactive process. Supply chain members are responsible for assessing, analyzing, and evaluating the risks associated with the transportation of these medicinals.

Rafik Bishara, Ph.D.
Bishara is the chair of the Pharmaceutical Cold Chain Interest Group (PCCIG) within the Parenteral Drug Association (PDA). He had a distinguished 35-year career with Eli Lilly & Co. as director, quality knowledge management and technical support.

Q: What global trend do you think will have the biggest positive impact on clinical trials and why?

Get your head in the cloud. We are in the midst of a mind-boggling transformation brought about by unprecedented access to variables that will take hypothesis testing supersonic. Big Data requires a new level of collaboration and engagement across industry and around the globe to realize our dream of precision medicine. The cloud will provide real-world information to combine with traditional trial data to navigate the complex disease pathways and more efficiently and effectively identify new treatments. During a recent talk, Thomas Kolopolus, president and founder of Delphi Group, shared his opinion that the next generations will be so used to collaboration that they will shun the assumption of knowledge ownership, or that anything can be learned without constant sharing and transparency. In this scenario, the concept of owned IP (an innovation inhibitor) is likely to become the next dinosaur.

Mary Rose Keller
Keller, a former VP of clinical operations, has proven success in planning, management, and delivery of global Phase 1 to 4 clinical trials for drug, biologic, and diagnostic products.

Q: How can manufacturers proactively avoid metal contamination?

On avoiding specific contamination risks, I like to come back to knowing your process intimately. What are the risks of various contaminants – equipment (shedding, wear), raw materials (vendor controls, incoming testing), and people (shedding, handling, open systems) from an end-to-end walk-down of your process, and create what mitigations are necessary to drive these risks to zero – equipment preventative maintenance and replacement, vendor audits and corrective actions, closing systems, and automation, respectively. Active monitoring of complaints and signals of extraneous matter in your process, cataloging extraneous matter found, and comparing to a library of potential sources (from your end-to-end process walk-down) helps to develop corrective actions when issues emerge.

Jim Robinson
Robinson is the vice president for vaccine and biologics technical operations for Merck & Co. In this role, he supports the manufacturing strategy, process development, technical transfer, approval, and production of Merck's vaccines and biologicals at eight internal sites in the U.S. and Europe, and several partner sites globally.

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CMS Guts Patient Protections In Part D

The Obama Administration welcomed in the new year by releasing a proposed rule that would eliminate patient access protections for Medicare beneficiaries in three therapeutic classes: anti-depressants, anti-psychotic, and immunosuppressive.

Currently, Medicare Part D plans must cover "substantially all" drugs in six protected classes, which ensures beneficiaries can continue to take particular drugs that work for them. The Center of Medicare and Medicaid Services (CMS) proposal would eliminate these protections immediately for anti-depressants and immunosuppressants and lift the protections for anti-psychotic medications in 2015.

Patient groups have reacted with outrage. Ron Honberg, director of policy and legal affairs for the National Alliance of the Mentally Ill said, "By undoing one of Medicare's signature protections for persons with mental illness, the rule disregards scientific understanding that psychiatric medications are not interchangeable. A medication that works for one person does not necessarily work for another person. Prescribing decisions must be individualized, based on clinical history, side effects, and personal history."

John McManus,
The McManus Group
jmcmanus@mcmanusgrp.com

Although the six protected classes were not created in statute, the Bush Administration used its administrative authority to establish the patient protections for these drugs at the outset of the program, recognizing that many dually eligible beneficiaries were enrolling from state Medicaid plans that generally did not restrict access to these products. In addition, the Administration understood that while patient adherence may increase the Part D spend — something contrary to the economic incentives of a free-standing prescription drug plan — it could substantially reduce overall healthcare costs to Medicare.

In 2008, the Democrat-controlled Congress enacted a Medicare law, overriding President Bush's veto, which created a two-part test to identify protected classes. The class of drug must be one which:

1. Restricted access would have a major or life-threatening clinical consequence; and
2. Beneficiaries have significant need for multiple drugs.

Importantly, that law neither explicitly affirmed the current six protected classes nor suggested that they were inappropriate. In addition, rulemaking by the Obama Administration in 2009 and enactment of the Affordable Care Act in 2010 did not change this two-part test or change the six protected classes.

Thus, it was a surprise to patients and pharmaceutical manufacturers alike that CMS chose to fundamentally deny critical beneficiary protections that have been entwined into the fabric of the program for eight years. Although Part D cost growth has declined from 3 percent to 1 percent in the three most recent years data is available, CMS said the policy change is necessary to provide plans with additional tools to constrain costs and deter overutilization.

Unfortunately, the Obama Administration's approach to this issue is entirely consistent with its implementation of its philosophy of healthcare "reform" — its misguided fixation on constraining costs trumps patient access.

Millions of enrollees in Affordable Care Act (ACA) plans are now painfully discovering that their provider networks are more akin to Medicaid than to the commercial plans they may be more accustomed to. A December 2013 McKinsey study of 20 metropolitan areas found that two-thirds of ACA plans had "narrow" or "ultra-narrow" networks, with at least 30 percent of the top 20 hospitals excluded. The median premium was 26 percent lower for these plans than comparable benefit packages with broad networks.

For example, Blue Shield of California asked providers to accept a 30 percent discount for its ACA plan, but discovered that 40 percent of the doctors and 25 percent of its hospitals that participate in its commercial offerings declined to participate in its Obamacare network.

If the CMS proposal goes through, only anti-retroviral, anti-neoplastics, and anti-convulsants will retain the protected status that has been critical to patient access and optimal clinical outcomes. Patients with severe mental illnesses or organ transplants will lose access protections to products that may be critical to their unique physiological needs.

The good news is that the Obama Administration's proposed abandonment of this core beneficiary protection is not final — yet. Patient and disease group advocates and other stakeholders have until March 6 to make their case, provide clinical evidence, and exert political pressure to get the Obama Administration to reverse this dangerous policy.

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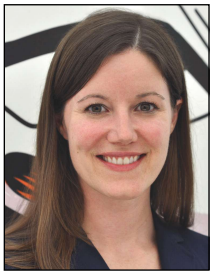

OUTSOURCING INSIGHTS

Biologics Development Continues To Rise At Traditional Pharma Companies — What Does It Mean For Outsourcing?

By Kate Hammeke, director of marketing intelligence, Nice Insight

Over the past two years, research results from Nice Insight's annual Pharmaceutical and Biotechnology Outsourcing survey indicate a rise in the percentage of respondents who work at traditional pharmaceutical companies that are engaged in the development of biologic-based therapeutic drugs. Perhaps surprisingly, the largest increase comes from respondents who work for emerging pharmaceutical companies, up 14 percentage points over last year (34 percent, 2013 to 48 percent, 2014), followed by specialty pharmaceutical companies with a 13 percentage points increase (52 percent, 2013 to 65 percent, 2014), and Big Pharma with an increase of 6 percentage points (76 percent, 2013 to 82 percent, 2014).

These changes coincide with an increase in the percentage of one's outsourcing budget spent on biologics as compared to small molecule therapeutics — up a substantial 11 percentage points among specialty pharma respondents, 6 percentage points in the emerging pharma group, and a modest 2 percentage points among Big Pharma respondents. This makes sense, considering biologics have traditionally been more expensive to develop than small molecule therapeutics, but as the patents for existing biologics continue to expire — an expected market value of $54 billion will go off patent in the next five years — the need for reducing costs in biologic development will become more crucial. So, while both outsourcing expenditure and the percentage of expenditure going toward biologics development have both risen over last year, it should not necessarily be interpreted as rising costs; rather, it is more likely a reallocation of internal versus external spend on biologics development.

THE REASON FOR PARTNERING WITH CMOs/CROs HAS CHANGED

During the past few years, Nice Insight research has highlighted a change in the theory of outsourcing. A practice that started off as a purely client-vendor relationship centered on commoditized activities has evolved into more of a partnership, in which CROs and CMOs are engaged, in part, because of access to external knowledge, not just because of the ability to complete tasks. As a matter of fact, when asked to consider a dozen different quantifiable traits, 74 percent of survey respondents whose business is involved in the development of biologics stated "technical expertise" was *very important* when selecting an outsourcing partner, second only to having a "track record of success," 75 percent. Meaning, access to knowledge and experience, or technical expertise, are not only essential qualities, but they also drive CMO engagement when it comes to biologics. That being the case, it makes sense that businesses involved in developing biologics are considerably more interested in forming strategic partnerships — defined as a long-term, win-win commitment between two organizations — than those that focus strictly on small molecules (56 percent vs. 24 percent).

CROs and CMOs are engaged, in part, because of access to external knowledge, not just because of the ability to complete tasks.

WHO OUTSOURCES TO EMERGING MARKETS?

Interestingly, respondents whose business includes the development of biologic-based therapeutics are also significantly more likely to consider CROs and/or CMOs in emerging markets such as Brazil, China, or India (78 percent) than businesses that are strictly small molecule (50 percent). In addition, this group is more likely to already be working with emerging market providers than their counterparts (53 percent vs. 32 percent). Among respondents who outsource to emerging markets, almost two-thirds of the work is allocated to emerging markets, while one-third remains in established markets. The practice of outsourcing complex biologics projects that contain intellectual property further represents the shift in outsourcing beliefs. This change in outsourcing ideology — from subcontracting commoditized work to seeking expertise for specialized products — was bolstered by improved patent laws in developing countries, along with the strong education systems and access to an expanding pool of available patients to participate in clinical trials.

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% of Respondents Whose Business is Engaged in the Development of Biologic Based Therapeutic Drugs	Big Pharma 2013 to 2014: +6% 82%	Specialty Pharma 2013 to 2014: +13% 65%	Emerging Pharma 2013 to 2014: +14% 48%
% of Budget Spent on Biologics vs. Small Molecule Therapeutics	Big Pharma 2013 to 2014: +2% 55%	Specialty Pharma 2013 to 2014: +11% 55%	Emerging Pharma 2013 to 2014: +6% 58%
Interest Level in Strategic Partnership	Interested in strategic partnership 56% Develop Biologics 24% Strictly Small Molecule	Neither interested nor uninterested 32% Develop Biologics 45% Strictly Small Molecule	Not interested in a strategic partnership 12% Develop Biologics 32% Strictly Small Molecule
% Who Will Consider Emerging Market CROs/CMOs	Develop Biologics 78%	Strictly Small Molecule 50%	
% Already Working with Emerging Market CROs/CMOs	Develop Biologics 53%	Strictly Small Molecule 32%	

Survey Methodology: The Nice Insight Pharmaceutical and Biotechnology Survey is sent to outsourcing-facing pharmaceutical and biotechnology executives on an annual basis. The 2013-2014 report includes responses from 2,337 participants. The survey comprises of 240+ questions and randomly presents ~35 questions to each respondent in order to collect baseline information with respect to customer awareness and customer perceptions of the top 100+ CMOs and top 50+ CROs servicing the drug development cycle. Five levels of awareness from "I've never heard of them" to "I've worked with them" factor into the overall customer awareness score. The customer perception score is based on six drivers in outsourcing: Quality, Innovation, Regulatory Track Record, Affordability, Productivity, and Reliability. In addition to measuring customer awareness and perception information on specific companies, the survey collects data on general outsourcing practices and preferences, as well as barriers to strategic partnerships among buyers of outsourced services.


Walker

If you want to learn more about the report or how to participate, please contact Nigel Walker, managing director, or Salvatore Fazzolari, director of client services, at Nice Insight by sending an email to niceinsight.survey@thatsnice.com.

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BIO INNOVATION NOTES

Best Practices: Continuous Bioprocessing

Wider Adoption Signals Industry Maturation

By Eric Langer, president and managing partner, BioPlan Associates, Inc.

Batch processing, both up- and downstream, has long been the dominant bioprocessing paradigm. Bioprocessing fluids are piped and transferred as a batch from one holding vessel or process equipment to the next. This finish-one-step-and-move-on-to-the-next approach works rather well, and advances over the years have resulted in a lot of experience and data. In fact, upstream and overall process yields have tended to double about every five years.

However, batch processing is not the norm in most other major product manufacturing industries. Outside of the biopharmaceutical industry, manufacturing processes tend to be continuous. This is exemplified by assembly lines and petroleum refining, where processing involves a continuous flow from one unit of operation to the next. Continuous bioprocessing for upstream operations in the pharma industry is often defined as the process of running a bioreactor at a fixed volume and fixed cell concentration for 30 to 90 days (or longer) with a constant flow of cell culture media, giving a constant harvest volume to be processed. According to some observers, within 15 years, continuous processing will become the prevalent bioprocessing platform. It's interesting to note that continuous processing tends to be employed in more mature industries. And with recombinant proteins marketed only since the early 1980s, the biopharmaceutical industry is just now being considered mature enough to move toward continuous vs. batch processing.

From our 10th Annual Report and Survey, Figure 1 shows the likelihood of specifying a perfusion bioreactor by biomanufacturers. Here we can see that single-use, perfusion bioreactors were indicated by a quarter of respondents for commercial applications and nearly a third for clinical-scale bioprocessing. This is only slightly higher than the responses to this question in 2012. But the trend is clearly continuing.

Fed-batch cell culture, involving fully loading, running, then emptying a bioreactor, has been the dominant method for decades. This batch processing requires larger equipment that costs more, takes up more space, and requires more robust infrastructure, utilities, and labor. The process is sporadic and uneven. In contrast, continuous bioprocessing allows more predictable steady manufacture of the same or more product at smaller scales with associated cost-savings and benefits.

Continuous bioprocessing, particularly perfusion — its upstream implementation — is currently experiencing relatively rapid adoption. With perfusion, bioreactor harvest is withdrawn continuously, simplifying downstream operations and allowing purification to be done more repetitively at smaller scales, with fewer, smaller holding tanks. Most adoption of continuous bioprocessing has involved upstream perfusion, while adoption of continuous downstream purification operations is proving more difficult, with fewer technology options, and is lagging behind. Continuous chromatography methods, such as simulated moving bed (SMB) and periodic counter-current chromatography, are generally not quite ready for widespread adoption.

But commercial products have been produced for years using elements of continuous processing. So this is not a novel area. Examples of products currently manufactured using perfusion bioreactors include Kogenate (factor VIII) from Bayer Schering, ReoPro (anti-platelet mAb) and Remicade (tumor necrosis factor mAb) from Centocor/J&J, Campath (CD52 , mAb) from Genzyme/Sanofi, and Xyntha (a modified factor VIII) from Pfizer.

The current leading perfusion technology in terms of adoption is the alternating tangential flow-based (ATF) system from Refine Technology. At a 500 kg/year commercial manufacturing level, using single-use equipment, annual upstream bioprocessing costs are projected at $33.1 million for perfusion vs. $106.7 million for fed-batch. In comparison, stainless steel-based costs are $44.1 million for perfusion and $103.9 million for fed-batch manufacture. These figures suggest that perfusion technologies will see increasing consideration in coming years.

GROWING PAINS

Problems that have restricted wider adoption of continuous bioprocessing and, particularly, perfusion, include misperceptions and lack of knowledge within the industry. In 2011 our survey of bioprocessing professionals documented this. The industry continues to associate perfusion/continuous processing with greater difficulties. "Process complexity" was the primary concern, cited by 66.4 percent. Given a list of 17 problems encountered in bioprocessing, respondents consistently rated all of

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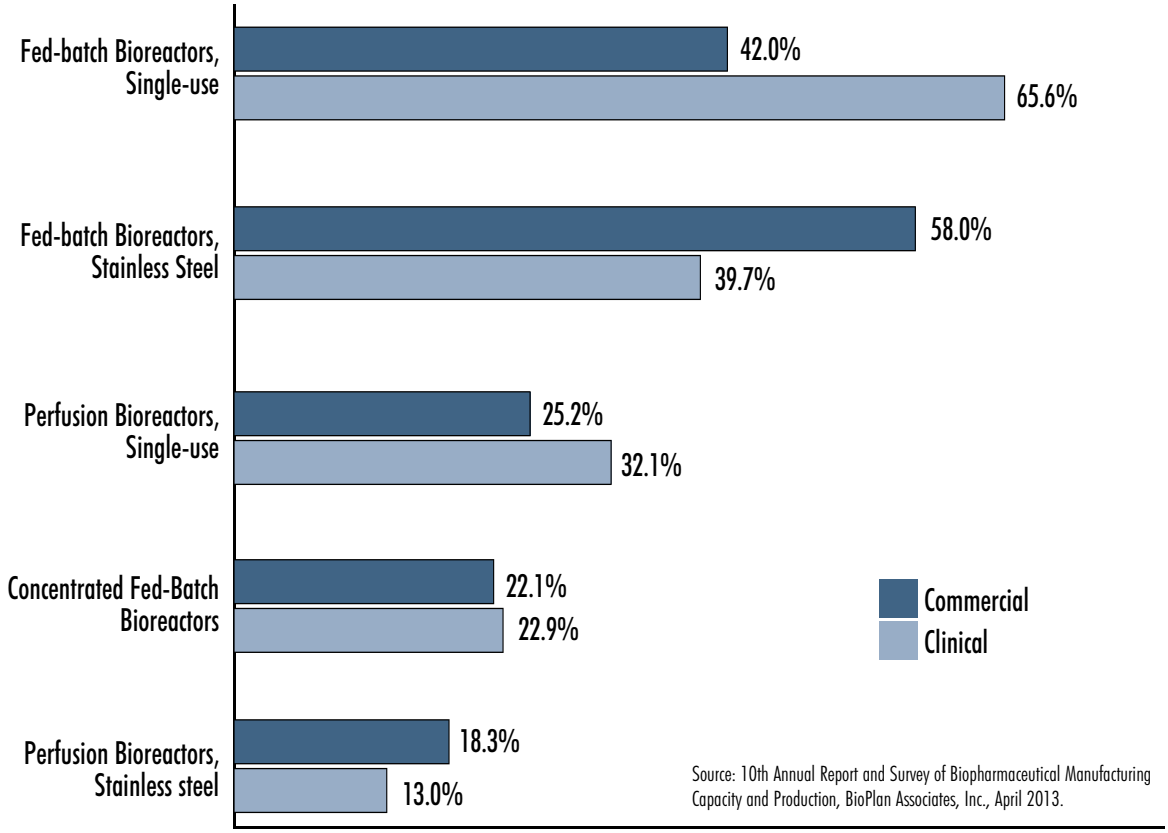
these as significantly more serious concerns with perfusion than with batch-fed systems — even though this is often not the case. In fact, perfusion/continuous processing now tends to be generally less complex, less prone to contamination, and more readily scalable than fed-batch methods. These fears and growing pains include addressing concerns of regulators who have yet to fully understand some aspects of this technology, such as defining lots/batches and doing QA/QC with continuously manufactured products.

THE FUTURE OF NEW PERFUSION TECHNOLOGIES

New perfusion technologies may ultimately mature and revolutionize bioprocessing. For example, a 50 L bioreactor with cells bound to capillary fibers in development by FiberCell will be able to manufacture the same quantity of product, at better quality, than a 1,000 to 5,000 L bioreactor over the same time period using the same amount of culture media. Similar bioreactors were in common use for hybridoma (non-recombinant monoclonal antibodies) manufacture back in the 1980s. So increasing adoption in coming years will actually be nothing new. Much of the adoption of perfusion will be associated with single-use equipment, particularly as current products being developed by single-use manufacture graduate to commercial manufacture.

Figure 1
Likelihood Of Implementing Bioreactor (By Type)



Source: 10th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production, BioPlan Associates, Inc., April 2013.

Survey Methodology: The BioPlan annual survey of biopharmaceutical manufacturers yields a composite view and trend analysis from over 300 responsible individuals at biopharmaceutical manufacturers and CMOs in 29 countries. The survey included over 150 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, 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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JANET WOODCOCK'S QUALITY AGENDA AT CDER

NEW MANDATES, NEW USER FEES, AND NEW UNCERTAINTIES OCCUPY THE FDA'S DRUG CENTER IN 2014.

By Wayne Koberstein, executive editor

Speaking in whole sentences may become an ever-rarer practice in this, the Abbreviated Age of texts and tweets — but Janet Woodcock, head of the FDA's Center for Drug Evaluation and Research (CDER), is someone who speaks in whole paragraphs. She is not reading from a script; she spontaneously composes succinct, lucid, and informative statements based on logic and knowledge, requiring none of the editing we usually expect with extemporaneous speech. Woodcock speaks with the perspective of a builder, not an observer. Over many years, she has helped shape and construct the agency as it is today. Consequently, she has become the most consistent, reliable voice of the FDA for most people in the life sciences industry.

In general, the political and economic environment for the world's largest drug regulator has grown even more difficult since we last spoke with Woodcock for the cover story of our November 2011 issue. Broad austerity in the federal budget has largely replaced the targeted anti-regulatory assaults of two years ago, but the agency still faces the challenges of doing more with less, perhaps for many years ahead.

With new responsibilities covering more regulatory and geographical territory, the FDA cannot simply add resources. Although it stands to gain new income from industry user fees, the agency carries a backlog of work and needed expenditures. Its only other option is to reorganize and redeploy the resources it has. Most of the FDA's recent assignments are mandated by law, specifically the Food and Drug Administration Safety and Innovation Act (FDASIA), the Generic Drug User Fee Act (GDUFA) and similar user-fee legislation for biosimilars, and the Drug Quality and Security Act, which amends FD&C Section 503A to establish registration and fees for certain compounded drugs, as well as track-and-trace provisions for FDA-regulated drugs.

CDER's responsibility includes the bulk of items driven by the mandates: implementing the new user-fee programs, an accelerated review process for new drugs, and pushing overall improvements in drug manufacturing and quality. To those ends, Woodcock has overseen an extensive reorganization of the drug center, including elevation of the new Office of Generic Drugs (OGD) and creation of the Office of Pharmaceutical Quality (OPQ). The changes involve shuffling existing duties and adding new ones wherever needed — sometimes to the chagrin of affected personnel. At the same time, Woodcock prefers to emphasize continuity.

"We are continuing a balanced-portfolio approach across drug development, post-marketing surveillance, drug safety, scientific innovation, and controlling illegal activities," she says. "We regulate everything from drug advertising down to INDs (investigational new drugs) and first-in-human studies, and I work to make sure we have all those covered at a strong level — along with our communications office and other functions necessary for us to communicate and work with our diversity of stakeholders."

GDUFA: AN OPPORTUNITY FOR BALANCE

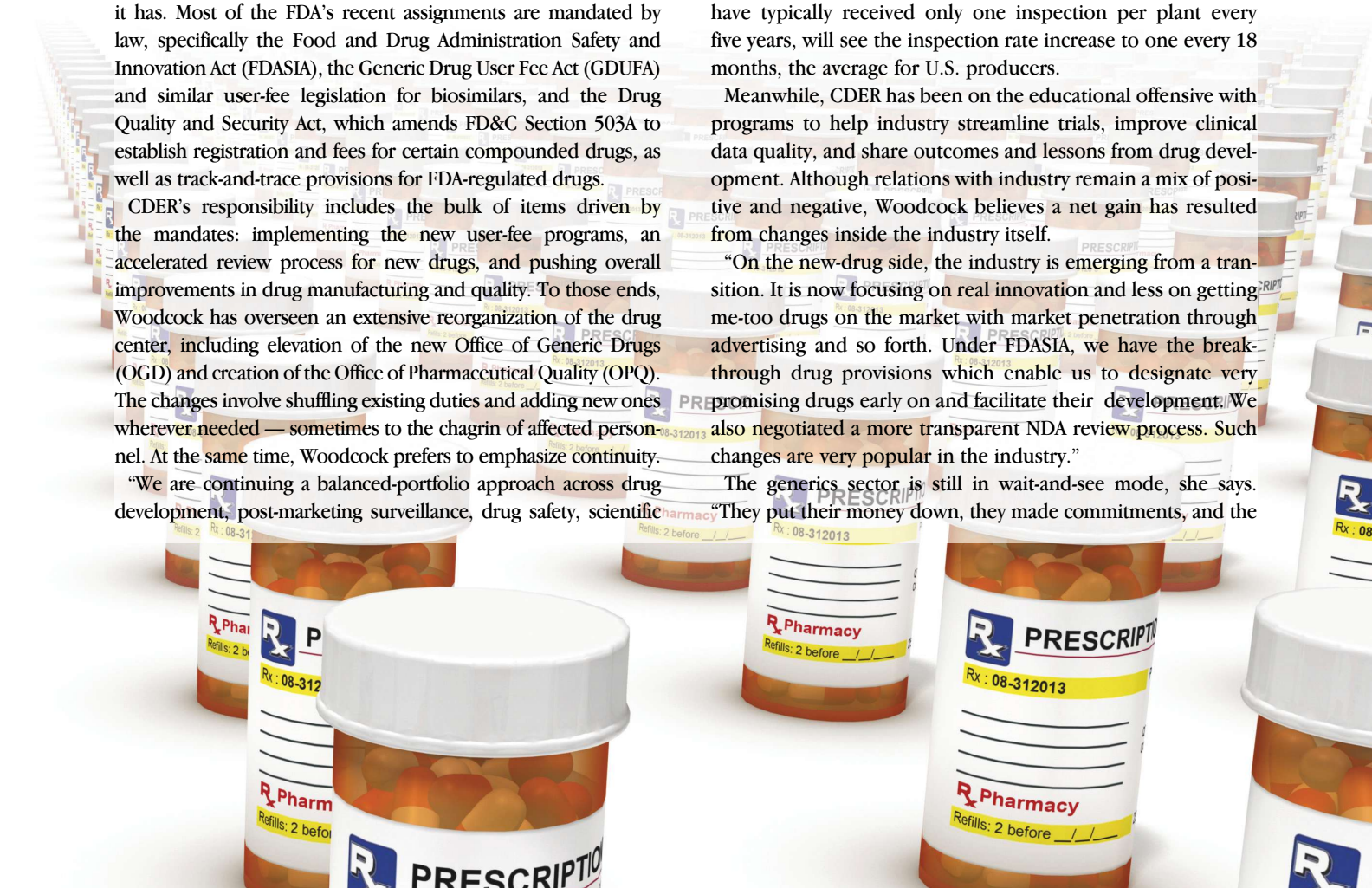
But Woodcock then proceeds to describe how the "balance" in CDER's portfolio has profoundly shifted: in this case, toward a more even-handed system for regulating the majority of prescription medicines consumed by U.S. patients — generics. "The success of the generics program had outrun its resources. We now get about a thousand ANDAs (abbreviated new drug application) every year, compared to about 200 in 1990," she says. "The staffing has increased somewhat, but not at all proportionately, and we have developed a huge stack of pending applications. So GDUFA is an opportunity to get all that back into balance."

Partly because of GDUFA, but also affecting the pharma industry as a whole, CDER's reach is extending across the globe. "Our inspectional forces were always a domestically based group," says Woodcock. "But one hallmark of GDUFA is that we will now have the same regulatory scrutiny of all manufacturers, regardless of where drugs are produced around the world." For example, non-U.S. drug manufacturers, which have typically received only one inspection per plant every five years, will see the inspection rate increase to one every 18 months, the average for U.S. producers.

Meanwhile, CDER has been on the educational offensive with programs to help industry streamline trials, improve clinical data quality, and share outcomes and lessons from drug development. Although relations with industry remain a mix of positive and negative, Woodcock believes a net gain has resulted from changes inside the industry itself.

"On the new-drug side, the industry is emerging from a transition. It is now focusing on real innovation and less on getting me-too drugs on the market with market penetration through advertising and so forth. Under FDASIA, we have the breakthrough drug provisions which enable us to designate very promising drugs early on and facilitate their development. We also negotiated a more transparent NDA review process. Such changes are very popular in the industry."

The generics sector is still in wait-and-see mode, she says. "They put their money down, they made commitments, and the



agreement cannot be amended in the first two years of the GDUFA program. We are doing our best to get the whole program organized so it can operate on a much larger scale. OGD must work through all the backlog and start operating in a steady state as PDUFA does."

QUALITY — CAN'T GET AROUND IT, SO GET ON BOARD

If Woodcock has made any single issue the hallmark of her tenure at CDER, that issue would be quality in pharmaceutical and biopharmaceutical manufacturing. When we visited her in 2011, her group was working to develop an industry-wide consensus on defining quality above and beyond minimum GMP or product standards. Such a definition is still at the heart of current CDER initiatives, including OPQ.

"I think you would do a great service if you could explain how we think about this," Woodcock says. "Actually, we defined the quality of a pharmaceutical product a long time ago: fitness for use. It delivers the properties described on the label and is not contaminated. But the other piece is, what is quality in manufacturing? And that's really what we are focusing on. Right now, a lot of the industry delivers quality products by throwing away, by wasting, up to 35 percent of what's produced, and we don't believe that amounts to quality manufacturing. We've been exploring this question extensively with industry in a very open process: 'What metrics might we use that would measure the quality of your manufacturing processes?'"

An April 2013 article in our web portal, *Pharmaceutical Online*, quoted Woodcock as saying that the FDA has no way of measuring drug-manufacturing quality, putting the agency in the same predicament as manufacturers. Here, she elaborates: "What is the inventory of facilities we regulate today? We are now conducting an extensive IT effort to create the inventory and then define the state of that inventory. How many API manufacturers earn a Six Sigma rating or have a very high level of defect-free products, no recalls, no problems? Which ones are in the bottom 10 percent?"

Manufacturing quality — or a lack thereof — has received much of the blame for drug shortages, though some suppliers have faulted low-margin or below-cost reimbursement and puny contract prices for driving good manufacturers away from producing essential off-patent drugs. Claiming no expertise in economics, Woodcock seems to see some common sense in the argument.

"You might pay $3.50 for a cup of coffee, but only 45¢ for a vial of propofol. Yet sterile injectables, in particular, are very hard to make right. They are very hard to make consistently sterile, without any particles or endotoxin in them, which they must be because they're given intravenously."

Still, she stresses quality as the underlying issue, citing the inefficiencies built into manufacturers' legacy systems and technology. Besides coaxing industry to update and upgrade its facilities, she believes the FDA can also help widen payers' perspective. "We are trying to make quality of manufacturing more transparent to purchasers. Quality of manufacturing predicts reliability of supply." Internally, with no intent to impose or even publish the results, CDER is establishing a "framework" of quality metrics to help it characterize the variations among facilities in its database, she says.

"Someday we might publish an annual report on the spread of performances, without identifying the companies. It would then be up to purchasers, in their due diligence, to go beyond the issue of cost. I don't think they've ever taken reliability of supply into account before now, because it has not been an issue. But shifts in the industry, probably including pricing structure, have consolidated suppliers and limited the sources for essential drugs."

QUALITY ORGANIZING

As the objective expression of a quality-promoting agenda, Woodcock has championed the creation of the new Office of Pharmaceutical Quality. Still in its infancy, the OPQ now consists of a "reorganization package," essentially a proposal that CDER must formally submit to all concerned parties for their review and sign-off. "We know how we want to work in the future, and this organization will reflect that, and it's going to

FDA'S FUTURE-INDUSTRY VISION: CONTINUOUS PRODUCTION

As payers recognize the problem of reliability in the drug supply chain, they will gravitate toward the most reliable suppliers — and ultimately, perhaps, to an entirely different supply-chain model. That is the view of Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research (CDER). Are you ready for the concept of continuous drug production? Get ready, advises Woodcock:

"A number of companies are on the verge of adopting continuous manufacturing and other advanced manufacturing techniques which are not susceptible to many of the problems of traditional manufacturing models. Continuous manufacturing can transpire in a single small room, starting with raw materials on one end and finishing with tablets on the other. We believe the new technologies are highly superior. They have a very small environmental footprint and they require high-tech workers experienced with advanced technologies.

"Continuous drug manufacturing creates opportunities that haven't existed before. It will help personalized medicine, because it's very flexible, unlike traditional operations where everything has to be rigidly validated and so on. There are many new dosage forms that could be made with the new techniques. It is also perfect for clinical trials because you don't have to scale-up — you just run your machine longer. Bioprocessing also has some promising alternatives on the horizon. Plant-based protein production and single-use manufacturing equipment parallel the advancements with small-molecules.

"In the United States, we lost our industrial base of drug manufacturing, and we ought to seize the day to bring it back. We ought to support academia in drug manufacturing innovation; states or other organizations could set up high-tech drug manufacturing centers; and the federal government should do its share of funding and incentives. It's a brave new world, and our nation would be well-advised to foster this new drug manufacturing paradigm. CDER will continue to take a progressive stance, doing our best to enable and actually stimulate the new methods of manufacturing."

be quite different, but we're very happy with it. I think most people are pretty happy with it and excited about what's going to happen now, which is good."

Creation of the OPQ is a key part of the larger reorganization of CDER. In mid-December 2013, the center announced its plans to "elevate" the Office of Generic Drugs (OGD) to report directly to CDER's director. Although movement of new people into positions at the OPQ cannot begin until its plan is approved, Woodcock says the process of recruitment and reassignments has already begun.

Another announced change is that all drug chemistry and microbiology review, including that formerly conducted by the OGD, will move to the OPQ. Woodcock says OPQ will also assume facilities review from the compliance office and set up a new surveillance function, which will develop the manufacturing quality metrics and conduct the related assessments. "The Surveillance Office will be the owner of a large database of manufacturing facilities, where we will house all the quality information."

Woodcock has publicly criticized the agency's traditional inspection procedure, which concentrates on individual steps and components in the process rather than an overall view of manufacturing quality at any given site. "We will be changing how we do the surveillance inspections," she says. "We want our investigators to go in armed with the history of the company, including recalls, field alerts, or anything that affected the performance of the facility. We can also examine and verify any metrics that manufacturers send us."

CDER is collaborating with industry on the metrics development; in late 2013, for example, it participated with industry leaders in a PDA (Parenteral Drug Association) meeting devoted to the topic of measuring manufacturing performance. "Companies are learning they can save money with quality," says Woodcock. "Most other industries, when they adopted high-level quality, found they could reduce waste, customer complaints, and recalls while improving scale-up and safety."

A FAIR HAND FOR THE FAST TRACK

Possibly because of fewer NDA submissions in 2013, the FDA approved only 27 new medicines last year compared to 39 in 2012. But one new issue drew even more attention than drug approvals during the year: expedited development. Of 120 applicants for breakthrough status, the agency awarded it to only 36 candidates. A separate, accelerated-approval program also disappointed some companies, as well as patients and their families.

A case in point was Sarepta's drug eteplirsen for Duchenne mus-

cular dystrophy (DMD). In the opinion of its supporters, the drug caused significant improvement in patients' walking ability along with boosting the levels of dystrophin, a putative biomarker for DMD symptoms. When the FDA asked the company for more information from its dataset on eteplirsen to support its request for accelerated approval, the head of the main DMD patient group sent a long, petulant email to Woodcock in response.

No one expects Woodcock to comment specifically on the eteplirsen case, but she has this to say: "Sometimes people do pitch their case to me, and they're just so convinced they have a breakthrough. They may come in with incredible clinical data, but we say, 'Well, just repeat it, open label; take another 30 people and show you get the same results, and then we'll talk about accelerated review. It depends on what the results are and how convincing the data are."

Woodcock says she identifies with the patient-community advocates and could even see herself joining them if she faced a disease such as ALS or AIDS. "HIV was the instigation for accelerated approval; we said we were going to approve drugs based on a surrogate marker if it was reasonably likely to predict clinical benefit. And we've done a large number of accelerated approvals since then, many of them for orphan or rare diseases but also for cancer and so forth. But the data, even if it's Phase 2, must be convincing."

"The science now can't be any better for developing new medicines and for improving manufacturing. We are hopefully on the verge of revolutions in both those areas."

Janet Woodcock, director of the Center for Drug Evaluation and Research (CDER) at the FDA

Data quality in general needs industry's attention, Woodcock says. Academic data is especially problematic, with some estimates that up to 50 percent of it cannot be reproduced. She believes pharma companies are much more careful about validating the research data they generate, considering the money at stake in selecting development candidates.

Yet, she says, strange as it may seem, companies still routinely fall short with clinical research data, often because of poor practices by individual investigators. But poor trial design, rather than poorly run trials, may compromise trial results as well, she believes. A solution? More data transparency, ideally shared through a "trusted third party" or custodian as proposed by GSK and others, would allow companies to learn from past errors and successes, according to Woodcock.

GHOST OF THE SEQUESTER

The ability of the FDA and CDER to conduct industry-friendly policies and services ultimately rests on the federal budget. Although the end-of-year budget deal restored some level of stability to the process, the same political powers that forced sequestration and shutdown on the U.S. government continue to promise more confrontation than compromise. Uncertain funding in the future can be more intimidating than sure scarcity in the present.

"We would like to receive a budget each year at the beginning of the fiscal year that we can execute with confidence," says Woodcock. "That hasn't happened in a very long time. When we do get the money, we don't know how much of it we will get because of the various cutbacks, sequestration, and so on. All this uncertainty makes it very difficult to manage a program as complicated as a drug regulatory program. So, the situation is very suboptimal. But we just do the best we can because we have an important mission."

Framing the budget as just another problem, among many to be solved, seems like a sensible solution for an absurd predicament. For example, Woodcock says the funds from the PDUFA programs were sequestered last year, "So we didn't get the increase that we negotiated very carefully with the industry for additional services we would provide. Now we can't provide services at the level we promised."

As always, however, and in all our conversations with Woodcock through the years, she remains not only optimistic but also sincerely excited about her job and the agency she has helped shape in that time. "The science now can't be any better for developing new medicines and for improving manufacturing. We are hopefully on the verge of revolutions in both those areas, which will create great benefits for the public, and the industry you see today will not be the industry you see in 10 years." It is a safe bet that, during most of the changes she foresees, Janet Woodcock will be there to help them along.

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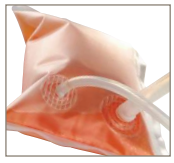

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Lilly's Approach To The CLINICAL TRIAL PARADOX

BY ROB WRIGHT

When I sat down with Eli Lilly (NYSE: LLY) and Company's chief medical officer and co-leader of the company's Development Center of Excellence, Timothy Garnett, it was shortly after the drugmaker's annual investment community meeting where bankers grilled the leadership team with questions. Although sensationalistic headlines of Lilly's recent Phase 3 trial failures (e.g. the antidepressant edivoxetine) may have attracted the eyes of the uneducated, those of us in the industry know that long-term success in drug development — like investing — requires patience and perseverance. That's why it should come as no surprise that when I asked Garnett what he is doing to speed up clinical trials he responded, "Sometimes you have to slow down in order to speed up." Indeed, a counterintuitive notion when you consider Lilly will be losing patent exclusivity for another one of its blockbusters, Evista, this March. Yet during our interview Garnett, a 20+ year industry veteran, made a strong case for following this paradox (slowing down to speed up) if improved productivity and performance is your goal.

SLOW DOWN TO SPEED UP

Businesses fearful of losing their competitive advantage make the common mistake of spending too much time and resources seeking ways to pick up the pace, when instead they should try slowing down. Here's why. A *Harvard Business Review* (HBR) study of 343 businesses revealed that companies that embraced business-accelerating initiatives in order to gain an edge ended up with lower sales and operating profits than those pausing at key moments. Firms that "slowed down to speed up" improved their top and bottom lines, averaging 40 percent higher sales and 52 percent higher operating profits over a three-year period.

These findings appeal to Garnett who revealed Lilly's average lifetime development cycle for a molecule is about six months longer than the industry average of 12 years. The company wants to shorten its clinical development

time by five years by the year 2020. But Garnett admits there is much work to be done and unfortunately no magic bullet. "We know there are a number of approaches we can take to really improve our chances of clinical development," he states. One of these is to make sure you have done the right Phase 2 studies. According to Garnett, many companies go into Phase 3 without having performed the proper experiments. As a result, these companies end up having to do large Phase 3 studies. "They are essentially doing their dose findings in Phase 3," he says. "You can't afford to do that. Though one of the most basic components of Phase 2 studies, dose finding is also that which gets compromised most frequently." Rather than trying to rush through Phase 2 in an attempt to get quicker approval, Garnett advises taking more time in Phase 2 if you want to accelerate your Phase 3 study. In addition, he suggests looking closely at comparator data. "In the current environment it is no longer just about proving efficacy and safety, but about proving you have an innovation that is an advance on what is already available," he states. Garnett thinks the sooner you can get comparator data the better. Then, be honest with yourself about what you find, making sure your study is big enough to give you a sense of confidence that it is reproducible. Garnett attributes many of the recent Phase 3 failures to companies failing to slow down in Phase 2 or seeking a shortcut. "Researchers have not confirmed they have a differentiated molecule with a strong enough signal and, unfortunately, discover this fact in Phase 3," he says.

Conducting scenario planning during Phase 2 may have the appearance of slowing you down, but will actually speed you up when entering Phase 3. Garnett says, "By scenario planning during Phase 2 you are attempting to anticipate various outcomes, potential development programs, and so on, based on a subset of data." Doing so, he says, can accelerate a company's ability to enter Phase 3 by a year or more. He admits there are certain limits to how quickly you can move from Phase 2 to Phase 3 (e.g. meeting with the FDA), yet he admonishes, "There is really no excuse for it to take a year or a year and a half, which is quite common."

One of the challenges with attempting to implement clinical trial scenario planning is that, often, scientists want full data — to ensure certainty — before planning. Garnett suggests communicating the value of scenario planning to scientists in not only time and dollars saved, but the potential revenue generated for your company. "I think you can easily shave six to nine months off of every development program if you do it properly, and that means getting the drugs to the patients sooner."

STAYING ON TASK

When I had the opportunity to visit Lilly's global corporate headquarter in Indianapolis, I was impressed with the size of its campus. With 10,000+ employees, it was larger than the town in which I grew up. However, Chief Medical Officer Tim Garnett quickly reminded me it is not the biggest company in the pharmaceutical industry. Though still in the top 10, Lilly generates about one-third the revenue of J&J and half that of Merck. "So when it comes to therapeutic focus, we have to be pretty disciplined on where we choose to play," he states. For the moment, those areas are primarily neuroscience, diabetes, endocrine oncology, and auto-immune disorders.

Having a focused approach and staying on task can prove to be a challenge when it comes to drug discovery. "You don't always know the potential indications of the compounds when you are first discovering them," Garnett states. "History points us towards many molecules that weren't what we thought they would be." For example, Pfizer was seeking a new treatment for angina, but instead found a medicine for erectile dysfunction — Viagra. Similarly, Lilly's blockbuster osteoporosis drug, Evista, started off as an oncology agent. "I think there was a time when industry had the freedom to run with those potential new therapeutic areas and indications," reflects Garnett. "These days, we are a little more cost conscious." To stay on task, Lilly seeks to find alternative ways of developing drugs — such as partnering with the NIH.

In September 2013, Lilly announced it had received financial support from the NIH Therapeutics for Rare and Neglected Diseases (TRND) program for its preclinical-stage research of a potential treatment for hypoparathyroidism, which causes a lack of parathyroid hormone. This can lead to a number of symptoms, such as anxiety, depression, cataracts, muscle cramping, convulsions, and irregular heartbeat. Lilly was the first major pharmaceutical company to gain support from the TRND program, which seeks to de-risk development of rare disease treatments. Rare disease drug development is clearly not a focus for the folks at Lilly, but neither is turning down the opportunity to deliver timely and valued medicines to patients. "We have a finite capacity to spread the R&D dollars," Garnett reminds. "We can't afford to place our bets too broadly, but we don't want to be turning down the next potential Evista." Participating in this type of program, as well as developing others (e.g. Lilly's open innovation platform), facilitates staying on task and therapeutically focused, while also allowing for the serendipity of drug discovery.

PRACTICALITY OF PATIENT CENTRICITY

It should come as no surprise that treating a person as a human being, as opposed to a number, results in better patient outcomes. Why can't these same patient-centered healthcare delivery principles be applied in the clinical trial space? "We talk a lot on the commercial side about patient experience as being one of the triggers for why a patient presents for treatment," says Garnett. Lilly is starting to apply lessons learned on the commercial side in the clinical trial world — starting with patient recruitment.

"The biggest determining factor of how long it is going to take to run a Phase 3 study is the amount of time it takes to recruit patients," says Garnett, who sees no reason why companies can't have patients ready from the start. One way to do that is to get better at engaging with patient support groups, something done well by rare/orphan disease drugmakers. "Why can't you do that for Alzheimer's?" he asks. "There is

"The biggest determining factor of how long it is going to take to run a Phase 3 study is the amount of time it takes to recruit patients," says Timothy Garnett, chief medical officer, Eli Lilly

no shortage of Alzheimer's patients." Garnett believes if patient engagement works well for healthcare providers like hospitals, why not take the same approach when trying to recruit for clinical trials. "We are looking at running a Muscular Dystrophy trial. As a result, we are in very close contact with MD support groups," he shares. "We know that when we are ready to start, we will have every patient ready to be screened and entered." Getting better at recruiting is a critical component to successful clinical trial execution. So too is getting folks to want to participate more than once.

One of the realities in the clinical trial space is the majority of patients and investigators who participate in a study do so only once. "What factors make this an experience participants often don't want to repeat?" asks Garnett. "How can we become more patient and investigator friendly in an ever increasingly competitive environment?" Garnett thinks the industry needs to challenge itself to improve the patient and investigator experience. One solution involved the collaboration between Lilly, J&J, and Merck to share trial investigator good clinical practice (GCP) training information. Prior to this, if investigators worked for one of these companies, they had to do three separate, and essentially the same, training sessions. The collaborative effort to share the GCP info was well received by the industry. It eliminated redundant training, saving money for everyone, and the investigators' most valuable resource — time. TransCelerate BioPharma, which now numbers nearly 20 member companies, built upon this in developing its site qualification and training resources.

There are a number of ways to improve the clinical trial experience for patients. For example, participating in a placebo-con-

trolled trial is not very appealing for someone seeking real therapeutic benefits. Garnett admits in early phases it is difficult to avoid the placebo problem. Though it can't always be eliminated, it can be mitigated through modeling via new statistical approaches. "These models allow you to create a very large virtual placebo group so the actual placebo group can be small."

Garnett believes improving communication with participants can also be helpful — especially when you consider the likelihood of increased reliance on patient-reported outcomes. A means of doing this will be through the use of patient-friendly devices (i.e. their smartphone) to gather information and provide real-time feedback. Device familiarity and real-time feedback can create greater patient engagement. "As a result, it is a little easier to educate them about what the clinical research is all about," he states. "Further, they become an active partner, as opposed to a passive participant."

He says another opportunity for improvement is the reduction of the number of pages in informed consent documents, which can range from 20 to 50+ pages. The key is to try new approaches and have a willingness to learn from failures as well as successes.

LEARNING FROM FAILURES AS WELL AS SUCCESSES

"Like every other company, Lilly has had Phase 3 failures, which are extraordinarily expensive and demoralizing for an organization," admits Garnett. For example, the company announced in December that edivoxetine did not meet primary end points of Phase 3 clinical studies as add-on therapy for major-depressive disorder. Prior to this, Lilly announced Phase 3 failures of enzastaurin for large B-cell lymphoma, solanezumab for Alzheimer's disease, and ramucirumab for breast cancer. Despite these and other setbacks, the company continues to plow forward, announcing an additional late-stage trial of solanezumab and an FDA priority review of ramucirumab for the treatment of gastric cancer. The lesson to be learned here isn't to fear failure, but rather to learn from it and overcome — a key longstanding component of the Lilly culture. For example, in 1999 Lilly halted trials of an experimental chemotherapy drug, Alimita, after discovering three significant adverse events. Many thought this might be the end of Alimita. However, researchers did not want to give up on the drug because of the strong evidence it could reverse tumor growth. In this case, persistence paid off with the drug gaining FDA approval in 2004. Today, Alimita has four different FDA-approved cancer indications. More recently, positive Phase 3 results for Lilly have led to a record seven regulatory submissions of four molecules in 2013 and the expectation of launching three drugs in 2014 — empagliflozin, which was codeveloped with Boehringer Ingelheim for type 2 diabetes; dulaglutide, a once weekly treatment for type 2 diabetes; and ramucirumab.

Just as Lilly continues to learn from its failures, it also does so from its successes. The company designed and conducted an adaptive, dose-finding, seamless Phase 2/3 trial study with dulaglutide. According to Garnett, the design was outstanding, something to be proud of, and probably saved the company about a year on the entire Phase 3 program. "But that savings was lost because we spent a year gaining agreement on the design with the FDA, as well as internally," he laments. Being one of the first companies to do a substantial Phase 2/3 adaptive trial design may have been one of the reasons why it took so long. "We need to take that learning and apply it to the next program. We paid a high price in terms of time because not only did we need to familiarize regulators to the approach, but internally, we needed to develop a level of comfort and confidence with the adaptive design concept," Garnett states. "There were a lot of people within the organization who were nervous about it." The lessons learned from this success include gaining alignment on the design internally first, and communicating your intentions with regulators clearly, frequently, and proactively throughout the process. Garnett feels there is no question the dulaglutide adaptive trial design saved the company time. In addition, he suspects more companies will begin using adaptive trial design because it provides high-quality data, reduces risk, and results in a much clearer direction for Phase 3 trials. "This is true as long as you aren't spending too much time on getting folks internally aligned on the design," he concedes. Obviously, there is a fine line to managing the clinical trial paradox when determining how much you need to slow down if you want to truly capitalize on the possibility of being able to speed up while improving productivity and performance. Having produced the strongest pipeline in its 137-year history, Lilly appears to have struck the right balance. At this writing, the company had 13 potential medicines in Phase 3, the final stage of clinical study, or under regulatory review. In addition, Lilly has 26 more projects in Phase 2, which is five times more than it had a decade ago. For the time being, slowing down and staying the course seems a sound strategy.

SO YOU WANT TO BE A CHIEF MEDICAL OFFICER?

Since completing his medical degree, Lilly's chief medical officer (CMO), Tim Garnett, has spent the bulk of his professional career working in the pharmaceutical industry. One of the greatest challenges he sees physicians face when making the decision to enter the industry is adapting to the corporate culture. "Physician training and practice are based on the concept of individual decision making and personal accountability," he attests. "However, pharma companies are based on collective decision making and joint accountability." This is a concept Garnett thinks many physicians struggle with when joining pharma companies. He says it also can prevent talented medical doctors from realizing their true potential to becoming industry leaders. "I initially struggled with the decision-making processes of the companies in which I worked," he admits. "But success in this industry requires an understanding of the corporate culture and your role within the company. Once I came to understand this, I became less frustrated with what I saw as slow or illogical decision making, and I was able to more constructively contribute to the organization's mission." If you want to be a successful CMO, Garnett believes you need more than just the technical ability to perform the role. "Understand how decisions are made and influenced in an organization so you can best represent the medical function at the highest level," he advises.

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companies to watch - 2013 Roundup

Snapshot analyses of selected companies developing new life sciences products and technologies

By Wayne Koberstein, executive editor

Each month, Companies to Watch spotlights one company that has received scant press coverage but, nonetheless, contains an especially interesting story. At the end of this past year, we thought it would be useful to check in on our 2013 Companies to Watch with a "roundup of updates" on how all of the companies have fared since our coverage. We contacted each company, asking for responses to three questions:

- What have been the most important developments for your company since it was featured in the ___ 2013 edition of *Life Science Leader*'s Companies to Watch?
- How would you summarize, in a single quotable sentence, the present status of the company in light of those developments?
- What developments or milestones do you anticipate in 2014?

We received full responses from 11 of the 12 Companies to Watch featured in 2013. Their input varied from highly cautious and formal to genuinely "excited." Together with our own brief summaries of the companies' progress, we offer their assessments and updates here, in our 2013 Companies to Watch Roundup. (Company statements appear in quotes.)

January — Acetylon

Careful target selection — meant to help surround and overcome tumor cells' defenses by cutting off one of two pathways they use to degrade waste proteins — was the theme of our CtW analysis of Acetylon early last winter. Since then, the tune has changed to following up on promising clinical data — and with a new strategic partner. President and CEO Walter Ogier summarizes the company's current status: "Acetylon is capitalizing on its recent agreement with Celgene and the positive activity we've seen in clinical and preclinical studies to date by significantly expanding our clinical program for selective HDAC6 inhibitor, ricolinostat, with advancement of our ongoing trials plus new combinations in multiple myeloma and a new indication, lymphoma."

DEVELOPMENTS TO DATE

- July: Acetylon entered into an exclusive strategic collaboration with Celgene, structured with $100 million payment up front, a minimum $500 million future cash purchase price if or when Celgene exercises its option to acquire, plus up to $1.1 billion in regulatory and sales milestones.
- December: Reported that its selective HDAC6 inhibitor, ricolinostat (ACY-1215), showed "striking" signs of therapeutic activity in its Phase 1b trial in combination with Revlimid (lenalidomide) and dexamethasone for the treatment of relapsed or refractory multiple myeloma. In the interim data, 69 percent of patients reported partial or better response. Positive results on ricolinostat also came from interim data in a Phase 1b trial in combination with Velcade and dexamethasone, as a single agent in lymphoma, and in separate combinations treating either multiple myeloma or lymphoma: with each of three proteasome inhibitors; with two PI3K inhibitors; and with a Bruton's tyrosine kinase inhibitor.

COMING IN 2014

- initiation of two additional clinical trials of ricolinostat for the treatment of multiple myeloma in combination with standard-of-care drugs
- initiation of a clinical trial of ricolinostat for the treatment of lymphoma
- completion of the Phase 1b portion of the currently ongoing trials in combination with Revlimid and Velcade and initiation of Phase 2 clinical development

February — Auspex

Gone dark. Not officially, but for all practical purposes, this developer of deuterium-based compounds has ceased shedding light on itself for journalists. Repeated attempts to contact the company about this report went unanswered. The long-time PR person for the company was let go a few weeks after a major management turnover. In October, Pratik Shah replaced former CEO Larry Fritz, who left at mid-year. At the same time, the company replaced the COO and CFO, and it added a "chief development officer." The company has issued no press releases or public statements since that time. The following comes from limited public disclosures:

DEVELOPMENTS TO DATE

- March: Square 1 Bank granted a terms loan, or "credit facility," to Auspex to help fund Phase 3 clinical trials for its lead compound SD-809.
- July: initiation of Phase 3 Trial of SD-809 for treating chorea associated with Huntington's disease, with opportunities in two additional indications, tardive dyskinesia and Tourette's syndrome
- October: major management turnover; replaced most of the management team including the CEO, and added new officers

March — Centyrex

A company inside a company. Much of J&J's pharma group consists of small units enveloped or overlapped with other parts of the organization. Centyrex has been an exception. It's an entrepreneurial business more or less making it on its own as any other bio start-up. But having developed its novel molecular-scaffold Centyrin platform to the point of creating original products, it is becoming more integrated into the Janssen R&D Biotechnology Center of Excellence (BCE). Summarizing the company's progress, CEO Robert Hayes says, "Centyrex has delivered on its goals to develop a therapeutic platform that complements the strengths Janssen R&D has in monoclonal antibodies." The company remains vague about the therapeutic areas and entities it is pursuing, as reflected in its responses for the CtW Roundup below.

DEVELOPMENTS TO DATE

- "making good progress on therapeutic targets in the oncology space"
- "Janssen R&D made the decision to continue support

of the Centyrex venture by transitioning the technology into the Janssen R&D BCE and expanding the use of the Centyrin platform." That means Centyrex will essentially feed the pipeline with newer, early-stage products, handing them off to the BCE at the clinical development stage. The BCE has also assumed responsibility for Centyrin products already in development, as well as taking in a handful of Centyrex employees.

COMING IN 2014

- "We look forward to further studying and progressing our work in oncology. We also look forward to applying the Centyrin technology to targeted therapies that have increased safety and efficacy."

April — StemCells

"Things are now starting to get really interesting," says CEO Martin McGlynn about the company's new-year status. He cites early clinical data from trials of its proprietary purified human neural stem cells (HuCNS-SC) in spinal cord injury, dry AMD (age-related macular degeneration), Pelizaeus-Merzbacher disease (PMD), and Batten disease. "Confirming the extraordinary results seen in the various animal models used to justify the initiation of the clinical trials now underway or already completed." Phase 2 trials will get underway in 2014, with interim efficacy results planned for mid-2015.

StemCells also recruited some industry veterans, such as Eliseo Salinas, M.D., as EVP R&D; and Greg Schiffman, former CFO of Dendreon. Earlier in the year, the company built and commissioned its own state-of-the-art cGMP cell-processing facility in Sunnyvale, CA. It raised money in several ways, receiving the first tranche ($3.8 million) out of a $19.3 million California Institute for Regenerative Medicine funding of an IND (investigational new drug) for restoration of lost memory in Alzheimer's disease, a $10 million loan from Silicon Valley Bank, and $25.3 million in equity-based financings.

DEVELOPMENTS TO DATE

- August: Promising two-year data from patients with Pelizaeus-Merzbacher disease (PMD) treated with HuCNS-SC cells began showing gains in neurological function and more pronounced myelination compared to year one.
- June – October: Phase 1/2 clinical trial for chronic spinal cord injury was expanded to the U.S. and Canada. Eight of the 12 patients in the current study already have been transplanted in Switzerland.
- September: The FDA approved the expansion of the number of clinical sites from two to five in the company's Phase 1/2 dry AMD trial and a five-fold increase in the cell dose. Seven of the 16 patients in the study already have been transplanted.

COMING IN 2014

- determine next steps for the advancement of the PMD program
- complete dosing in Phase 1/2 chronic spinal cord injury and dry AMD trials
- initiate controlled Phase 2 chronic spinal cord injury and dry AMD trials
- report data from the current Phase 1/2 spinal cord injury and dry AMD trials

May — Immune Pharmaceuticals

Survival by merger. In the spring when we covered this Israeli developer of in-licensed cancer and inflammation drugs, the company was in the early stages of a merger with troubled EpiCept, primarily with the aim of buying an entry into the U.S. public capital markets. Since then, its focus has been divided between completing the merger — actually structured as a reverse merger — and pushing along its pipeline products: chemo-related pain drug AmiKet and chemokine blocker bertilimumab. Reading between the lines of its roundup responses, it seems the company has made progress on both fronts, as CEO Daniel Teper expresses in this summary of the company's status: "Immune has the ability to finance through public markets and execute its clinical milestones in 2014 to 2015."

DEVELOPMENTS TO DATE

- August: closed merger with EpiCept with Immune historical shareholders owning approximately 85 percent of the combined company on a fully diluted basis
- November: listed on OTCQX (New York) and NASDAQ OMX First North Premier (Stockholm)
- During 2013: identified and planned Phase 2 clinical trials for bertilimumab in an orphan indication (Bullous pemphigoid), which will add to the already launched Phase 2 trial in ulcerative colitis

COMING IN 2014

- up-listing to NASDAQ (New York)
- full two-year financing through secondary public offering
- partnering of Phase 3-ready AmiKet with fast-track designation for chemotherapy-induced neuropathic pain
- Phase 2 data for bertilimumab in Bullous pemphigoid, an orphan autoimmune skin disease

June — Cempra

A blockbuster in its pipeline? That was the central question in Cempra's CtW in mid-2013. Proof is everything, especially for a company that claims it has created both a new class of antibiotics, the "fluoroketolides," and a new way of delivering them, "loading dose formulation," exemplified by its lead drug candidate, oral solithromycin. Cempra's founder, President, and CEO Prabhavathi Fernandes says, "We have reached significant milestones in the second half of 2013, propelling our company to its next stage of development." On the heels of its June CtW, the company raised $54 million in a public offering of common stock and secured up to $58 million from a BARDA (Biomedical Advanced Research and Development Authority, HHS) drug development contract to develop solithromycin for pediatric use and biodefense.

DEVELOPMENTS TO DATE

- September: Oral and IV solithromycin became the only antibiotic to receive the FDA's qualified infections product designation (QIPD) for the treatment of CABP (community-acquired bacterial pneumonia). "Solithromycin demonstrated safety and tolerability in patients with chronic liver disease without a change in pharmacokinetics so that there will be no change in dosing of patients with hepatic insufficiency."
- October: Taksta gained orphan drug designation for the treatment of prosthetic joint infections.
- November: Preclinical results suggested solithromycin may provide effective prevention and treatment of intrauterine infections during pregnancy. "No new antibiotic has been developed for infections in pregnancy in over 20 years."

COMING IN 2014

- Mid-year: release of Solitaire-Oral Phase 3 trial top-line data in CABP

July — Soligenix

Biodefense drives this company. With U.S. government support, Soligenix continues to develop an anti-ricin vaccine, a treatment for radiation poisoning, and other products based on its ThermoVax platform. In September, it nearly doubled its previous funding with a new $23.6 million BARDA contract and a $6.4 million NIAID (National Institute of Allergy and Infectious Diseases) contract for its radiation drug OrbeShield. Not bad for a company with a tiny market cap of only about $40 million (twice what it was in June). "Now with the proper funding in hand, our primary focus moving into 2014 is on the quality execution of all our development programs," says Christopher Schaber, chairman, president, and CEO.

DEVELOPMENTS TO DATE

- December: initiated two Phase 2 clinical studies: SGX942, the company's first-in-class innate defense regulator technology in oral mucositis; and orBec in chronic GI graft-versus-host disease (GVHD), supported by a $300 million NIH grant

COMING IN 2014

- initiation of a Phase 2/3 clinical study with SGX203 in pediatric Crohn's disease and a Phase 2 clinical study with SGX201 in acute radiation enteritis
- completion of oral mucositis Phase 2 clinical study and chronic GI GVHD Phase 2 clinical study
- preclinical data supporting vaccine/biodefense programs, most notably OrbeShield, RiVax (ricin toxin vaccine), and ThermoVax (vaccine heat stabilization technology

August — CogRx (Cognition Therapeutics)

Still a tough cookie in a tough area — this developer of neuroscience drugs for Alzheimer's disease (AD) and possibly other conditions, such as Parkinson's and ALS, has been chalking up a series of firsts since its appearance in Companies to Watch. "CogRx's small molecule drug candidates represent the first ever reported to directly target toxic Abeta oligomer proteins and their receptors and stop their bad effects on memory," CEO Hank Safferstein says. "CogRx is rapidly advancing these exciting drug candidates toward clinical trials."

DEVELOPMENTS TO DATE

According to the company, CogRx has:

- become "the first group to demonstrate siRNA (small interfering RNA) knockdown of a specific receptor on neurons and glia; lowers oligomer binding more than 90 percent
- become "the first group to demonstrate dose-dependent reduction in Abeta oligomer binding in post-mortem human AD brain sections using our proprietary small molecule drug candidates and antibodies raised against specific receptor epitopes"
- "developed first-in-class, highly brain-penetrant, orally bioavailable small molecule receptor antagonist (IND candidates) that stop memory deficits in Alzheimer's disease models"

COMING IN 2014

- conducting a pre-IND meeting with the FDA with the goal of filing an IND by the end of the year
- closing on Series B to fund the AD program into the clinic and into patients diagnosed with Alzheimer's disease
- "Use of funds will also support further mechanistic work on the soluble Abeta oligomer protein receptor/receptor complex we have identified and its potential role in other CNS diseases characterized by abnormal protein aggregation"

September — Esperion Therapeutics

On track and on target. Another company with blockbuster potential, and one of the fresh crop of IPOs in 2013, this drug developer aims at the still needy area of cholesterol reduction. Esperion's strategy is carefully planning studies and trials to prove its concept and define its target patient groups. "We are on track to deliver, in 2014, top-line results from two large robust Phase 2b clinical trials that will transform Esperion into the leading developer of an oral, once-daily, small molecule LDL-C (LDL cholesterol) lowering therapy for the treatment of patients with hypercholesterolemia," says CEO Tim Mayleben. He says the company set clear goals for its LDL-C lowering drug, ETC-1002, in 2013 and achieved all of them on time.

DEVELOPMENTS TO DATE

- October: commenced a large Phase 2b study of ETC-

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1002 in patients with or without statin intolerance
• November: announced positive Phase 2a results for ETC-1002 as an add-on to statin therapy
• November: at the American Heart Association meeting, presented positive Phase 2a results in patients with a history of statin intolerance

COMING IN 2014
• initiate robust Phase 2b ETC-1002 add-on to statin therapy study (Q1)
• announce results from two Phase 2b ETC-1002 clinical trials (Q4)
• announce top-line results from nonclinical studies (Q4)
• target several important medical meetings for data presentations (throughout 2014)

October — Inovio

Into and beyond a big partnership. A small-cap player in the cancer vaccine space, Inovio was just beginning its co-development alliance with Roche. Now, as it cements the relationship in clinical trials, the company is thinking even more strongly beyond its first partnering deal, anticipating others on the horizon. Contacted just three months after our coverage of Inovio, CEO J. Joseph Kim explains, "We completed our first Big Pharma partnership and progressed our Phase 3 program to the point of getting data. By all measurements — financial, technical, and clinical — it was a banner year. We expect 2014 to be an even better year and dwarf our 2013 accomplishments." Kim agrees a large factor in attracting Roche's interest is the potential of the company's T-cell targeting and boosting technology in future combination cancer immunotherapies — a potential $35 billion market, as projected by Citibank. Now, he says, Inovio is in "deep discussions" with Roche's peers in Big Pharma about partnering in that area and others.

DEVELOPMENTS TO DATE
• November — December: completed Roche codevelopment alliance, involving two of Inovio's clinical-stage products, one (INO-5150) for prostate cancer and the other (INO-1800) for chronic hepatitis B, a common cause of cirrhosis and liver cancer
Present: In addition to focusing on lead products such as INO-3100 and INO-3112, the company is working with Roche to take INO-5150 to the clinic in a Phase 1 trial. INO-1800 for chronic hepatitis B is about a year behind.

COMING IN 2014
• First half: launch Phase 1 clinical trial of INO-5150 for prostate cancer, triggering the first milestone payment from Roche
• First half: launch Phase 2 trials of nonpartnered product INO-3112, in advanced cervical and advanced head and neck cancers. Also, run small, uncontrolled exploratory trials to prove comparable T-cell generation in other cancers and bolster the Cellectra Electroporation Delivery Technology platform concept
• Midyear: report results from a current double-blind placebo-controlled Phase 2 efficacy study in cervical pre-cancer involving 150 patients — the first Phase 2 results from the company's pipeline

November — Vivaldi Biosciences

Victory in a sea of failures. That is Vivaldi's aim, as it plies its course in developing the only live vaccines among many competing candidates for prevention of pandemic and seasonal flu — namely, its live attenuated influenza vaccines (LAIVs). With few updates since Vivaldi's end-of-the-year appearance in Companies to Watch, CEO Douglass Given emphasizes the company's goals for the new year, which include raising more money. "Vivaldi's strategy to demonstrate clinical proof-of-concept for its LAIVs for seasonal and pandemic influenza is realizable with venture financing, and offers investors an attractive valuation, potential for significant ownership, and an exit opportunity through partnering with a pharmaceutical company." Vivaldi is pursuing a cost-effective means of advancing its LAIV pipeline candidates, hoping to partner for further development and commercialization.

COMING IN 2014
• follow-on investments in Series B financing round
• initiate program to develop a preclinical LAIV candidate for highly pathogenic H7N9 influenza
• advance clinical development of LAIVs for seasonal influenza to address unmet medical needs in elderly and/or pediatric populations

December — Proteon Therapeutics

Relief for dialysis patients. That is what this developer of a drug to address vascular access failure intends to bestow. The last company to be featured in 2013 Companies to Watch has had scarce time for subsequent developments. But it has plenty of hopes for the new year. "Proteon is preparing to initiate Phase 3 of PRT-201 to address vascular access failure in hemodialysis patients, a serious unmet medical need in an orphan population," its president and CEO, Timothy Noyes, says modestly. Proteon is currently identifying sites to participate in the Phase 3 trial of PRT-201 in chronic kidney disease patients undergoing surgical placement of an arteriovenous fistula for hemodialysis. The trial is scheduled for a mid-2014 commencement. About the same time, a Phase 1 trial investigating another application of PRT-201 will yield data.

COMING IN 2014
• secure financing to complete AVF Phase 3
• initiate enrollment in AVF Phase 3
• conclude peripheral artery disease (PAD) trial and report data

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How To Launch A Biotech Start-Up

By Suzanne Elvidge, contributing editor

Whether in the early days of DNA cloning in the 1970s, or the boom of the 1980s and 1990s, biotechnology and biotech start-ups have represented the cutting edge of the biopharma and healthcare industry. For those fascinated by the idea of entering the hurly-burly start-up world, Index Ventures hosted "Playground" in October 2013, covering the entire process, from thinking up the idea for a new company to planning for the exit.

FRAMING THE IDEA

There are start-ups being created all the time, from university technology transfers to company spinoffs. And all of these are based on what seem — at the time, at least — to be brilliant ideas. "The idea needs to be far enough from conventional wisdom to be exciting, but not so far that people won't listen," says Stelios Papadopoulos, former vice chairman at Cowen & Company, an investment banking services firm.

So what differentiates an idea that will make it through to a trade sale or IPO, and the one that falls at the first hurdle? And more importantly, how do you tell the difference? To have a realistic chance of making it through, a company needs to start with a robust technology. The technology needs to meet the following conditions:

- It must be novel enough to patent; otherwise, there will be nothing to fund.
- The company must have freedom to operate in the given arena, with rights to the IP and no overlapping patents.
- There must be a good biological and clinical rationale behind the idea, and it must have at least the first signs of efficacy and safety.
- The target market must be underserved, or the potential product must have clear advantages over those already in the market, such as lower cost, a more durable response, easier to use, or more convenient dosing and administration.
- The predicted development path must be consistent with the potentially available funding — meaning a fast R&D timeline and relatively small clinical trials.

Once the idea has been formulated, the entrepreneur next has to validate the market. As Ben Miles, who created Flow Microfluidics (a company that fabricates microfluidic chips to a customer's design) while still a doctoral student, says, "There is no point working on a technology if there is no market."

The route to market validation may not always be smooth. Miles initially tried to validate the potential market for his technology by creating a website where people could sign up, but only eight people registered, and only one of them converted into a customer. He found more success when he actually spoke to people in the relevant markets.

FINDING THE FUNDING

Because biotechnology companies are capital-intensive and very heavily regulated, and the research often has a long timeline, funding is vital, as Kevin Johnson, partner, Index Ventures, explained, "Companies need cash, or there is no company." So, the next step is talking to investors. But before negotiations actually begin, it is important to take time to think about what the investors are looking for, and make sure that the idea behind the company fits what they need.

The aim of a venture capitalist (VC) is to fund an idea that will provide a return — usually around $3 to $4 for every $1 invested — in order to cover the value of the fund and the VC's fee, and return a dividend to investors. In order to do that, ideas need to be both outstanding and strategic. Unpacking this concept further, an idea has to be outstanding not only today, but also in 5 or 10 years, when a lot may have changed in the science or the market. To be considered strategic, an idea has to be able to unlock a new market, or meet a critical, unmet need. Being able to fulfill both of these criteria will increase a company's chances of getting funding. However, while it may seem that the investor always holds the strongest card, it is important to remember that the fate of the investor really is in the hands of the entrepreneur.

Investors are about more than just a supply of cash. They can also provide access to a network of contacts and routes

to finding other sources of funding. This is why it is important to select the investors carefully, rather than just picking the first ones who show an interest. Get as much information as possible, through desk research and by talking to other entrepreneurs, as well as by asking the right questions of the investment team.

After all this, it's worth remembering that however good the idea is, funding isn't guaranteed. As Graham Defries, partner at Dechert LLP, explains, "Great ideas don't necessarily always attract money."

MAKING AN EXIT

VCs are often focusing on the end, considering how to make a profitable exit for themselves and for their investors. This may be described in terms of a "realistic cash distance to exit," or more simply, how much money there needs to be put into a project before something with a commercial value emerges. "The VCs have to be certain of an exit, and this should be visible within the first 5 years of a 10-year fund," says Johnson.

One of the key decisions is how to make the exit. Once upon a time, exits used to be relatively straightforward, involving a simple cash-based trade sale or an IPO. Of late, trade sales are the most likely exit route, and more often include up-front and contingency payments. However, the IPO window is opening up again. Though this is a growing opportunity, going for an IPO is a big decision for a relatively small or inexperienced company, and it takes up a lot of time — planning for the IPO process needs to begin one to two years in advance, and it involves a lot of documentation. But what makes a good IPO? Well, according to Papadopoulos, that depends. For a CEO, it's lots of cash. For a VC, it's a huge valuation. For a fund manager, it allows them to trade up. And for an investment banker, it's where everyone is happy.

As well as choosing the exit route, the timing of the exit is all-important. Exiting too early could mean not getting the full value, and exiting too late could mean missing an opportunity.

As a start-up entrepreneur, especially early in a career, it's important to get people on board. Miles managed to gain support from his peers, his supervisor, and his lab manager. "Find people who want to change the world with you," he suggests.

Surfing The Peaks And Troughs Of The Biotech Ocean

By Suzanne Elvidge, contributing editor

Since its founding 20 years ago, German biotech MorphoSys has come from a tough start as a company fighting patent battles and struggling to get funding to success as a profitable, fee-for-service organization. Today, MorphoSys is well on its way to becoming a fully integrated biotechnology company, primed to take its own products from concept to patient.

So how has the company survived through some of the most turbulent economic times the industry has seen and succeeded where many others have failed? To find out, let's start at the beginning.

MorphoSys was founded in Martinsried, Germany, in 1992 as a fee-for-service antibody company, and its team of founders included the current CEO, Simon Moroney, Ph.D. The company is based on its proprietary technology HuCAL, its human combinatorial antibody library containing several billion fully human antibodies, and a proprietary phage display technology, which it describes as "the most successful antibody library technology in the pharmaceutical industry." In 1997, the company signed its first commercial partnership, with Pharmacia-Upjohn, and followed this up in 1999 with an ongoing collaboration with Bayer.

GETTING THROUGH THE TOUGH TIMES

As many companies soon realize, early successes don't always equate to ongoing triumphs. MorphoSys and Cambridge Antibody Technology (CAT, now part of AstraZeneca) both developed antibody platforms based on phage display. In 1999, MorphoSys filed a lawsuit against CAT seeking to invalidate one of CAT's patents. In 2001, CAT filed a number of lawsuits against MorphoSys, claiming infringement of a patent covering antibody expression libraries and their generation.

After a lot of legal wrangling, claims, and counterclaims, the two companies agreed to settle in 2002. The agreement gave MorphoSys the freedom to develop and commercialize its HuCAL technologies. Under the agreed terms, CAT received an annual payment of €1 million (about $1.4 million) a year over five years, along with milestone and royalty payments for products developed using the HuCAL libraries, and an equity stake in MorphoSys.

Around this time, MorphoSys was also trying for the first time to develop its own proprietary pipeline, but was struggling to raise the funds it needed. These two endeavors combined to have a devastating impact on the company, resulting in a need to restructure. The company cut its spending on its own pipeline and changed its business plan to partner proprietary products before it moved into clinical development. It also had to reduce headcount from 120 to 91 employees. These spending cuts assured that the company could continuously operate for at least three years. As Moroney's goal had always been to develop the company's own products, this was a tough decision to make, but it allowed the company to get through the tough times.

"We went back to our core skills and refocused the company on fee-for-service. We had to downsize, unfortunately, but this meant we could work our way through the difficult times and survive. It took two to three years to get back on our feet, but I think we emerged stronger," says Moroney. "We had to accept that morale would suffer. It's important to know how to manage it. The best way to handle the situation is to be honest and explain what is going on, why it's happening, and what people should expect. When people see things play out as predicted, it restores faith and confidence."

REBUILDING AND VALIDATION

This refocusing, under Moroney's leadership, helped MorphoSys to move to where it is now — a company with a strong financial position that's able to fund its own internal development activities and still remain profitable. This rather enviable position is not one that many development-stage biopharma companies can match. The first significant step was the deal signed with Novartis in 2004 to discover and develop therapeutic antibodies using HuCAL technology. This included a €9 million (around $12.3 million) investment in MorphoSys and more than $30 million in R&D funding license fees over three years. In 2006, Novartis extended the deal until May 2011. Other partners included Boehringer Ingelheim, Daiichi Sankyo, GlaxoSmithKline, Janssen Biotech, Merck, Pfizer, and Roche.

In December 2007, the two companies announced the deal that would create new opportunities for MorphoSys by reducing its reliance on fee-for-service deals for ongoing income and freeing it up to allocate more investment into proprietary drug development. The 2007 deal, which made MorphoSys Novartis' main technology collaborator in the area of antibody discovery and development, also allowed the biotech to gain experience in drug discovery and development within the security of an alliance.

MOVING TOWARD FULL INTEGRATION

It was deal making again, this time in June 2013, that allowed MorphoSys to set itself firmly on the route to becoming a drug development company rather than a service provider. In the first-announced deal, validating its in-house pipeline of clinical-stage proprietary antibodies, MorphoSys signed an agreement licensing MOR103 to GSK. MOR103 is a fully human HuCAL antibody directed against GM-CSF (granulocyte macrophage-colony stimulating factor). It has completed a Phase 1b/2a in rheumatoid arthritis and is the first anti-GM-CSF antibody to have shown clinical efficacy in this disease. Based on promising preclinical data, MOR103 also has moved into a Phase 1b trial in multiple sclerosis.

Under the terms of the agreement, MorphoSys will receive an up-front payment of €22.5 million (around $29.2 million) in a deal that could be worth up to €445 million (around $578.2 million), as well as tiered double-digit royalties. GSK will assume responsibility for all subsequent development and commercialization of MOR103.

Perhaps more significantly, MorphoSys also announced a joint development deal with Celgene for MOR202, a fully human HuCAL antibody directed against CD38. This is in a Phase 1/2a in patients with relapsed or refractory myeloma, and also has potential in leukemias.

MorphoSys and Celgene will collaborate on the development of MOR202 in multiple myeloma and other indications, with Celgene covering two-thirds of the development costs. Under the terms of the agreement, MorphoSys will receive an up-front license fee of €70.8 million ($92 million), and Celgene invested €46.2 million ($60 million) in MorphoSys. MorphoSys may also receive additional development, regulatory, and sales milestones, as well as a 50/50 profit share in its co-promotion territory and tiered double-digit royalties outside this area. The deal could be worth up to €628 million ($818 million).

"These deals were turning points for us; they provided us with income and convinced our investors that we have the capabilities to develop our own pipeline of drugs, allowing us to raise the funding we needed," says Moroney. "Though we don't plan to initiate any new partnered programs, we will continue with our commitments to the

existing projects, and these will continue to generate royalties for us. Our plan is to work with future partners as codevelopers rather than licensing out products completely."

FINDING AND CREATING FUNDING

In September 2013, MorphoSys raised around €84 million, which it will use to fund the clinical development of MOR208, a humanized monoclonal antibody that targets CD19 and is in Phase 2 trials for the treatment of B-cell acute lymphoblastic leukemia (B-ALL) and non-Hodgkin's lymphoma. Licensed from Xencor, MOR208 (then known as XmAb5574) also has potential in other B-cell malignancies and in autoimmune disease.

The money is also earmarked for further development of MOR202 and to move other proprietary pipeline candidates into further preclinical and clinical development.

As a sign of its success, MorphoSys created a new funding initiative last year. Under this initiative, MorphoSys provides innovation capital and collaborative support for promising start-ups in protein design, generation, and screening, including technologies, targets, and compounds. In exchange, MorphoSys will seek access to innovative development candidates or technologies.

"These deals were turning points for us; they provided us with income and convinced our investors that we have the capabilities to develop our own pipeline of drugs."

Simon Moroney, Ph.D., CEO

As an example of this, MorphoSys made an equity investment in Dutch biopharma company Lanthio Pharma in November 2012. MorphoSys and Lanthio Pharma are collaborating to use their technologies to create and screen libraries of lantipeptides — therapeutics with high-target selectivity and improved drug-like properties. MorphoSys has the option for an exclusive license covering Lanthio Pharma's LanthioPep technology for drug discovery.

SECRETS OF SUCCESS

Drug development is a high-risk endeavor, with high rates of attrition between concept and market. MorphoSys' approach to reducing this risk has been to maximize the number of products and therapeutic areas in its development portfolio, which currently includes 81 products across a variety of different diseases, including oncology, autoimmune and inflammatory disease, musculoskeletal disorders, cardiovascular disease, and others. Of these, 21 are in clinical trials, with the rest in discovery and preclinical studies. While the majority of the compounds are part of partnered programs, the company's in-house proprietary projects are gaining strength. MorphoSys also has access to a number of proprietary technologies in addition to HuCAL: Slonomics, an automated process for generating double-stranded DNA triplets to create diverse combinatorial gene libraries; arYla, a platform that generates combinatorial libraries for antibody optimization; and Ylanthia, MorphoSys' largest and most recent Fab (fragment-antigen binding region) library.

Another of the secrets of MorphoSys' success is the fact that the company is, perhaps unusually, still led by one of its cofounders. After 20+ years, Moroney still displays infectious enthusiasm for what he does. "Why am I still here? It's interesting and exciting, and I feel that I can contribute," says Moroney. "Developing differentiated drugs is an exciting challenge."

Good internal communication has been a key strand of MorphoSys' story, through the good times and the bad, as well as being prepared to tackle problems head on.

"With the Novartis deal, this changed how the company worked — we switched from fee-for-service to drug development as a result of this one single big deal, and moving the company's focus brought challenges. We needed to bring people onboard with new skills and different mindsets, and the integration wasn't always easy," says Moroney. "For example, drug development requires a higher spend than other parts of the company, which caused some internal questions. It's about communicating internally and executing the research. We needed to work hard to bring everyone on board and to dovetail the new project into our existing structure. But once people understood the motivation behind the change, they rallied."

Looking back, Moroney says he has changed how he has done things over the years. However, he doesn't feel he would have done many things differently.

"There are always small things that I would change — for example, clauses in contracts — but you always have to accept some compromises in negotiation. My advice to my old self would be to do everything that we have done, but sooner," says Moroney. "It's a very exciting time for us. We have a lot of compounds approaching proof-of-concept in the clinic, and we are not far off from reaching the market. We have the opportunity to build and grow, and it has never felt more positive."

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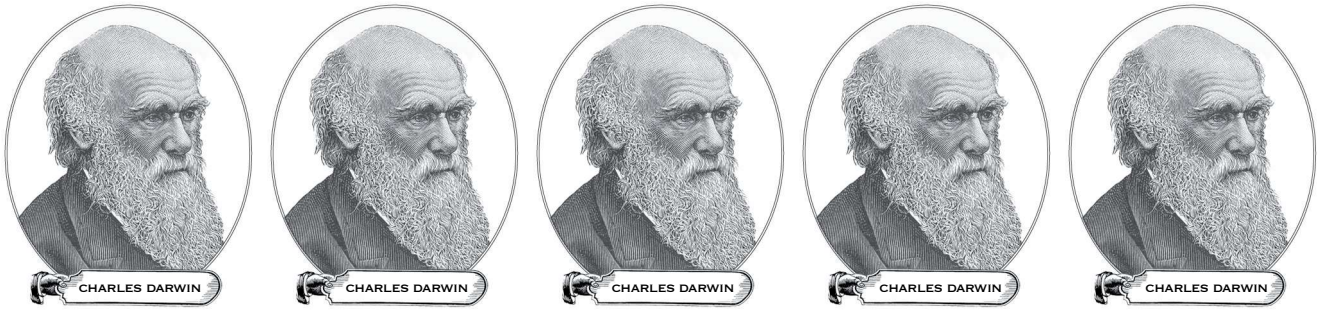

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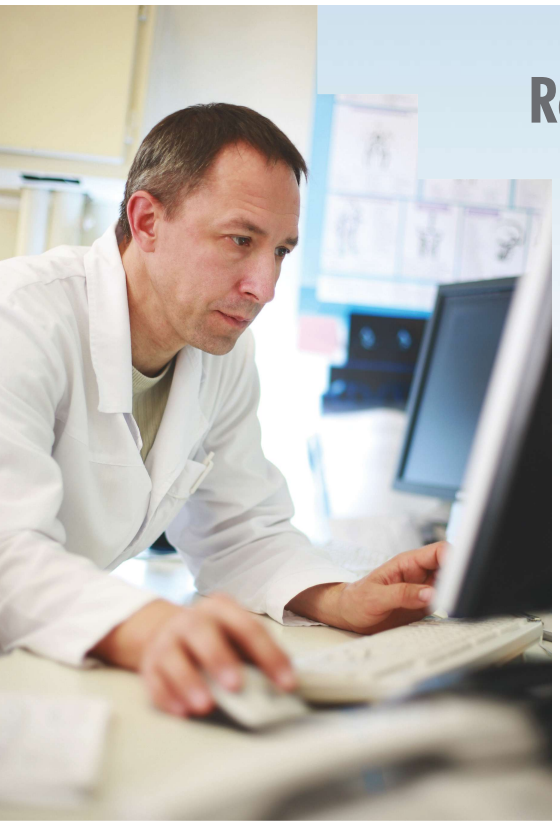

Technology Considerations To Increasing Clinical Trial Efficiencies With Risk-Based Monitoring

By Chip deVillafranca and Jonathan Andrus

When it comes to site monitoring, pharmaceutical companies have traditionally taken a conservative approach, performing frequent on-site monitoring and 100 percent verification of all data. This practice goes beyond what's required, says the FDA in its *Guidance for Industry: Oversight of Clinical Investigations — Risk-Based Approach to Monitoring,* issued in August 2013. The agency asserts that sponsors adopted current practices based on a "perception" that 100 percent source data verification (SDV) was the FDA's preferred way to meet monitoring obligations. Now it is trying to change that perception, citing academic- and government-sponsored research that has been successfully completed with less extensive on-site monitoring methods. The agency suggests monitoring strategies with a modern, risk-based approach and encourages greater use of off-site and central monitoring that employs technological advances in replacement of 100 percent SDV.

TransCelerate BioPharma, Inc. is helping to drive and speed adoption of this approach, making it the first of five key initiatives aimed at improving clinical trial efficiencies. Its *Risk-Based Monitoring Methodology* position paper issued in May states, "Current operational practices used in clinical trials are expensive and do not guarantee data quality." The consortium points to modernization utilizing technology enablers that create efficiencies without impacting subject safety. Both the FDA and TransCelerate suggest making this change allows a shift in focus from manual aspects of data quality to what's really important: patient safety, endpoints, informed consent, drug management, protocol training, and other study aspects.

In the current model, estimated costs for on-site monitoring with 100 percent SDV range between 20 and 30 percent of total study costs. A significant amount of the monitor's time is spent checking for data entry errors, when in reality the FDA is looking at the overall data quality plan, not at every data element. Previous studies have shown that only 2.4 percent of data corrections occur as a result of SDV. With appropriate metrics and remote-review techniques, reduced verification can be employed with no loss of data quality.

TECHNOLOGY CONSIDERATIONS

Comprehensive risk-driven approaches rely on visibility into clinical data and operational key performance indicators to enable centralized review and monitoring. An electronic data capture (EDC) solution that captures site activity and clinical data in real time is essential, but this must be integrated with metrics from a clinical trial management system (CTMS). Achieving a holistic view of clinical sites, both past and present performance, through robust reporting and analytic tools is the cornerstone of any risk-based monitoring strategy.

As sponsors rarely work with a single vendor, multiple eClinical systems are typically already in place. Before a new monitoring approach can be implemented, an organization must ask: "Are we able to get the data out of where it is and into an analytic system to review and act on it?" Sponsors will need the ability to view data from across all systems, such as site initiation, document approvals, subject enrollment, data capture metrics, protocol deviations, adverse events, timeliness, and staff turnover — essentially all study activity.

A system's location is immaterial as the Internet allows it to be located anywhere, whether cloud-based, on-site, or elsewhere. However, the APIs and interfaces are critical. Shifting to a strategic risk-based approach hinges on having immediate access to clinical and operational data, both current and historic. Continual assessment of data over the life of the study will indicate whether the site-monitoring plan needs adjustment.

WHAT'S YOUR DATA TELLING YOU?

Centralized monitoring allows monitors to see patterns and detect problems early. It helps them to identify whether something is meaningful and requires action, such as when a protocol change is needed or a site needs extra support. Consider the example where a monitor is looking at 100 sites and

sees that data entry took three weeks to do at all but one site, which finished in one week. An anomaly like this should prompt the monitor to check into whether there is a systemic problem, fraud, or something else. With the right analytic tools in place, potential issues can be seen and resolved before they escalate.

All of this data presents a challenge for executives and project leaders: With so many metrics across multiple domains, how do you boil them down into something useful? Each study sponsor must decide how to weigh certain metrics at the program and site level and even by study phase. Tools are available to execute the plan in the field and guide monitors at the site level. The EDC system guides them as to what data needs to be verified, and a robust CTMS collects operational data to drive the process. Reporting and analytical tools are available to aggregate data across multiple systems and even multiple studies. The aim is to get a 360-degree, high-level, real-time view across all of your clinical trials with the ability to drill into specific studies and sites to take action.

RESHAPING THE MONITOR'S ROLE

Monitors have been conditioned to check every data element in the casebooks they review. This new risk-based approach transforms their role. Monitoring this new way requires a behavioral as well as cultural shift, one that takes some getting used to with new thinking on everyone's part. Reduced SDV allows monitors to focus on more important site activities of higher value. With a solid plan and the right tools in place, monitors can be selective in what they review, based on a documented and objective monitoring plan.

ACROSS-THE-BOARD ADVANTAGES

Simply put, this is a better way of monitoring and a more effective use of resources. Efficiency, quality, and the ability to scale and run studies without unnecessarily overburdening personnel are just some of the advantages. As monitors visit sites less frequently, it will also lower costs. Finally, from a clinical operations perspective, leveraging technology makes better use of data, allowing an organization to detect problems earlier, make more informed decisions, and efficiently plan for future studies.

About the Authors

Chip deVillafranca brings more than 30 years of experience to lead product management for BioClinica's eClinical solutions. Prior to BioClinica, he worked for Phase Forward and Oracle.

Jonathan Andrus manages study and project operations for the eClinical Division of BioClinica. He joined BioClinica in 2003 as V.P., QA and corporate compliance.

EU Sets The Stage For Increased Pharmacovigilance Oversight And Harmonization

By Amanda Sibley

With the overarching goal of improving transparency and accountability, the European Medicines Agency (EMA) has been taking a more comprehensive approach to pharmacovigilance, introducing a set of good pharmacovigilance practice (GVP) guidelines to the European market.

Integral to the GVP guidelines was the introduction of the pharmacovigilance system master file, or PSMF, which is a detailed description of the pharmacovigilance system used by the marketing authorization holder (MAH) with respect to the holder's authorized medicinal products. The PSMF has been required for new marketing authorization applications since July 2012; it will be optional for existing applications until July 2015.

The PSMF is much more than a regulatory document. It describes in detail every aspect of the way a company handles a product's pharmacovigilance and safety in general. In so doing, it serves as a useful and robust tool for both regulators and the MAH by ensuring that all aspects of GVP are being practiced, that there is clearer structure to the management of product safety issues, and that noncompliance issues or deficiencies in the pharmacovigilance system will get detected.

In addition, complex and constantly changing regulations require higher levels of interdisciplinary expertise, which in turn increases the need for good tools to detect and respond to safety concerns. Yet many life sciences companies remain reluctant to introduce the PSMF — in part because the 2015 deadline for compliance makes it seem less urgent, and in part because the new GVP guidelines require investment in training relevant staff, which can be costly.

UNDERSTANDING THE HOW AND WHY

Before introduction of the PSMF, companies were required to maintain two documents: the Detailed Description of the Pharmacovigilance System (DDPS) and the Summary of Pharmacovigilance Systems (SPS). The DDPS was submitted with the license, and the SPS was requested by inspectors before inspection. Producing two documents led to companies' duplication of effort, but perhaps more important, neither document provided the needed oversight or level of detail regarding pharmacovigilance activities, nor did either include the detailed compliance metrics that are integral in the new pharmacovigilance document.

The PSMF reflects the existing pharmacovigilance system of a product and must be maintained and submitted to authorities upon request, thereby making it transparent and accountable. The document must be available to the assessors within seven days of a request. A document that does not include sufficient details regarding the existing pharmacovigilance system as defined in PSMF GVP Module II could trigger a safety inspection. What that means in practice is that the PSMF should be permanently available for inspection.

Preauthorization inspections are possible for those MAHs that are new to submitting of centralized applications in Europe. Upon submission of a marketing authorization application, a Summary of Pharmacovigilance Systems has to be submitted, and the PSMF produced upon request. Failure to comply with such a request would result in an inspection finding, as was revealed during the GPvP Symposium in London in March 2013. The MAH should continue submitting variations to update the DDPS for existing marketing authorizations when a system summary has been submitted in a new marketing authorization application but not yet introduced for all products.

WHAT THE PSMF DOES

The PSMF is intended to be a live, bespoke document that accurately reflects the pharmacovigilance system that is in place for a given product. The PSMF provides insight into timelines, roles and responsibilities, interfaces between the various pharmacovigilance departments, review of frequency of the process documents, validation of status of the safety database, a description of online data management tools, persons responsible for the various pharmacovigilance processes, and key performance indicators.

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The document is also expected to provide insight into audit findings, including open corrective actions and preventive actions related to the GVP processes of the product. GVP Module II states that, "A description of the approach used to plan audits of the pharmacovigilance system and the reporting mechanism and timelines should be provided, with a current list of the scheduled and completed audits concerning the pharmacovigilance system maintained in the annex." For example, when an MAH contracts pharmacovigilance services to a third party, a mechanism of oversight is required, which could include an audit. Any planned audits of the service provider and any significant audit findings should be recorded in the PSMF in accordance with European Union legislation and GVP Module II.

GVP Module II also states that, "The master file shall also document deviations from pharmacovigilance procedures." The impact of either planned or unplanned deviations should be assessed when deciding whether to record them in the PSMF — for example, if the MAH identified (outside a quality system audit) that a large number of cases had not been transferred from an affiliate office to pharmacovigilance. That type of deviation, along with the proposed corrective actions and preventive actions, should be recorded in the quality system and a note placed in the PSMF until resolution.

The document is intended to be meticulous in its level of detail. The PSMF is to be used for assessing whether an MAH complies with current GVP guidelines. It also reveals how soon the MAH was able to disseminate important patient safety information to the relevant audience — for example, Direct Healthcare Professional Communication letters or Summary of Product Characteristics (SmPC) variation submissions that inform the competent authorities and the EMA.

MANAGING METRICS

Central to the PSMF is the inclusion of metrics or key performance indicators in the annex, alongside the results of those measurements. The GVP guidance lists the minimum metrics for inclusion, but it also states that companies should develop their own company-specific metrics for their unique situations and systems. Inclusion of metrics is a useful tool not just for regulators but also for the company and its qualified person responsible for pharmacovigilance (QPPV) to ensure compliance and identify deficiencies in the pre-existing pharmacovigilance system.

The MAH should determine the most useful and correct metrics for providing an effective overview of the functioning of the company's pharmacovigilance system. Targets for the pharmacovigilance system's performance should be described and explained in either the PSMF section on pharmacovigilance system performance or in the annex.

MANAGING THE INTERFACES

As is the case in most departments in pharma today, many companies are choosing to outsource either their entire pharmacovigilance function — or aspects of it — to reduce fixed overhead costs, avoid high up-front investments, secure additional capacity, increase resource flexibility, or augment the performance of an activity not considered a core area of the business. Companies, however, retain overall responsibility for the safety of their products and must ensure that a third party or parties can provide the necessary support, understand the ever-evolving guidelines, and demonstrate necessary compliance with the regulations.

Preparation and maintenance of the PSMF relies on a cross-functional team of subject-matter experts to develop all annexes covering information for all products. The PSMF has enormous importance in both the preapproval and postmarketing phases of a product's life cycle. More transparency and more communication from companies to third-party vendors are required with regard to process updates, such as standard operating procedures, validation updates to the company database, and compliance information. All updates must be documented in the PSMF, which will be the first thing auditors scrutinize.

SEIZE THE DAY

A number of companies have started writing the PSMF; few are in a hurry to implement it. But postponing implementation of the PSMF could increase costs and lead to greater complexities later because the PSMF is a document that can take a great deal of time and a great deal of thought to prepare and construct. In addition to laying the groundwork for the PSMF, the QPPV and other pharmacovigilance and regulatory staff will need to interact with other parts of the company as well as third parties, including service providers, distributors, and affiliates.

The PSMF also helps provide a better framework for the GVP guidelines, because rather than being included in a detailed explanation of the way pharmacovigilance was handled for the product being submitted, such explanatory information is contained in the PSMF in a structured way.

With so much to consider and with so many benefits to be realized in oversight and harmonization, companies would do well to consider early adoption or at least to begin preparing the way for the PSMF.

About the Author

Amanda Sibley is head of safety services, managing all of ProductLife Group's postmarketing pharmacovigilance services. Drawing on more than 18 years of pharmacovigilance experience, she serves as the senior contact for all postmarketing PV activities.

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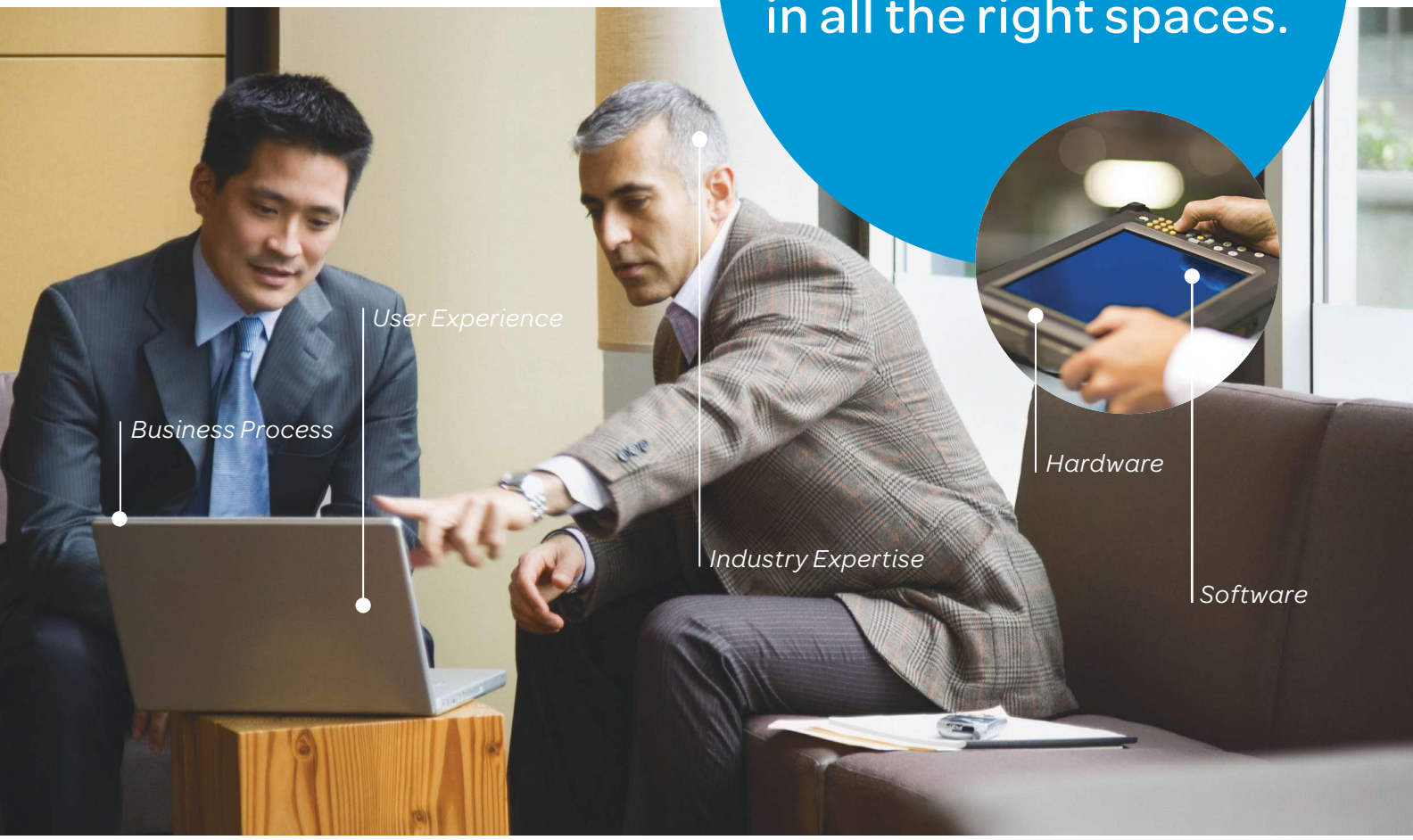

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Leadership By Fear — Falling Off The Tiger

By Bob Garner

Winston Churchill once said, "Dictators ride to and fro upon tigers which they dare not dismount. And the tigers are getting hungry." Though Churchill was speaking of dictators of countries, the same statement can be applied to leaders of companies who prefer to ride the tiger called leadership by fear.

While leading by fear or intimidation may work to increase short-term profits, in due course, employee morale sinks, key employees leave, and productivity and performance falter. The remaining employees will secretly begin to despise their leader, which will be transferred to their work and, ultimately, the customer. Eventually, this affects the bottom line, and the leader will be forced to dismount the tiger and face its wrath (i.e. the board, bad media reports, etc.).

Instead of leading by fear, wise executives understand the need to lead by admiration and respect. While not as ego-gratifying for some executives as the use of fear — generally, insecure people use fear as a control strategy — leading by admiration and respect fosters communication, creativity, and cohesiveness:

- Communication — Ideas and opinions are asked for, listened too, and discussed.
- Creativity — Employees are encouraged to utilize current skill base and cultivate new skills.
- Cohesiveness — All departments unite to achieve small and large goals.

This three-prong strategy enhances employee self-worth, which delivers not only a heightened sense of interest to one's job, but also improved customer service and an increased bottom line. Additionally, should the leader encourage employees to act on their ideas, as well as disagree with the leader without fear of retribution, then the leader earns the respect and admiration of all, both during and after their years of working together.

Churchill was known for treating his staff, as well as others who worked with him, with respect and loyalty. Wartime aide Lord Bridges wrote of Churchill, "I cannot recollect a single minister, serving officer, or civil servant who was removed from office because he stood up to Churchill and told Churchill that his policy or proposals were wrong."

Instead of riding a tiger, Churchill knew that it was far better to walk freely amongst those with whom he worked — asking for ideas, encouraging others to use their talents, fostering teamwork, and treating people with respect and loyalty. Maybe that is why Churchill was — and still is — regarded as a great leader. People didn't follow him because they were afraid of him; they did so because they respected him. He never had to worry about falling off the tiger.

Recognized as a funny motivational speaker who actually has something to say, Bob Garner speaks on enhancing performance and productivity, and appears at meetings and conferences of Fortune 1000 corporations worldwide. For more information, go to www.bobgarneronline.com.

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