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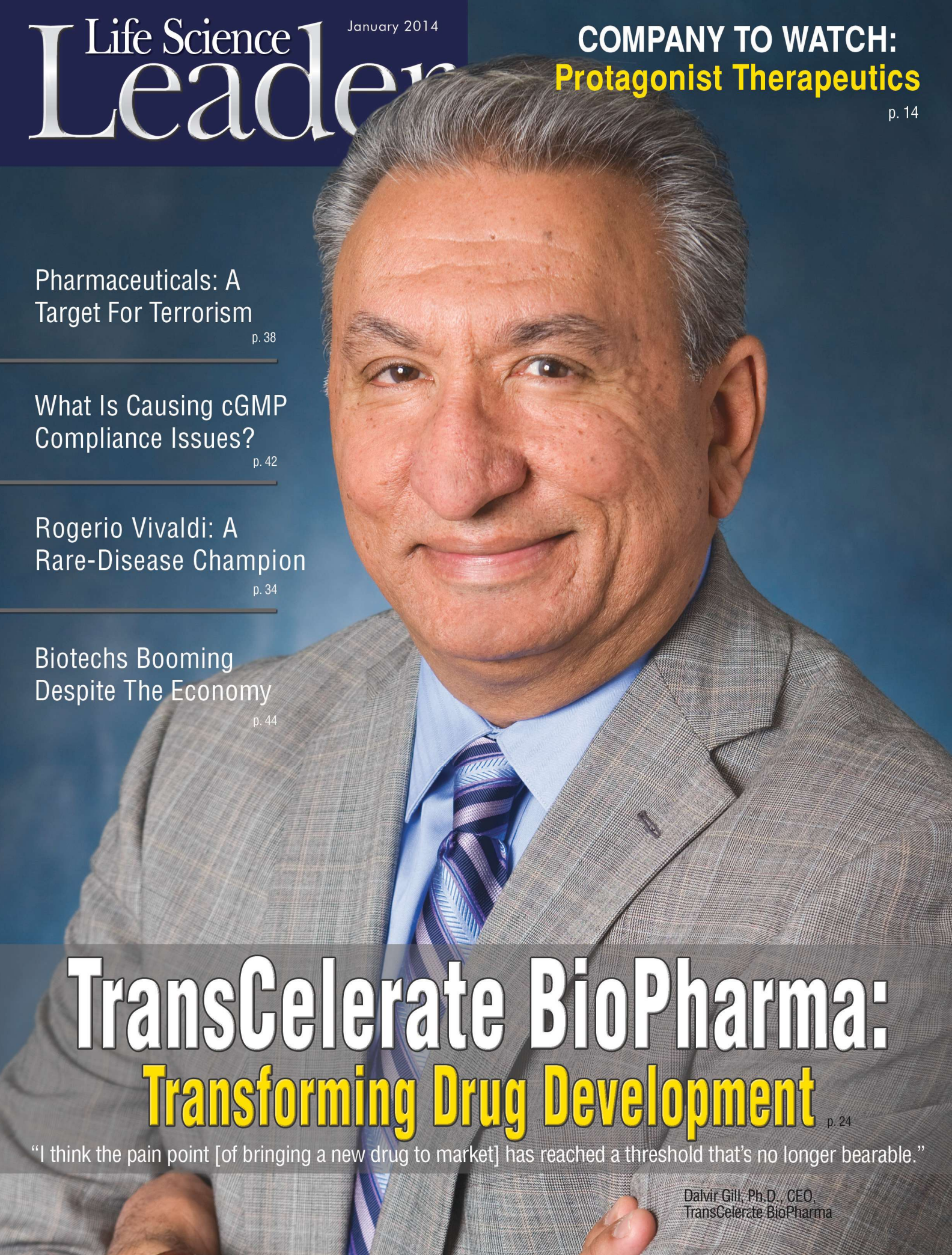

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"I think the pain point [of bringing a new drug to market] has reached a threshold that's no longer bearable."

Dalvir Gill, Ph.D., CEO, TransCelerate BioPharma

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24 FEATURE: TRANSCELERATE

Dalvir Gill, Ph.D., CEO of TransCelerate BioPharma, reveals the biggest roadblock to TransCelerate's success and how it was overcome.

January 2014

Welcome to *Life Science Leader*

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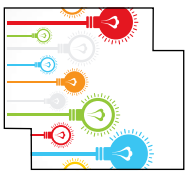

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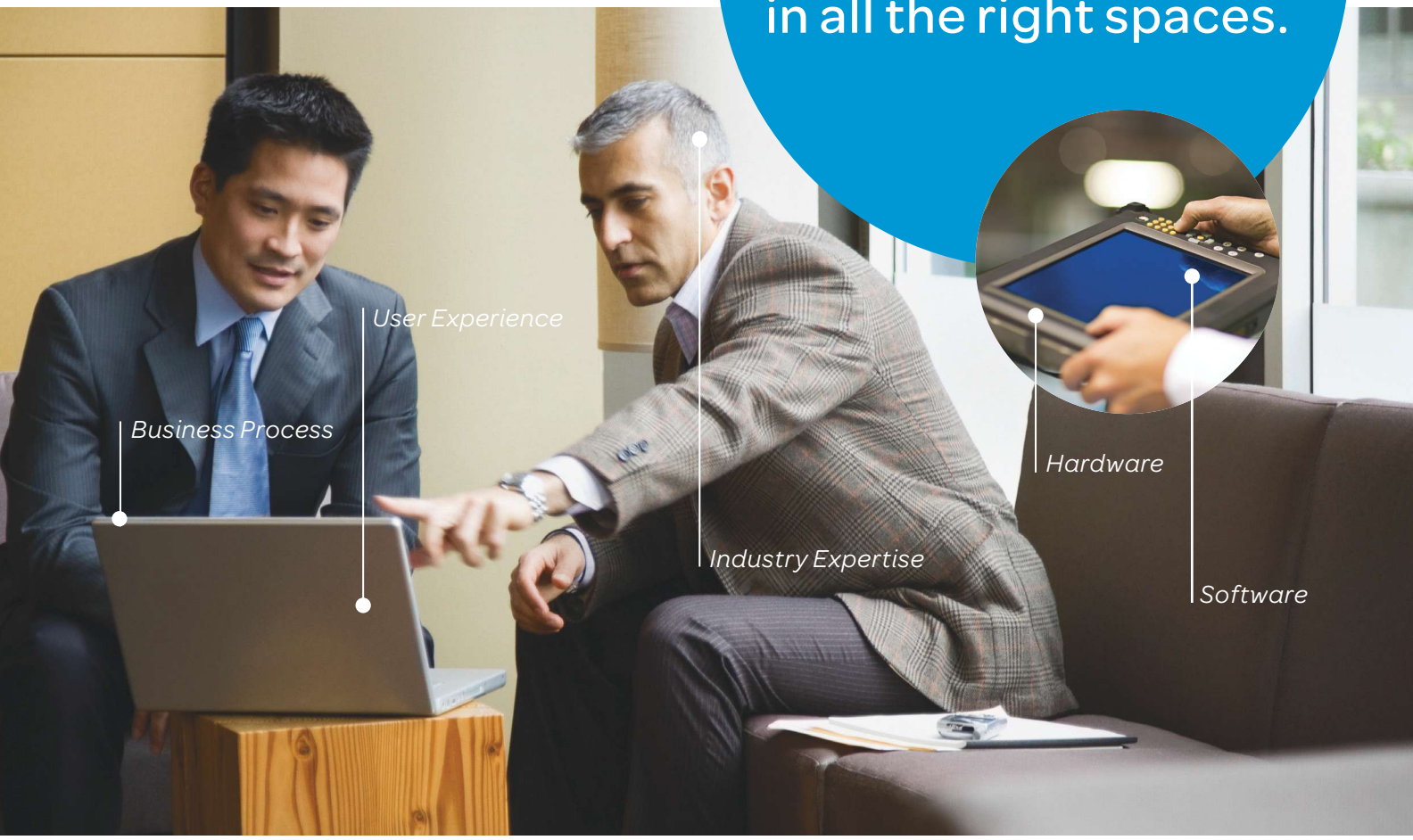

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Don't Be Stupid, Keep It Simple

Ever heard of the KISS (keep it simple, stupid) principle? The general idea behind it is that systems perform best when the design is simple, not complex. My favorite example demonstrating the application of KISS, as well as the impact of failing to do so, is captured in a scene in the 1995 movie *Apollo 13*. An incident necessitates three astronauts use the lunar module (LM), a ship built just for landing on the moon, as a lifeboat to survive. The LM is designed and equipped to provide two people 36 hours of life support, not three crew members the 96 hours it will take to get back to earth. As a result, the ship begins to develop an unsafe build-up of CO^2. The LM CO^2 filtration system uses cylindrical filters, all of which have been used up. The command module's CO^2 filters are square. This fact exemplifies a failure in executing the KISS principle between the designers of the LM (Northrop Grumman), the command and service modules (North American Aviation), and NASA. When NASA ground control realizes this, engineers are pressed to concoct a solution, demonstrating the successful application of KISS. In the movie, the engineers enter the room and dump a box of supplies (available to the astronauts) on a table. The lead engineer defines the problem verbally, visually, and simplistically. "We gotta find a way to make this [holds up the square filter in his right hand], fit into the hole for this [holds up the cylindrical filter in his left hand], using nothing but that," he concludes, placing both filters back on the table and pointing to the available materials. When you see it, the problem seems obvious, the solution simple, and something which could have been prevented with better front end planning — KISS.

This is how I imagine former J&J VP Gary Neil felt when he first had the idea for creating a stand-alone nonprofit organization in an attempt to tackle skyrocketing drug discovery and development costs. "If we were to come together and try to define standards, it would be an enabler for efficiencies for everyone," he stated. Though Neil's epiphany may not have been original, his execution on a solution — TransCelerate — has proven to be. Its formula is simple. Bring pharmaceutical companies together to solve common, precompetitive problems, and all will benefit. Want to learn more about TransCelerate's approach? Check out the article on page 24 featuring TransCelerate CEO Dalvir Gill. As you read, keep in mind that though the solution is simple, the key to success is execution — which can be challenging when applying the KISS principle across all the member companies.

Simplification seems to be a consistent theme nowadays in the pharmaceutical R&D space. At a recent executive thought leadership roundtable sponsored by NextDocs, the focus was on how to improve clinical trials. The consensus among attendees was — if you want better clinical trials, and want them to go faster, spend most of your time planning the design. Start by first determining if you are asking the right questions. "Don't ask a bunch of useless questions," said one drug development veteran. "The more data you ask for, the higher your costs are going to be." Try applying the KISS principle to prevent your drug development costs from going sky high.

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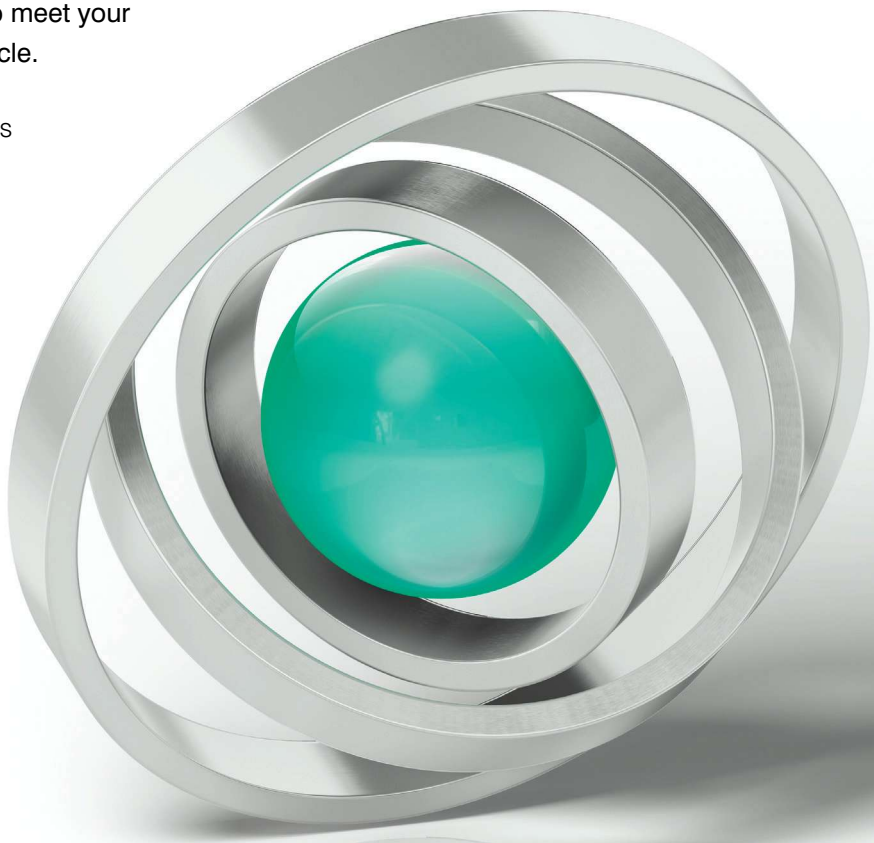

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ASK THE BOARD

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Q: What are chief concerns you have regarding R&D and the regulatory environment, and what solutions can be implemented?

Regulatory advances intended to speed development and availability of new treatments, such as orphan drugs, have positively impacted certain sectors of the life sciences industry. It is important to continue to accelerate the development and commercialization of drugs and biologics that treat serious, life-threatening conditions and address unmet medical needs. At Cubist, we have benefited from the Generating Antibiotic Incentives Now (GAIN) Act, allowing for incentives related to the development of new antibiotics. It is especially important at a time of escalating global public health needs. For example, in our sector (antibiotic resistance and rising hospital-acquired infections), industry continues to develop partnerships with regulators, policy makers, and other stakeholders. Together we can foster innovation through the right economic incentives and provide unique health value, and bring even more flexible regulatory approaches to bear.

Barry Eisenstein, M.D.,
Dr. Eisenstein is senior VP of scientific affairs at Cubist Pharmaceuticals and editor of *Antimicrobial Agents and Chemotherapy.*

Q: What is a costly pharma manufacturing mistake that executives fail to consistently pay attention to, and what can be done to avoid it?

One of the most costly mistakes is yield losses in manufacturing due to wasteful process steps or flows. For example, excessive hold-up volumes, extended processing times, or just the wrong choice of filter membrane materials, to name a few, all create extensive yield losses. The lack of optimization in yield improvement happens far upstream in the process-development cycle where tests could support optimization of either individual process steps or the entire process. Extensive equipment and/or unit operation turnaround times represent another, though diminishing, cost driver. Current single-use technologies reduce this problem with flexibility and ready-to-use options. In addition, the industry starts recognizing that process flexibilities have to be a match with facility flexibilities. New flexible facility concepts support such efforts.

Maik Jornitz
Jornitz is COO of G-CON Manufacturing and founder of BioProcess Resources. He has more than 25 years of experience and supports the biopharm industry on a global basis.

Q: Do you think many companies will develop the "me-too" drugs like we had in the days of the SSRIs (selective serotonin reuptake inhibitors), especially if the burden of proving superiority is too great?

Most companies are into projects before the concept behind the program has been proven in Phase 2. Thus, the decision a company will have is one of timing. To be honest, it is pretty hard to know the full profile of a drug until you have completed the Phase 3 program. While you may have a good sense of efficacy before then, it is only with Phase 3 that you begin to get a sense of the risk-benefit profile. Thus, if you are in second place with a new class of agents, unless you clearly are inferior in some way, it behooves you to move the program forward because no two compounds are identical in the clinic.

John LaMattina, Ph.D.
LaMattina is the former senior VP at Pfizer Inc. and the president of Pfizer Global Research and Development. In this role, he oversaw the drug discovery and development efforts of over 12,000 colleagues in the United States, Europe, and Asia.

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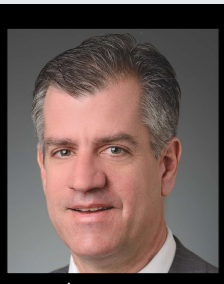
Obamacare Is Vaporizing Retiree Drug Coverage

The headlines have been filled with reports of thousands of individuals losing their health insurance because many plans in the individual market do not conform to certain requirements of Obamacare. But what is not well-known is that employer-sponsored retiree drug coverage for Medicare-eligible beneficiaries has virtually evaporated as a result of enactment of Obamacare.

Some background: The Medicare Modernization Act of 2003, which integrated prescription drugs into Medicare, provided for a tax-free "retiree drug subsidy" to employers that offer qualified drug coverage to Medicare-eligible retirees. That subsidy is equal to about two-thirds of the value of the subsidy for Part D drug plans. This retiree drug subsidy was meant to leverage — but not replace — the private coverage in the market. By doing so, it would help individuals retain their current coverage and limit the expenditure of taxpayer dollars. To the degree retirees retain drug coverage from their employers, Medicare saves money.



John McManus,
The McManus Group
jmcmanus@mcmanusgrp.com

Analysis from the CMS Office of the Actuary (OACT) shows that the subsidy achieved that goal for the first five years of the program. From 2006 to 2010 the number of individuals receiving the retiree drug subsidy remained stable at about 7 million.

But in 2011, the number dropped to about 6 million. In 2012, it declined to 5.7 million. Then in 2013 the bottom dropped out of the market, with the number of individuals receiving the retiree drug subsidy plunging to about 3 million. OACT projects this number to fall to less than 1 million by 2016 and beyond. (See chart on page 12.)

WHAT HAPPENED?

Obamacare made two substantial changes to the Medicare drug benefit. Most importantly, it filled the "donut hole" — the $3,610 gap in coverage in 2010 between the initial benefit and the catastrophic protection. That feature of the benefit was a result of the limited resources available when Congress enacted drug coverage in 2003, and Democrats vowed to address the issue when they took power.

Starting in 2011, brand-name pharmaceutical manufacturers were required to provide 50% discounts for drugs purchased in the donut hole. This made a substantial difference for many beneficiaries as the Congressional Budget Office observed that about one-fifth of spending by non-low-income beneficiaries was for drugs in the donut hole.

Simultaneously, the statute closes the donut hole by gradually increasing the initial benefit threshold and dropping the catastrophic attachment point over 10 years. By 2020, the donut hole is eliminated and beneficiaries will receive 75% coverage, on average, of their drugs before the catastrophic protection kicks in.

Secondly, Obamacare repeals the tax-free nature of the retiree drug subsidy. (This was, interestingly, the provision that sealed the bipartisan deal between then Ways and Means Chairman Bill Thomas [R-CA] and Finance Ranking Member Max Baucus [D-MT] 10 years ago.) By making the retiree subsidy taxable income, this had the effect of decreasing the value of the subsidy by the corporation's marginal tax rate — up to 35 percent in many cases.

PhRMA agreed to the 50 percent discount, in part, to deter a worse alternative — Medicaid rebates on the Part D drug benefit. But the industry also benefited from the provision because it had noticed that many beneficiaries often discontinued their prescriptions when they hit the donut hole. The 50 percent discount helped beneficiaries stay on their meds and get to the catastrophic protection, where 95 percent of costs are covered.

Employers also took note that this more generous coverage is available in Part D prescription drug and Medicare Advantage plans, but not under their own retiree plans. Employers, of course, are in the business of producing widgets, not providing health coverage. And it is economically irrational to leave money on the table. IBM, for example, discontinued retiree drug coverage and directed their retirees to coverage available under Medicare drug plans and Medicare Advantage.

WHAT LESSONS CAN BE LEARNED?

The press has been understandably focused on the disastrous rollout of Healthcare.gov and the relatively few individuals who have signed up for coverage.

But a more troubling concern over the long term will be whether employers react similarly for their current work-

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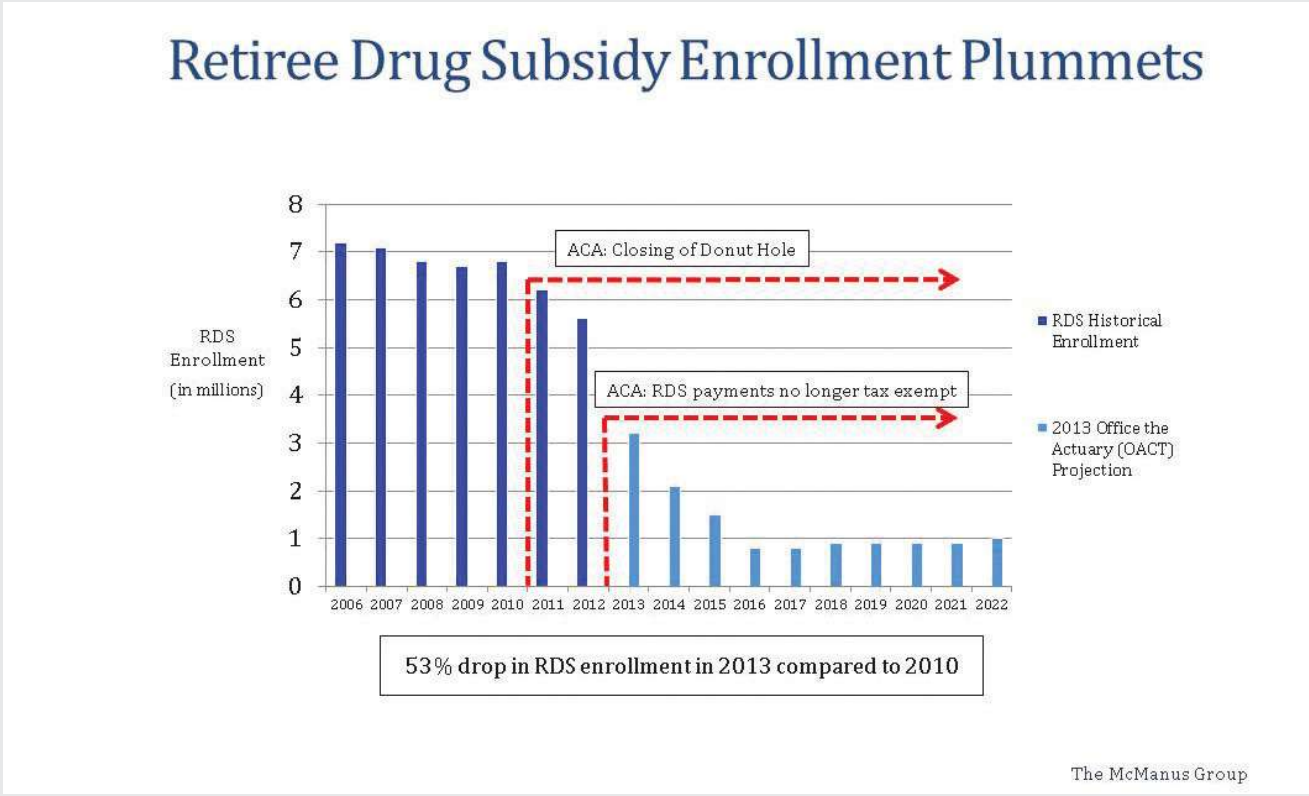
ers as they have for their retirees' drug coverage.

My first column for *Life Science Leader*, published last spring, detailed the compelling math for an employer of lower- or middle-income workers to dump their employees into Obamacare. The modest $2,000 penalty for large employers failing to provide coverage pales in comparison to the substantial subsidies available in Obamacare to lower- and middle-income workers. For example, an employer offering typical coverage to a family of four with an income of $48,000 would save $7,400, even after it covers the increased income and payroll taxes that result from moving nontaxable benefits into taxable wages.

So the real risk is not whether too few sign up for Obamacare, but too many. The Congressional Budget Office predicts that only 8 million individuals will lose their employer-sponsored coverage. But if just 10 percent of employees with employer-sponsored coverage are dumped into the exchange, that number will double to 16 million.

Employer dumping of coverage will result in painful coverage disruptions with more narrow provider networks and tighter drug formularies in Obamacare. Just as importantly, it will require greater government subsidies that will, in turn, result in greater scrutiny over pricing and increased pressure to restrain costs.



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

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By Wayne Koberstein, executive editor

Protagonist Therapeutics

The world has long awaited stable oral peptides as a potential replacement for many injectable drugs. Will this company be the hero?

SNAPSHOT

Protagonist Therapeutics has created a technology for making stable oral peptides capable of replacing injectable-only drugs and is developing entirely new oral-peptide therapeutics for GI patients. Its initial development areas are irritable bowel diseases (IBD) and irritable bowel syndrome (IBS). Two compounds, one an injectable peptide to block IL-6, and another, an oral peptide to block integrins, will enter clinical trials in 2015.

Dinesh Patel, President & CEO, Protagonist Therapeutics

LATEST UPDATES

- Q4 2013: advanced IL-6 injectable peptide antagonist project to preclinical development stage with IND (investigational new drug) candidate nomination expected in 2014
- Q4 2013: advanced integrin oral peptide antagonist project from inception to preclinical development stage with IND candidate nomination expected in 2014
- 2013: raised $18M in Series B financing to fund development of an oral peptide through initiation of Phase 1 clinical trials

WHAT'S AT STAKE

Protagonist, like many originator companies, took years to develop a platform, but all along it intended to develop its own drug treatments with its oral-peptide technology rather than become a CMO. So its contributions could be earthshaking in two ways — offering a long-sought alternative to existing injectable antibodies and peptides, as well as unleashing a new breed of oral medicines with superior potency and safety — and in the company's words, convenience, compliance, and affordability.

In between the world of small molecules and proteins is the realm of peptides: essentially strings of amino acids with unique therapeutic potential, but, in the traditional oral formulations, peptides have serious drawbacks in stability and pharmacokinetic properties. "Our intent is to create novel chemical entities that will capture the best of both worlds, meaning the convenience and PK (pharmacokinetics) characteristics of small molecules including oral delivery and oral stability, and the important potency characteristics of big biologics, meaning the ability to work with large protein-to-protein interaction targets," says Protagonist President and CEO Dinesh Patel. In the company's research, such targets include IL-6, IL-23, TNF, and integrins.

The GI areas — IBD and IBS — are natural candidates for drug development, considering that the first hurdle for oral peptides is the gut. "For us, IBD is not like a secondary application; it is the primary application, and we have chosen it on purpose so that we can capture the full advantages of an orally delivered peptide drug," Patel says.

Protagonist is not alone in this field, nor even the furthest ahead in oral-peptide drug development. Roche is partnering with Chiasma on an oral somatostatin analog using the smaller company's Transient Permeability Enhancer (TPE) platform. Enteris BioPharma recently resurrected the Peptelligence platform acquired from Unigene. And Ironwood Pharmaceuticals, which has partnered with Protagonist since 2011, has already launched linaclotide, a once-daily oral peptide GCC agonist for constipation-dominated IBS. Others have sought the oral-peptide answer in protease inhibitors, permeation enhancers, nanoparticles, liquid emulsions, water-oil micro-emulsions, and liposomes.

Patel has this to say about his company's position in the field: "Healthy competition is not a bad thing, and we are glad to see a strong interest in the field of oral peptides. While almost all of our competition has embarked on various formulation strategies, Protagonist has leveraged its proprietary technology platform to uncover peptidic new chemical entities (NCEs) that are both potent and orally stable."

Patel adds that both of Protagonist's partners, Ironwood and Zealand Pharma, saw his company's platform as "complementary and synergistic" to their own expertise and experience. "These collaborations are the first important validation of Protagonist's technology. The next step is funneling peptidic assets into all of our companies' internal clinical pipelines."

Regardless of who wins the race to the top of a future oral-peptide pack, some reports in the press have been unjustifiably blasé about the new technologies. One recent analysis regards the Protagonist platform as offering just another alternative in drug delivery, apparently missing the plain fact that the world has eagerly waited for the oral solution to injectable peptide limitations. Oral-peptide delivery will be a major breakthrough, not an incremental improvement.

VITAL STATISTICS

- Employees: 27
- Headquarters: Milpitas, CA
- Finances: Total of $27M in private financing to date with participation by Johnson & Johnson Development Corporation (JJDC), Lilly Ventures, Starfish Ventures, Inbioventures, and QBF
- Research partnership funding: Ironwood Pharmaceuticals (IRWD) and Zealand Pharma (ZEAL.CO)

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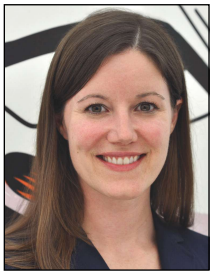

OUTSOURCING INSIGHTS

2014 Trends In Strategic Outsourcing — Changes In The Qualities That Drive Outsourcing Partner Selection

By Kate Hammeke, director of marketing intelligence, Nice Insight

The 2014 results from Nice Insight's annual pharmaceutical and biotechnology outsourcing survey show positive news for both sides of outsourcing relationships. Just as there was an increase from 2012 to 2013 (up 7 percent, from 31 percent to 38 percent) in respondents with an outsourcing expenditure between $10M to $50M, there was another 9 percent increase in this expenditure bracket for the year ahead. Slightly under half of all survey respondents (47 percent) stated they will spend between $10M and $50M on outsourced projects in 2014. The respondent group who will spend less than $10M on outsourced projects continues to shrink, now comprising only 29 percent of respondents. One key difference in this increase in expenditure over the 2012-2013 change was that respondents indicated they would outsource a greater number of different services — up from 4.7 on average in 2013 to 6.4 in 2014.

> Forty-seven percent of survey respondents stated they will spend between $10M and $50M on outsourced projects in 2014.

QUALITY, RELIABILITY TAKE TOP SPOTS

This year's results show that, as a whole, survey respondents prioritized the outsourcing drivers as follows: quality, reliability, regulatory, productivity, affordability, and innovation. In the past three years, CROs and CMOs have taken notice that drug innovators — across all buyer groups — consistently prioritized quality and reliability in the top two positions. It becomes clear that the contract organizations have made efforts to improve upon these customer perception measures, which have in turn been reflected in improved scores offered by sponsor organizations across several categories. For example, the benchmark for quality increased among both CROs (up 1 percent, from 71 percent to 72 percent) and CMOs (up 2 percent, from 71 percent to 73 percent) from 2013 to 2014.

CMOs fared better in terms of improving upon reliability, with a 1 percent upturn, from 72 percent to 73 percent, while the CRO benchmark remained the same as last year at 72 percent. Interestingly, there was a small decrease for the CRO regulatory benchmark, down 1 percent from 74 to 73; CMOs held steady at 74 percent for regulatory for both 2013 and 2014. The small drop in averaged regulatory scores across all CROs coincided with a 5 percent downward shift in the percentage of respondents who will engage a CRO or CMO for regulatory support. These could be related. If sponsors were disappointed with the regulatory knowledge their contractors possessed, it makes sense they would be less inclined to acquire their assistance.

The prioritization of an outsourcing partner's productivity has shifted each of the last three years, moving from fourth place in 2012 to fifth in 2013 and back to fourth for 2014 — this year edging out affordability for the first time. When it comes to how sponsors evaluated CROs' and CMOs' performance on this measure, the data showed a 2 percent decline in the CRO benchmark, down from 73 percent to 71 percent. However, CMOs on average maintained their scores, with the benchmark sticking at 73 percent.

In light of increased outsourcing expenditure for 2014, it was not too unexpected for affordability to drop in rank — now holding fifth position, as compared to fourth in 2013 and third in 2012. Interestingly, at the same time this measure has dropped in priority among buyers of outsourced services, both CROs' and CMOs' affordability scores have climbed. The affordability benchmark for CROs increased 1 percent from 69 to 70, and among CMOs, the benchmark increased 3 percentage points from 69 to 72.

There was some variation in ranking from the different buyer groups. For example, among emerging pharma respondents, affordability ranked third as compared to fifth across the other buyer groups. Biotechs prioritized productivity slightly higher than the pharma groups or emerging biotechs, but perhaps the most notable difference was that emerging biotechs ranked innovation third, whereas the rest of the buyer groups ranked innovation sixth. The innovation benchmark for both CROs and CMOs was set at 72 percent in 2013. This was another area where CROs slipped in performance, with their averaged score at 71 percent in 2014. Yet, CMOs once again maintained their scores, with the benchmark staying at 72 percent.

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CRO Benchmarks

	Quality	Reliability	Regulatory	Affordability	Productivity	Innovation
2014	72%	72%	73%	70%	71%	71%
2013	71%	72%	74%	69%	73%	72%

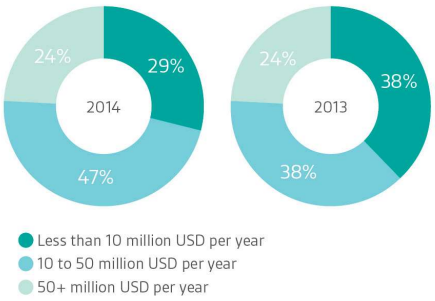
CMO Benchmarks

	Quality	Reliability	Regulatory	Affordability	Productivity	Innovation
2014	73%	73%	74%	72%	73%	72%
2013	71%	72%	74%	69%	73%	72%

The Average Number of Services Outsourced

	Big Pharma	Specialty Pharma	Emerging Pharma	Biotech / Biologics	Emerging Biotech/Biologics	Overall
2014	7.3	5.6	5.5	6.0	7.6	6.4
2013	5.7	5.0	4.0	4.9	5.4	4.7

Annual Outsourcing Expenditure



Outsourcing Drivers in Ranked Order of Importance

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

Survey Methodology: The Nice Insight Pharmaceutical and Biotechnology Survey is deployed to outsourcing-facing pharmaceutical and biotechnology executives on an annual basis. The 2013-2014 report includes responses from 2,337 participants. The survey is comprised of 240+ questions and randomly presents ~35 questions to each respondent in order to collect baseline information with respect to customer awareness and customer perceptions of the top 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

Who's Improving Bioprocessing In 2014?

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

Last month we discussed the broad trends in innovation in bioprocessing that will shape the next five years. These include better single-use devices, assays, connectors and system integrations, and alternatives to chromatography. This month we drill down into areas where product innovators are actually investing in these improvements and technologies. Below is a sampling of key bioprocessing innovations. A thorough treatment would require an encyclopedia; this is an appetizer for what's to come.

2014 will be another year of advancement for biopharmaceutical bioprocessing and manufacturing. This will include continued incremental advances that allow manufacturers to do more with less: less capital investment, lower operational cost, less time (speed to market), and better labor usage. Some specific examples include the ability to manufacture using smaller-scale equipment and facilities aided by ever-increasing process yields; better cell lines, expression systems, and optimized culture media; increased adoption of single-use bioprocessing equipment; and better downstream/purification technologies and equipment.

Of course, biopharmaceutical development and manufacture is not an area conducive to rapid revolutionary changes (e.g. having a significant impact in a single year). For example, it has taken more than a decade for single-use bioreactors to dominate the small- and mid-scale manufacturing market. The industry retains an inherent conservatism in adopting new technologies in this highly regulated environment, which is partially due to the expectation that new inventions used in manufacturing can potentially delay a drug product's approval.

NEW AND INNOVATIVE BIOPROCESSING:

Membrane Adsorbers: Downstream purification has been thoroughly dominated by chromatography columns, generally stainless steel (recycled, non-single-use). In contrast, membrane adsorbers involve multiple layers of adsorptive filters, are much smaller, processing is faster, and are single-use, requiring no column packing, cleaning, sterilization, etc. Although these are mostly for cleanup of recombinant protein/antibody purification streams to remove targeted impurities, their applications are advancing as binding capacities increase and costs are reduced. Upcoming membrane adsorbers include those used in classic bind-elute mode, allowing them to replace more cumbersome separation non-single-use media-packed columns. For example, Natrix Separation has launched NatriFlo HD-Q Membranes that deliver binding capacity which exceeds resin-based columns with fast flow-rates typical of membrane adsorbers. According to our 10th Annual Report and Survey of Biopharmaceutical Manufacturing, membrane adsorbers are the fastest-growing bioprocessing market segment. New membrane adsorbers continue to be launched, including products from the current market leaders Sartorius Stedim and Pall Corp. and from Natrix Separations, Asahi Kasei, BIA, and others.

Modular Bioprocessing: Beyond just single-use bioprocessing systems, whole unit facilities and bioprocessing unit operations are becoming single-use. This essentially involves portable, modular cleanrooms, often fully fitted with single-use bioprocessing equipment. For example, G-Con offers trailer-like modular cleanrooms with bioprocessing equipment preinstalled, and GE Healthcare Life Science offers KUBio pre-assembled biopharmaceutical factories. In 2013, JHL Biotech (China) contracted with GE for delivery of a KUBio GMP biopharmaceutical factory in China, with this to be fully ready in as short as 14 to 18 months. And G-Con, a major innovator in modular systems, formed a collaboration with Foster Wheeler, a major engineering and construction firm, to offer G-Con modules globally. Modular bioprocessing facilities are particularly attractive for use in developing and other GMP-challenged countries. For example, in 2013, the Brazilian government licensed beta-glucocerebrosidase carrot cell culture manufacturing technology from its developer, Protalix BioTherapeutics, and contracted with GE Healthcare and iBio, Inc., a company with plant expression technology, to build a large manufacturing facility in Brazil to supply the country's need for this product.

Biosimilars Manufacturing: The FDA is slowly issuing needed biosimilars development and approval guidelines, but no applications have yet been filed in the U.S. However, innovations to streamline the production of biosimilars is now a major worldwide focus, considering biopharmaceuticals have >$100 billion in current sales, and nearly 100 products are coming off patent in the U.S., EU, and other major markets in the next three to six years. More than 550 biosimilars, most in the earliest stages, have been reported in the development pipeline, along with more than 400 biobetters (see www.biosimilarspipeline.com). Biosimilars are resulting in a rapid expansion of bioprocessing, with literally hundreds of new potential entrants worldwide viewing biosimilars as a route to

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U.S. and EU markets. Thus, any innovation that streamlines, simplifies, or reduces bioprocessing costs will likely be viewed positively by this market segment.

Protein A And Replacements: For a long time, Protein A has dominated initial recombinant antibody capture and purification. And with original Protein A-related patents held by Repligen and GE expiring, new entrants are rapidly entering the market. This includes higher-performing (e.g. high antibody-binding) and more generic broadly applicable Protein A separation resins, all essentially targeted to capture the markets held by the market leader, the Mab Select SuRe product line from GE. With Protein A quite expensive and essentially involving the use of one GMP-produced recombinant protein to purify another, the industry continues to seek more cost-effective alternatives. Other alternatives entering the market include high-capacity ion exchanger (CEX) resins; recombinant camel- (camelid) and llama-derived antibody-based resins, such as from BAC BV (now Life Technologies, Inc.); and custom-designed binding ligands, such as from Prometic Biosciences. Crystallization, polyethylene glycol (PEG) precipitation, expanded-bed absorption (EBA), and simulated moving-bed (SMB) chromatography will likely be among the other technologies entering the market in coming years that will be used for initial antibody capture and purification steps.

Process Monitoring: Sensors and other devices to monitor processes are another area where new products and technologies continue to enter the market. Single-use sensors are in great demand, and available sensors are often not robust enough for use in bioreactors. Adoption of process analytical technology (PAT) continues slowly, with it not yet reduced to precanned software.

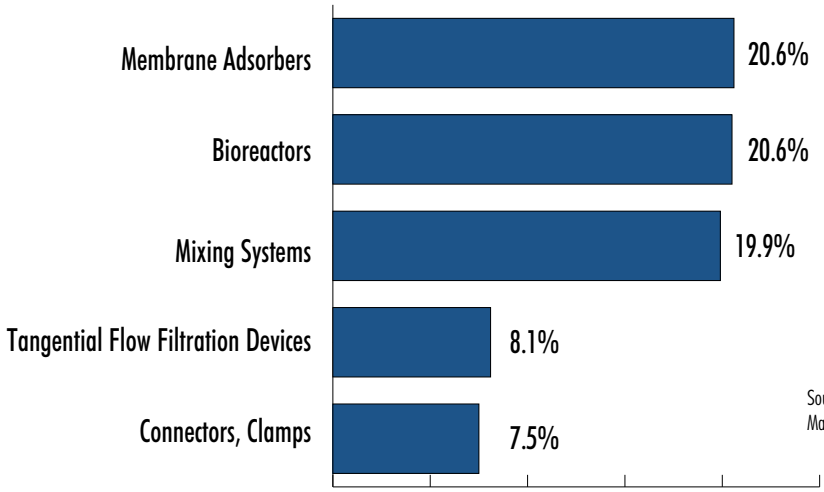
Prepacked Chromatography Columns: Prepacked chromatography columns, generally used several times, are not yet single-use, but this is another area where suppliers are rapidly launching new products. BioPlan survey data shows that 27% of decision makers are now at least considering adopting prepacked columns. The number of vendors and variety of products available continues to increase. Protein A prepacked columns are expected to be launched in 2014.

SUMMARY

There continues to be widespread dissatisfaction with the pace of innovations in bioprocessing. For example, 44 percent of respondents to our annual study desire improvements to basic single-use components, 27 percent want analytical assays improvements, and 25 percent want to see cell culture products and technologies improve. This kind of demand will fuel the industry's R&D expenditures for the foreseeable future.

Growth Rate (CAGR) For Single-Use Products, All Stages R&D And Manufacture

Note: Not growth in sales; this is growth in application-first usage within a facility.



Source: 10th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production, 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 methodology 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.

If you want to learn more about the report, please go to bioplanassociates.com.

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Mission TransCelerate:

Transforming The Drug Development Terrain

By Rob Wright

During the ill-fated 1970 Apollo 13 mission to the moon, it was astronaut Jack Swigert who alerted ground control that something had gone terribly wrong when he uttered the phrase, "Houston, we've had a problem here." Those same words seem very fitting to the current state of affairs around the skyrocketing costs of drug discovery. Recent estimates place the expense of successfully bringing *just one* drug to market at between $350 million and $1.2 billion. However, in the last decade, companies having brought 4 to 13 drugs to market have watched the price tag reach stratospheric heights — orbiting $5 billion+. "I think the pain point has reached a threshold that's no longer bearable," states Dalvir Gill, Ph.D., CEO of TransCelerate BioPharma.

A nonprofit organization founded in September 2012 by 10 member companies, TransCelerate set out on a bold mission — to collaborate across the global pharmaceutical and biotech R&D community to identify, prioritize, design, and implement solutions to simplify and accelerate the delivery of innovative new therapies. This is easier said than done in an industry with a history of companies working in secret, racing to be first to market. Now totaling 18 (see Table 1) participants, TransCelerate members include private, public, and VC-backed companies, ranging in age from a little over one year to nearly 300, and hailing from Japan, the EU, and the United States. With combined annual revenues in excess of $300 billion and nearly 800,000 employees worldwide, the prospect of TransCelerate being successful must be similar to imagining the United States and the former Soviet Union actually collaborating to put a man on the moon during the height of the Cold War. And yet, having only been in existence a little over a year, TransCelerate is transforming the drug development terrain faster than many thought possible. Dr. Gill, a 25-year drug development veteran, reveals the biggest roadblock to TransCelerate's success and how it was overcome. In addition, he explains the important role organizational structure plays in driving results, as well as the science behind the initiative selection process.

THE SIMPLE KEY TO OVERCOMING SKEPTICISM

"When I first heard about the TransCelerate opportunity, it was a scary proposition," recalls Gill. Skeptical about if it would actually work, he began gathering insight into the organization's mission and leadership commitment. As he did, the former president of Phase 2 to 4 drug development at PharmaNet-i3 (now known as inVentiv Health) began to believe that it could not only work, but it ***had*** to work. "The drug development industry was running out of options. We had to find a way to collaborate to remove drug development inefficiencies," Gill affirms. Reflecting on his decision to "seize" the TransCelerate opportunity, he says, "I took on this position, and I have not regretted it for one day. How often does a person encounter an opportunity in their career where taking a slightly different, perhaps riskier, path can have such massive implications on bringing more medicines to people?" The path was riskier because Gill was walking away from a successful career. In addition, the path would be much more difficult, because nothing as bold as the TransCelerate initiative had ever been attempted before in the clinical space.

Some may think sending a man to the moon to be difficult. However, discovering the cure for cancer or Alzheimer's is *more* difficult. Otherwise, it would have already been done. Many are skeptical if we will ever find cures for these kinds of diseases. Skepticism proved to be one of the biggest roadblocks to TransCelerate gaining lift-off. "The history of these kinds of not-for-profit, precompetitive collaborations has yielded mixed results, at best," he asserts. According to Gill, the key to overcoming skepticism is getting results. "As TransCelerate quickly started to produce and publish tangible, pragmatic, actionable, deliverables (e.g. its risk-based monitoring paper at the end of May 2013), some of the initial skepticism started to dissipate. Next came the announcement of a plan for a common clinical-site qualification and training initiative. This was followed by TransCelerate delivering on other successful initiatives. Thus, the key to overcoming the initial skepticism was delivering results. But none of that would have been possible without an organizational structure that encourages and enables its members but also holds them accountable for delivering results.

TransCelerate: From 10 Members To 18

Founding Companies
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AstraZeneca
Boehringer Ingelheim
Bristol-Myers Squibb
Lilly
GSK
Johnson & Johnson
Pfizer
Roche
Sanofi

New Members In 2013
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Biogen Idec
Braeburn Pharmaceuticals
Cubist
EMD Serono
Forest Laboratories
Onyx Pharmaceuticals
UCB

RESULTS ORIENTATION REQUIRES THAT FORM FOLLOW FUNCTION

TransCelerate's organizational structure, which had been put in place prior to his arrival, was one of the reasons Gill was attracted to the position. "A big contributor to why consortiums fail is because they often don't have leadership at the right level," states Gill. In his experience, consortium projects are frequently managed and run by consultants and third-party providers. As a result, company people do not get deeply involved, and initiatives never really take off. To prevent this from happening at TransCelerate, the configuration was set up to involve member-company leaders at the highest levels and in a structure similar to a pharmaceutical company. For example, Gill reports to chairman of the board Paul Stoffels, CSO and worldwide chairman of pharmaceuticals for Johnson & Johnson. The organization has a board of directors representing each member company. "At the board level, we have some very senior-level leaders, some responsible for multibillion-dollar R&D budgets," he affirms. "They have accountability within the TransCelerate organization and need to be on board with how we operate, the projects we pick, and progress being made." According to Gill, they are consulted regularly through board meetings and other interactions. The operations committee, which also consists of senior-level people from member companies, handles the day-to-day running of the business.

"When you have these two layers of top-level support, you have the ability to move projects along quickly," says Gill. "More importantly, when results and deliverables are released, these individuals have the ability to drive implementation as opposed to having a nice white paper that people can pin up on their bulletin board."

In addition to having the right leadership, Gill stresses the importance that prioritization has played in TransCelerate's success. For example, once the organization gains approval to commission a project, it is treated within member companies like any other internal project. "We look for project leadership that makes sense, staffing the team with people from the member companies who fit with the right subject-matter expertise," he states. From there, the team drafts its time line, deliverables, and budget, refining the project from the original proposal. "These folks are held accountable to deliver to TransCelerate," Gill explains. "These projects should not be secondary priorities."

Gill recognizes that maintaining prioritization of TransCelerate projects is challenging for member employees, since they have their day jobs to contend with, too. That's why part of the budgeting process includes assigning full-time equivalent (FTE) contributions to indicate the necessary member-employee workload for a project. In some cases, the FTE is as high as 100 percent being dedicated toward a TransCelerate project. "Twenty-five to 30 percent is at the bottom end of the FTE commitment allocation," Gill shares. TransCelerate employs only two full-time employees; the rest of the work is completed by member-company personnel who define problems and come up with solutions. This strategy not only creates buy-in and accountability, it prevents projects from languishing. "We don't get calls saying, 'Hey, this project slipped by for three weeks, and we are sorry about that,'" Gill says. "People realize that's not an acceptable response, and they will have to justify these things to me and the entire operations committee."

THE SCIENCE OF PROJECT SELECTION

At its core, TransCelerate was created to cut through the red tape and duplicated work so often associated with skyrocketing R&D drug development costs. But the scope of such an endeavor was daunting, with potential projects including everything from improving efficiencies in collaborations, clinical/preclinical data sharing, and target validation. The initial potential-project list numbered 30. From there, TransCelerate leadership began the process of narrowing the focus to a more manageable number. To do this, member companies sent some of their best people to apply a tactical approach to project selection. "Initially we wanted to pick doable, tangible, quick-hitting projects that had enormous value and a return on investment from multiple perspectives (e.g.

reductions in dollars or FTEs) and for multiple stakeholders," he says. This process narrowed the list to 10 projects.

The next step involved conducting project-feasibility analyses to determine how much effort each project would require in terms of money, manpower, and expertise. The projects under consideration were also assessed from an intangible perspective (e.g. value to trial participants, higher safety). From that data, TransCelerate built a project road map. "If a project was foundational to the road map — meaning that to complete project 'B' we must first finish project 'A' — it got higher priority than a project that might deliver some immediate value but was not necessarily going to move the overall 'landscape' forward as quickly as we would like," Gill explains. Through this process, the list was narrowed to five projects for initial action: (1) risk-based monitoring, (2) site qualification and training, (3) clinical data standards, (4) comparator drugs, and (5) shared-investigator portal. Each project also included a targeted outcome. For example, the site-qualification-and-training initiative included target outcomes of common criteria for mutual recognition of GCP training and common forms to collect generic information about study sites. Of the initial five projects, TransCelerate has delivered actionable information on all but one — the shared-investigator portal.

Though Gill is proud of all of TransCelerate's accomplishments, he is most impressed with the success of the comparator-drug initiative. This is because it had the highest degree of skepticism as to its feasibility. "Very few people believed competitive companies would facilitate access to comparator drugs from each other for use in comparator clinical trials," he says. "Once the facts were presented, people realized companies almost always secured comparator drugs; it was just a matter of how painful we wanted to make the process." According to Gill, people began to understand the logical benefits this network would achieve. Companies would be able to launch trials faster. Acquiring drugs would cost less. Most importantly, studies would be safer by avoiding all the issues around drug stability and the possible inadvertent acquisition of counterfeit drugs. On Aug. 6, 2013, TransCelerate announced the successful establishment of the clinical trial comparator network and the initiation of its first transaction.

To look at future projects, TransCelerate created the aptly named future initiatives team. Representatives of this team evaluate the current state of clinical trials and postulate what technology, process, or regulatory changes will occur in three to five years. The team then creates a road map detailing how to achieve the clinical trial state of the future. Gill says this strategic process was used to help

determine the prioritization and fit of the recently announced additional TransCelerate initiatives: (1) common clinical trial protocol template, (2) special-populations clinical trial networks (pediatric and minority), and (3) investigator registry. Gill provides an example of why linking current and future initiatives is not only important but logical. "One of the current projects involves developing data standards in collaboration with CDISC [Clinical Data Interchange Standards Consortium] and the FDA. If we are standardizing data for certain therapeutic areas, it makes sense to start tackling the front end of the process, which is the protocol for those therapeutic areas." This is why TransCelerate launched the common-protocol template initiative, which will match therapeutic areas with agreed-upon data standards for each therapeutic area. "Similarly, if you have a shared-portal platform, it needs an investigator registry that allows unique identification, credentialing, and identity management for clinical trial investigators around the world," Gill contends.

In my discussion with Gill, he revealed how his performance as CEO of TransCelerate is measured — delivery on announced initiatives, organization operations, and organization governance. When asked how it has been going thus far, he replied, "I think overall we have made really outstanding progress this year. We have delivered on the projects we said we were going to deliver on." Interestingly, about six months prior to writing this article, I was contacted by a reader proposing the submission of a TransCelerate "call-to-action" article. They expressed how TransCelerate wasn't moving quickly enough. While I have yet to receive a rough draft of the proposed paper, during the same time period, TransCelerate has delivered results on four of its five initial projects and added three new ones, as well. Perhaps all consortiums should aspire to move as slowly as TransCelerate.

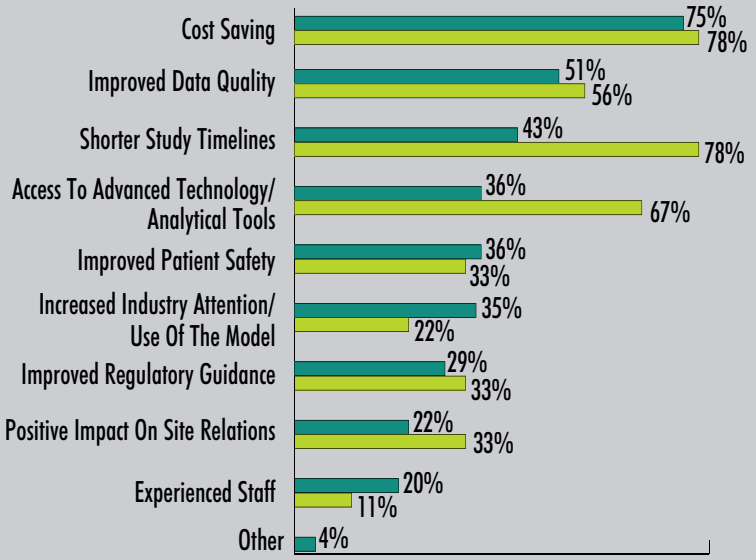
THE KEYS TO BUILDING A SUCCESSFUL CONSORTIUM

For the founding 10 TransCelerate BioPharma companies, the benefits of membership were very clear (e.g. reducing redundant costs). In addition, the structure provides members the autonomy to select (if any) which initiatives to implement at their organizations. For example, a survey conducted by Industry Standard Research (see graph) reveals a variety of reasons to adopt risk-based monitoring, one of TransCelerate's initial initiatives. However, just because you are a TransCelerate member does not mean you are required to implement the outcomes resulting from every initiative tackled. According to TransCelerate CEO Dalvir Gill, Ph.D., this flexibility is just one of the keys to building a successful consortium.

Adequate funding is another key. But at TransCelerate, it is not the type of funding you might imagine. "We are not an organization that is funded by a bucketful of money," he states. "Our funding is a fraction of a fraction of what funds many consortiums." TransCelerate's funding primarily comes in the form of time and intellect. "The member company defines a problem and then puts some of their best brains on coming up with a solution," he explains.

Finally, Gill suggests another key to creating a successful consortium is to create it so that it can easily be dissolved when no longer needed. He refers to this as project sustainability. "My job as CEO is to plan for all of our projects to be sustainable with or without the existence of TransCelerate." However, given the number of projects currently being undertaken, Gill suspects the organization won't be closing its doors anytime soon.

There could be many reasons to adopt risk-based monitoring.
Which of the following do you think are increasing the adoption the most? Select all that apply.



The TransCelerate member companies chose to focus resources on the most tangible projects that had enormous value and return on investment. Recent research by Industry Standard Research illustrates the perceived opportunity the industry sees in the adoption of risk-based monitoring, one of the TransCelerate project areas.

Industry Standard Research — www.ISRreports.com

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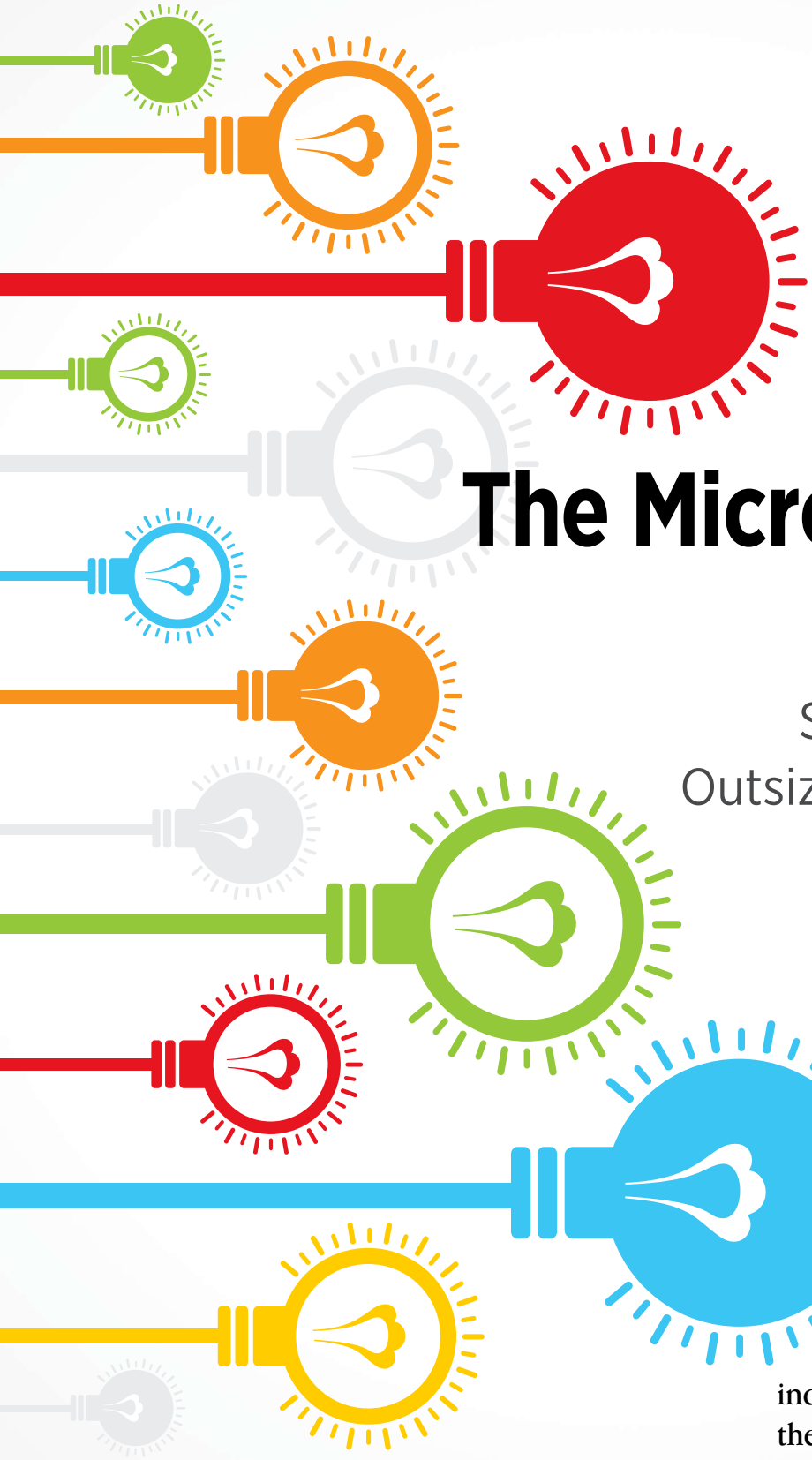

The Micro-Innovators Part 2

Small Enterprises Make Outsized Contributions With Novel Drugs.

By Wayne Koberstein, executive editor

Many companies may deserve coverage under the definition of "micro-innovators" as companies developing unique therapeutics they have themselves discovered. But here I have chosen three companies that have chosen the toughest possible route in the life science industry: taking an innovative path from the earliest stages of research through the entire course of product development.

I interviewed the CEOs of micro-innovators Sarepta Therapeutics, Melinta Therapeutics (formerly Rib-X), and Advanced Cell Technology (ACT). Sarepta has been in the news often for its Duchenne muscular dystrophy (DMD) drug, mainly concerning whether it will beat the competition, a GSK drug, to market. Melinta has striven bravely into the almost abandoned field of antibiotics with a product based on Nobel-winning research into ribosomes. ACT has pioneered a unique line of human embryonic stem cells for treating AMD and other conditions. From the three companies' collective and individual experiences, a set of tenets emerges, which I have framed as imperative responses to the conditions such companies typically encounter.

In Part One, we looked at how the companies began with groundbreaking science, built a business foundation for applying the science, and learned to aim their unique technologies at defined therapeutic targets. In Part Two, we see how they funded, planned, and are executing their clinical trials.

MANY WAYS TO PAY THE PIPER

"Funding the company was probably our biggest struggle," says Gary Rabin, ACT's president and CEO. Of course, many if not all micro-innovators would say the same, as do Sarepta and Melinta. But in ACT's case, some added twists developed that illustrate the lengths to which some companies will go to pay the high costs of drug development. It may also suggest another way small companies that discover and develop their own products stand out from the crowd in this industry — none of our three companies has followed the stereotypical venture-capital to IPO path.

ACT was not VC-financed; it went public through a reverse merger into a shell company, giving it access to capital market financing from the beginning — a tough accomplishment in its founding year 2005. At that point, however, it was still preclinical, with not even a gleam of a therapeutic product in its eye.

"Companies at that stage, without big venture capital behind them, struggle to raise capital, and this company did some really bad financing in that period, so it worked hand to mouth," Rabin says. "The coffee maker and the copy machine were actually repossessed at one point. We've come a long way since then."

ACT had the additional challenge of working in the controversial area of human embryonic stem cells (hESC). To this day, it is still pushing to persuade the NIH that its cell line meets the agency's hESC definition and qualifies for NIH funding.

Now a low-priced favorite on the bulletin board exchange, ACT contemplates moving up. "Being a penny stock on the bulletin board has offered some advantages to us in the past, but the volatility that excites penny stock investors is not always a desirable feature, particularly as a company matures," says Rabin. "We have been able to build an incredibly loyal base of investors – with more than 45,000 retail shareholders – and reached a market cap of almost $200 million. Now we want to take the next step, and we are actively working toward uplisting to NASDAQ or the like. This will give us access to an additional pool of institutional investors."

Sarepta also went public for its development funding, 15 years ago. But lately, it has felt the hot glow of stockholders' expectations over its shoulder. CEO Chris Garabedian sees the positive side: "It was critical that I could tap into the public market more easily than trolling for dollars in the VC community, which can be challenging without a track record of the technology's success." He points to the exceptional cases of early IPOism, such as Human Genome Sciences, Dendreon, and Alexion.

But Sarepta also went through an identity change before it began to make headway. With the move to focus on DMD came a corporate transformation, symbolized by rechristening the company from its former name, AVI Biopharma. "Every paragon of success today had been written off at one point because it had the wrong application," notes Garabedian. "Gilead is a perfect example; it moved to in-licensing nucleotide products and now is the largest market cap company in the industry, recently surpassing Amgen. So you work with what you have. We renamed the company. We changed the staff and executive team, and people describe us not as a start-up but a start-over."

Similarly, Melinta's name change, just as I finished this article, reflects a "strategic realignment," according to the company. Under its new management, Melinta will shift into full commercialization mode, pushing toward and preparing for product launch.

Sarepta, like Ariad and Garabedian's former company Celgene, has also skipped the partnership avenue. A year ago, Garabedian says, he would not have thought the company could make it to market without a major pharma partner. Now he no longer agrees with that premise. "There are many examples of sophisticated small companies successfully commercializing new therapies on their own, and that's what we aim to do here at Sarepta."

Garabedian agrees that structured deals with terms that favor pharma partners and stretch out the timeline with milestone payments make partnering less attractive. "We haven't taken it completely off the table, but it has to be the right circumstances to make sense for staying on the drug development path, doing the right thing by our shareholders, and ultimately getting our drugs to patients as soon as possible once we prove they're safe and effective. And large pharma has different priorities, without necessarily having the same sense of urgency we do."

Stock volatility has been an issue for Sarepta, at least as a topic of speculation among trade press and analysts. But the company's real test will only come when the FDA makes a key decision about the Phase 2b eteplirsen data — whether to approve eteplirsen early based on dystrophin levels as a surrogate marker of effectiveness or on the stabilization of function observed in clinical studies to date.

Melinta went the opposite direction with its funding — remaining private to this day. Venture capital and dedicated private investors have sustained the company for years and, according to CEO Mary Szela, will do so into the indefinite future. "The company is well-funded at this point to pursue the development and commercialization of delafloxacin and the additional anti-infective compounds in our pipeline. Our investors are focused on the long term and committed to realizing the potential of our pipeline," she says.

Melinta recently ended a partnership with Sanofi and reclaimed

all rights to its novel ribosome-targeting antibiotics (RX-04) program. "At the time the Sanofi deal was completed, we believed it was the best way to advance the RX-04 platform, and Sanofi contributed meaningfully to its advancement," says Szela. "However, with the clinical and development resources of our lead investor Vatera, and with a new management team in place, the company now has the resources to advance the program independently and has worked with Sanofi to obtain full rights. We were thrilled they agreed to return the rights since we believe we are in a strong position to move RX-04 into the clinic."

Szela says the company remains committed to developing its pipeline of novel antibiotics. It is conducting a Phase 3 clinical trial of delafloxacin for acute bacterial skin and skin structure infections (ABSSSI), the first of two planned Phase 3 trials for the drug in ABSSSI, the second one for an oral formulation later in 2013 or in early 2014. It plans to launch human trials for the lead molecule in the RX-04 program in 2014 for life-threatening, gram-negative pathogens.

"We are very lucky to have a group of investors who believe in the scientific and technological underpinnings of the company, and they are very supportive of our efforts, so we are well-funded to complete the development and commercialization of our products," Szela says. "Drug development is a difficult endeavor, and the main hurdles we face in the R&D of our products are achieving the clinical and regulatory milestones necessary to commercialize them."

For ACT, Rabin says, working with human embryonic stem cells gives it some uniqueness, which has attracted private investors and helped it weather the Bush-era moratorium on government funding. "The federal-funding issue has proved to be both a positive and a negative. While we would like to see greater NIH investment in our programs, as well as access to our human ES cells by other researchers in regenerative medicine, the moratorium actually gave us a gigantic advantage because we used private money and thus became a forerunner in both clinical development and in securing very broad patent positions in HES — as a consequence of getting there first."

STAY THE COURSE! — WHERE'S THE MAP?

By choosing the novel-drug development path, micro-innovators assume the mighty challenge of actually going down it. The first real step is proof-of-concept (PoC), but as we've seen, companies may spend years getting to the point of proving the particular concept that will drive development of their products' initial indications. Once there, they must design the preclinical and early clinical studies as carefully as possible to address safety and effectiveness in the targeted areas.

Rabin of ACT emphasizes getting the right experts to plan those studies. "Many of our scientists are trained as developmental biologists and have the ability to elucidate the conditions that occur during 'organogenesis' for any type of tissue — that is, to figure out the natural signals that occur as an embryonic stem cell becomes a differentiated cell as part of an organ in the body."

That solves the challenge of producing stem cells, but none of the company scientists had worked with animal models, so ACT turned to academic collaborations to explore how the cells might treat human diseases. Now, Rabin says, the company has some of the leading scientists in its targeted disease areas to guide its clinical development programs. It has achieved U.S. and European orphan status for its Stargardt's disease program, shortening the timeline and offering possible compassionate use, and its dry AMD program may be eligible for accelerated approval and priority review at the FDA, after Phase 2 studies.

"The cost of building our own GMP space has proved to be far less expensive than the CMO route and probably far speedier in terms of the time to get to clinical trials."

Gary Rabin, president and CEO, Advanced Cell Technology

"Some of the common issues in development include figuring out which 'box' your product fits in for the FDA or other regulatory agencies — particularly for cell therapies, how to be regulated as a drug versus device (and especially avoid being regulated as both) — and developing a strategy for educating regulators about your product so that your safety and efficacy studies are approved in a way that maximizes the chance for success," Rabin says.

"Another possible common feature relates to drug pricing and reimbursement. There are set CPT and HCPCS drug and product codes, and those existing codes may not always be ideal (or even work) when it comes to completely different approaches to treating a disease where existing therapies exist and can be equally problematic where there is no existing treatment for a particular disease."

Melinta is expediting its development programs under the U.S. Generating Antibiotic Incentives Now (GAIN) Innovation Act, passed in July 2012 to encourage drug development aimed at resistant pathogens. Delafloxacin was one of the first compounds to receive Qualified Infectious Disease Product (QIDP) designations under the Act, for ABSSSI and community-acquired bacterial pneumonia (CABP). Companies with QIDPs gain incentives such as an additional five years of market exclusivity, priority review, and eligibility for fast-track review status.

One critical component of drug development that generally seems to receive the *least* forethought is securing a supply of the product for clinical trials. ACT is exceptional in having a solid manufacturing capacity — an early priority for the company and its investors. "The reality is that GMP manufacturing capability is an absolute must for us to advance into human clinical trials, and it must be in place far earlier than the commencement of the trials," says Rabin. "We needed to demonstrate to the FDA that the RPE cells we intended to inject into human patients, when made by our GMP process, were safe in animal studies and showed some evidence of effectiveness."

Rabin says the company had to rely either on contract manufacturing — putting its special products in the middle of multiple, unrelated programs at a premium price — or building its own GMP facility where it has control over its process. "In the end, the cost of building our own GMP space has proved to be far less expensive than the CMO route and probably far speedier in terms of the time to get to clinical trials."

CATCHING THE WAVES

Every micro-innovator company confronts common as well as unique challenges. Others in the life science industry will recognize the situations and choices they share with the companies described here. Every company must build a foundation, find funding, focus its research, and forge through development. But not every one must cradle a unique and original creation along the way. Novel discovery and development are self-imposed burdens, a singular mission requiring special skills, resources, knowledge, and above all, persistence.

Sometimes, the persistence is in vain — spent in trolling aimlessly among endless possibilities for applying groundbreaking research. Other times, though, when science and business find a happy marriage, a company is able to tap the power of an unbroken, consistent, and dedicated line of development from invention to application.

That is the point of picking three companies out of the arguably elite club of micro-innovators to share their real-world experiences. The universe is full of business models and theories. It only makes good common sense to take a deeper look at the details of what happens to actual companies as they attempt the entire journey from lab to market. The surfer rises, steadies on the board, and catches the wave — will this one make it to the shore?

A Rare-Disease Champion

Rogerio Vivaldi's experience with rare-disease therapies teaches that drug development is never finished until simple and certain access for patients is ensured.

By Wayne Koberstein, executive editor

Rogerio Vivaldi, CEO, Minerva Neurosciences

Rogerio Vivaldi may be the most unique pharmaceutical executive I have ever met. His background, history in the industry, and long-time mission — all sound more like an adventure than a career, as if he slayed monsters and rescued fair humans to get where he is. And in a way, he did. If you see Gaucher Disease as monstrous and its sufferers as the humans in dire distress, Vivaldi will appear as the hero discovering his fate: delivering life-saving and life-redeeming therapies to those who need them.

Vivaldi's saga began in Brazil, where he won universal access to Genzyme's enzyme replacement therapy (ERT) Ceredase (imiglucerase). In doing so, his travels took him from the urban streets of Sao Paulo to the third-world regions of the Amazon. His odyssey progressed as he followed the same calling in many other countries, then went on to take command of a global business in treatments for Gaucher and other extremely rare diseases where patients previously had no hope.

Prior to his current position as CEO of Minerva Neurosciences, Vivaldi was the head of Genzyme's Rare Diseases Unit, which is an integrated commercial organization, one of only two independent Genzyme businesses remaining after the Sanofi merger; the other concentrates on multiple sclerosis. (Vivaldi moved to his new company just as this article went to press.)

I come not to praise Vivaldi but to understand what makes him tick. Overall, Vivaldi's story may enlarge the idea of precommercial product development to include a factor normally perceived as marketing: patient access. "There is no development without access," he says succinctly. Identifying new patients, guiding doctors through diagnosis and treatment, and building a sustainable supply chain are all essential to development before the market and delivery to the market.

CASE BY CASE, TO EVERY CASE

Vivaldi was instrumental in winning early access to Ceredase in Brazil and ultimately in many other countries, driven personally by experience with his first Gaucher patient in 1992. An M.D., he specialized in diabetes care, and a friend in academic research asked him to take care of a patient who was just beginning ERT.

"That was a turning point — for the patient and for me," he says. "The patient had his life transformed, but my life was transformed at the same time because I saw how the treatment was changing the natural history of that disease. It was a dramatic effect rarely seen before in any therapy, for any disease."

Once Vivaldi learned about Ceredase, which had just gained approval in the United States the previous year, he wanted to make it available to as many patients as possible. But his initial hurdle was paying for the drug. The therapy then cost about $200,000 per year, and it had to be administered every other week for life.

"Soon I probably had more Gaucher patients than the majority of documented cases in the world at that time, and several years later, Genzyme asked me to help the company make Ceredase available to more patients because I did have the first ones, but they were paying for the therapy out-of-pocket."

In Brazil, the payment challenge, though still daunting, was simplified by the universal healthcare mandate of its national health system. Vivaldi went straight to the top, appealing directly to the Minister of Health, who subsequently agreed to cover Ceredase and later listed it on the national formulary — the first and only time Brazil, or likely any country, paid for a product that had not yet received market authorization from the regulatory authority.

A key point in Vivaldi's argument for national government reimbursement was the need for pan-Brazilian access to Gaucher treatment: "I told the Minister that with a rare disease, a state-by-state approach would never work because you would have people migrating to different states just to stay alive." Vivaldi also persuaded the Minister to make the government coverage permanent and build the infrastructure necessary to maintain steady delivery of the medicine and supportive care for all Gaucher patients anywhere in Brazil. Since then, he and the company applied the same logic globally, winning reimbursement and logistical support wherever possible, so that any Gaucher patient in any location can be treated.

Vivaldi visited every hospital in Brazil, asking three questions: "Do you know what Gaucher disease is? Do you know Gaucher disease has a treatment? And do you know that the treatment is available

here in Brazil? It was fascinating to see the power of those three simple questions." In most places, no one had even heard about Gaucher, and where there was some knowledge of the disease, almost no one knew about the ERT or believed it could be obtained in Brazil.

Now Brazil has the second largest Gaucher population in the world. To achieve such growth, Vivaldi organized an education program that spread like tree branches. "I became a trainer of physicians, who trained other physicians, who trained other physicians, and so on." Meanwhile, Brazil built a supply chain for the ERT that covered all the disparate regions of the country, from its sophisticated urban centers to jungle villages in third-world environments.

When a mother from a local tribe saw a poster on Gaucher in a field clinic and recognized the symptoms her daughter was displaying, the attending doctor conducted a dried blood spot (DBS) filter test on the entire family and diagnosed the girl and a sibling with the disease. He then ordered regular shipments of Ceredase to the village, to arrive by boat on the same days he administered it to avoid spoilage in jungle heat. Now, says Vivaldi, "The patients are happy and doing phenomenally well, receiving therapy every other week."

GLOBALIZING ACCESS

Vivaldi joined Genzyme Brazil in 1995, and he was transferred to the United States in 2010, first to head the Renal division, then in 2011 to head the Rare Diseases Business Unit. In retrospect, the sequence of responsibilities looks like a logical and natural pathway to worldwide application of his approach to treatment access in Brazil.

Once Vivaldi moved to the United States, he connected with many rare-disease patient associations, support groups, and individual patients to learn not only about their therapeutic needs but also about the constellation of challenges each disease presents.

"Patients are all the same in one sense: If you treat them with respect, if they see you as trustworthy and committed to listening to them, and if you focus on the issues they have — not the issues you want them to have — you will succeed any place in the world."

CHOSEN BY THE CHALLENGE

Although Vivaldi is not a scientist or expert in drug development, he has a compelling answer for how pharma companies can find their way to a therapeutic target and approach. The process he describes is a blend of science and practicality. "I will put it simply and say sometimes the pharma company is selected, and sometimes the company is selected by the development candidate. You can't look at the biochemical target and say, 'Oh, what a wonderful target!' No, you need to look at the patients and try to understand how your technology and drug discovery could help the persons affected by the disease mechanism."

Some companies may pursue rare-disease or orphan indications with the long-term intent of exploiting the same drug mechanisms for indications in a larger market, but Vivaldi has a different take on what companies should emulate. "Rare-disease development would be interesting purely as a model for pharmaceutical companies to follow, because then they would start by trying to understand the problem rather than focus on what would sell a lot."

TRIALS & TECHNOLOGY

Although the practical challenges in development for rare-disease and common-disease drugs may be quite different, the ultimate purpose is the same: prove safety and efficacy. Genzyme's first trials in Gaucher, for Ceredase and Cerezyme more than 20 years ago, reflected the tiny patient populations and limited understanding of the disease at the time. Now, says Vivaldi, patient populations and knowledge have expanded along with the experience of using the treatments. The pivotal trial for Ceredase included only 12 patients. Genzymes' new Gaucher drug in development, the small molecule eliglustat, will undergo a Phase 3 trial with 400 patients.

Vivaldi points out that 400 patients amount to one-quarter of all Gaucher patients in the Unites States, or five percent of the total world patient population. "If you want to claim efficacy, you have to prove the drug has a chance to be at least as effective as the standard treatment or more. Gaucher Disease is now a much different disease than it was before treatment was available; the natural progression of the disease has been changed. So, now what else can we do for patients? Some patients still have bone disease or lung disease; others can't simply keep receiving infusions. So we consider convenience along with all the different mechanisms of action that we can target."

HIGH PRICE BUT TINY SLICE

When developing drugs for rare diseases, the issue of the high cost of such drugs is bound to come up. Most pharma companies argue that these high prices are needed in order to recover the costs of R&D and hard-to-produce treatments (e.g. ERT) while also making a profit for future growth and research. However, Vivaldi adds another twist for rare-disease drugs.

"When you have so few individuals being affected by a disease, even having a high cost compared with the average cost of other drugs, the total amount is small. So it is uncommon to see rare-disease treatments have an effect higher than two percent on the total budget of any healthcare system — yet it's fascinating to me that cost gets such tremendous visibility in the discussion. The total cost per day for a patient in an intensive care unit could be as much as a full year of enzyme replacement therapy."

Vivaldi also emphasizes the manifest cost-effectiveness of rare-disease drugs. "Look at Pompe Disease and the effect the treatment can have on a patient's family. You've rescued their whole family back to society. The family members who were not working because they have to take care of that child — now they can go back to work. So the benefits include the value the therapy has to society in a multiplicity of ways."

Because of his experience, Vivaldi sticks to his original, simple thesis: drug development must include patients' access, and society, which shares in the benefits, must be ready to bear the cost.

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Pharmaceuticals: Target For Terrorism

By Dr. Miri Halperin Wernli and Dr. Boaz Ganor

Slowly and steadily, terrorism, like a malignant cancer, has entered our lives. What once was an occasional event on the other side of the world can no longer be ignored as someone else's problem. Terrorists, alone, in cells, or part of expanding international networks, are affecting the way we live, the way we think, and the way we do business. Government facilities, planes, trains, ships, oil refineries, and luxury locations have all taken the biggest and most publicized hits.

The biopharmaceutical industry has seen it in the form of counterfeiting, adulteration, and diverted product, all of which are, perhaps, more disruptive than destructive.

But that can easily change. The ingredients, technologies, knowledge, and global distribution inherent in making and delivering medicines can be turned too easily from benefit to destruction. That's why we, a senior pharmaceutical executive and the head of a counterterrorism think tank, wrote this article. It is part of an ongoing initiative to explain why the biopharmaceutical industry needs to be alert to its vulnerabilities to terroristic influence and what it can do to reduce the risk.

WANING PUBLIC SUPPORT FOR BIOPHARM

Fundamental to understanding the problem is an understanding of the origins and motives of those who would do harm. It's a fellowship of strange bedfellows: people from different backgrounds and with different agendas willing to deploy extreme violence to send their messages and to get their way. What they have in common is the use of violence among other tactics to impose their will.

We also need to appreciate the cultural environment in which the drug industry exists. The negative image portrayed in popular media shapes how people think. There was a time when the industry was held in high regard by most levels of society. That has changed, and life-saving or life-enhancing benefits aside, there's little understadning within the general population of the way drugs are developed, marketed, and sold. A recent opinion survey of 600 international, national, and regional patient groups on the corporate reputation of pharma in general and 29 leading pharma companies in particular indicated that only 34 percent of respondents gave pharma a "good" or "excellent" rating. Among the areas patient groups rated pharma as having a "poor" record were 1) a lack of fair pricing policies leading to unseemly profits (50 percent); 2) a lack of transparency in all corporate activities (48 percent); 3) management of adverse event news (37 percent), and 4) acting with integrity (32 percent).

For a business concerned with health, such waning popular support creates an unhealthy reality. The biopharmaceutical industry is highly vulnerable. In response, industry executives need to expand their security thinking to protect against terrorist exploitation.

BANKROLLING TERRORISM WITH COUNTERFEITS

The US Drug Enforcement Agency recognizes that Hezbollah and Hamas make counterfeit drugs that are distributed and sold by established criminal networks throughout the Middle East and Latin America. This trafficking produces revenues that fund their terrorist activities.

They aren't alone. Other terrorist and criminal groups trade in counterfeits. It's a low-cost, high-margin business preying on a voracious market being robbed of the therapeutic benefits of the real thing.

As if the use of counterfeits to bankroll terrorism were not bad enough, think about the mass damage a zealot or other madman could cause by adding a lethal ingredient to these so-called drugs. Memory of the still-unsolved Tylenol killings in the Chicago area haunt those who recognize just how vulnerable unprotected pipelines can be.

TERRORISM RECEPTOR SITES

The equipment, materials, and personnel on which industry relies are potential terrorist targets. Laboratories, equipment, and other facilities that could be used to manufacture deadly pathogens are spread across the globe: the hospital in Karachi, the university chemistry lab in La Paz, the clinical research site in New Delhi.

Botulinum toxin, ricin, tetradotoxinm, conotoxin, and other deadly toxins already are present in many private-research laboratories. Is the security keeping them from us any more than a key to the front door and knowledge of what might be found in the fridge?

And, perhaps most significant, there is an ample supply of personnel trained to understand bioengineering processes. A 2009 WHO survey identified 466 biomedical and clinical engineering teaching units in 90 of its member states. That comprises a global educational infrastructure that has produced engineers, technologists, technicians, and assistants in the tens of thousands, if not more. There is no lack of talent that, with the right incentive or intimidation, could be redirected to harm.

The industry will never have total control of these risk factors, but it can take measures to minimize them. Toward this end, we have grouped security risks into "identity" and "security."

IDENTITY

Establishing a trustworthy framework for information and human resources is an essential first step in minimizing, if not preventing, the effects of insidious forms of terrorism.

Cyber-Terrorism

Use of the Internet for global collaboration opens the possibility that those we rely on are not who they present themselves to be. This possibility of cyber-terrorism masked as false representation can compromise drug discovery, development, manufacturing, and distribution by allowing the wrong people access to valuable intellectual property and other information assets.

Mitigating this risk is possible through the use of standardized digital identities. The global SAFE-BioPharma digital identity standard was developed by the industry and regulators, such as the FDA and EMA (European Medicines Agency), to provide high-assurance trust between parties engaged in secure Internet transactions. Many companies already are members of the nonprofit that manages the standard, and its IT, HR, and security groups can utilize its sophisticated cryptographic technology to guard against unauthorized access to protected information.

UPGRADING HR PROCEDURES

As vulnerable as IT may be, human resources is even more exposed. Conventional screening techniques are inadequate to reveal bad actors intent on infiltrating an organization for the wrong reasons.

And how often are existing — especially long-term employees — monitored without prejudice because of longevity or internal political alliances? History is littered with turncoats who have been denied promotion or whose pet projects have been defunded.

We recommend that HR executives re-examine background-checking protocols, especially in the terrorist-vulnerable areas of laboratories, manufacturing, and distribution. The access to technology, materials, and equipment should make careful screening of personnel staffing in these areas a priority. Routine reference checks and in-person interviews should be supplemented with psychological screening for personality disorders such as paranoia, narcissism, and anger management issues. There should be deep online searches, including checks for public records of instability and/or arrest. And CV-enhancing claims of publications, patents, speaking engagements, and other professional accomplishments should be carefully reviewed for plausibility and credibility.

Also recommended is a policy of ongoing personnel investigation and monitoring, especially of staff scientists and engineers with specialized pharmaceutical skills and purchasing responsibilities. They occupy roles that, given the right circumstances, can be turned against their employers. Common scenarios include retribution for cancellation of a favored program, a reprimand, refusal of a patent or paper, or losing a promotion. Issues less visible to management, but potentially exploitable by a terrorist organization, are alcohol or substance abuse, financial and other personal problems, sexual orientation, or family members living in high-threat nations. The determined terrorist will use blackmail to leverage these situations for access to equipment and expertise or to divert materials or to force the unauthorized purchase of critical substances.

SECURITY

Traditional brick-and-mortar security is needed in every industry. But new challenges require biopharmaceutical industry security executives to embrace a fully integrated approach, combining physical protection, access controls, and materials accountability. Combined with the information security and personnel screening described earlier, these will strengthen the company's physical and cyber perimeters.

We strongly advise biometric devices as part of the protection of laboratory and other facilities housing materials and equipment, and servers. We also recommend ongoing inventorying and proper chain-of-custody protocols for all terror-prone biologicals, chemicals, and equipment outside of access-controlled areas.

PROTECTING THE SUPPLY CHAIN FROM ADULTERATION AND COUNTERFEITS

Economically motivated adulteration (EMA) — the adulteration of ingredients — has resulted in widespread misery and loss of life. While deaths have generally been in the hundreds, sophisticated terrorists infiltrating a production facility and introducing assay-resistant toxic ingredients could alter that calculus dramatically.

This is no idle concern. In 2007 and 2008, dozens of U.S. patients experienced adverse events from heparin that had been adulterated while being manufactured in China. In 2009 a shipment of more than 125,000 vials of insulin was stolen and stored in unknown conditions before being sold to pharmacies and patients. And 115 Panamanians died from ingesting cough syrup in which cheap diethylene glycol had been substituted for more expensive glycerin.

Manufacturers need to adopt electronic pedigree techniques to track and trace drug ingredients. They also need to advocate more direct action by the FDA and other regulatory bodies.

The counterfeit problem is more severe. According to the Center for Medicine in the Public Interest, sales of counterfeit drugs are around $75 billion and growing rapidly.

Sales from counterfeit drugs are around $75 billion and growing rapidly.

SECURING THE FUTURE

It's said that awareness is the first step toward change. Growing numbers of pharmaceutical decision makers are becoming aware of the problems discussed in this article. More attention needs to be directed to hiring and personnel monitoring practices. Scrutinizing online identities needs to be standardized with sophisticated cryptographic technologies. Terrorist groups already are counterfeiting drugs and distributing them through criminal cartels. The industry needs more initiatives to identify bogus drugs and to inform pharmacy professionals and consumers of ways to avoid and/or detect them. Of greatest concern is the potential for terrorist groups to expropriate criminal cartel resources and turn them from a source of income to a form of targeted destruction.

The technologies to prevent that doomsday scenario will evolve. For now, companies need to be aware of the problem, take practical action, and remain vigilant. It is a matter of corporate — and public — health.

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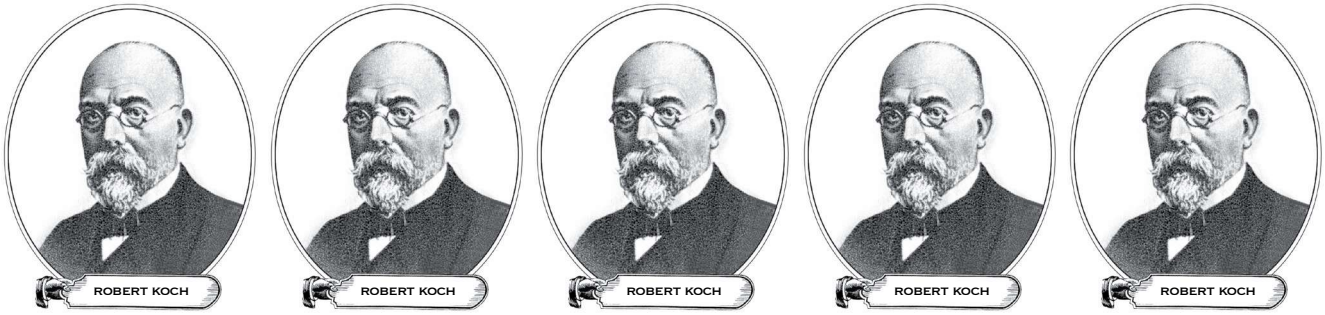

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cGMP Issues Are Increasing

By Gail Dutton, contributing editor

Big Pharma and small companies alike are failing when it comes to cGMP violations. The increasing number and complexity of global regulations, outsourcing, price pressures, and compressed time to market all contribute to these failures. Consequently, the number of compliance issues is expected to rise.

Between January 2010 and June 2013, the FDA issued 67 warning letters about cGMP compliance, affecting some of the world's largest and most reputable companies, including Bausch & Lomb, Bayer, Genentech, GSK, J&J, Sandoz, and others. During that time, API concerns decreased while finished product issues increased, according to the recent CPhI Annual Industry report.

After looking at drug recalls, withdrawals, and safety alerts, CPhI reported 178 incidents involving 120 companies. According to that data, 27 percent of the warning letters concerned undeclared ingredients, while 21 percent involved visible particulates, and another 21 percent were triggered by contamination.

LETTERS QUESTION DATA INTEGRITY

The increase in warning letters may be part of the normal political climate, notes Jim Stumpff, principal consultant at PAREXEL, a large CRO. "The FDA regulatory pendulum swings from very aggressive to less aggressive stances," he adds.

Others attribute the increase to the new scrutiny of compounding laboratories after last spring's meningitis outbreak. Before the outbreak, compounders were regulated only by state boards of pharmacy. Because they are new to FDA regulations, they are experiencing a high number of cGMP discrepancies. However, the increase began before the outbreak.

Many of the FDA warning letters cite a procedural lapse or a lack of data integrity. "There are many instances in which there's no known problem, but the FDA is concerned that procedural lapses will lead to future problems," notes Jonathan Berman, partner at the law firm Jones Day. Berman, who analyzed FDA warning letters last spring, found that most of the adulterated products worked properly and conformed to release specifications. His analysis determined the FDA cited procedural flaws more frequently than actual product failures. "Four of the seven most common violations relate to failure to establish written procedures," Berman says. Other common issues include a failure to develop written responsibilities for quality control units, failure to investigate out-of-specification batches, and the use of laboratory controls that have not been validated.

"Data issues range from being unable to produce the raw data to support information analysis certifications and submissions, to outright falsification of batch records, bioequivalency testing, or other data," Stumpff says. "This is an across-the-board issue. The EMA is talking about it, too. The problem could be as simple as a single employee who falsifies data." He recommends performing a robust data integrity evaluation. For example, "When a batch is released, quality assurance often sees only the test results. It trusts that the data provided by their lab showing sterility, pH, compound identity, etc. are accurate and that the tests were performed correctly. But, unless you examine the raw data, you don't know whether you have issues."

REGULATORY COMPLEXITY INCREASES RISK

The growing number of regulators, globally, who have slight variations in their requirements contributes to the complexity of cGMP issues even within major markets. "As companies go after business in newer markets that are developing their own health authorities and regulations, they must serve many masters," points out Amy Flynn, senior consultant at TayganPoint Consulting Group. That makes it easy for details to be overlooked.

The increase in global regulatory noise makes it imperative for regulators to express their requirements clearly. "Inadequate dissemination of the regulatory requirement by the regulator and frequent changes in the requirements contribute to the increase in FDA warning letters," says Dilip Shah, CEO at Vision Consulting Group. Frequent regulatory changes leave

little time for employees to absorb those changes, he explains.

"With all the data and information available, really understanding it is critical. So many competing regulations are creating complexity in the normal business process; they become distracting," according to Pat Horstman, senior consultant at TayganPoint Consulting Group.

Market pressures also contribute to the rise in cGMP issues. In addition to the rush to commercialize a product, there is significant pressure from customers to reduce products' sales prices. "Coupled with the increasing costs of raw materials, solvents, and energy, this can result in internal pressure to reduce manufacturing costs," says Catherine Dick, Ph.D., site manufacturing manager at Aesica Pharmaceuticals Ltd. "In this situation, the quality systems need to be robust enough to withstand that pressure and to ensure that compliance standards are maintained." She advises insisting upon realistic pricing. "Don't undercut prices just to win business." She also advocates ensuring that there is full understanding of the need for quality, giving realistic timings, and explaining why that extra week or month is necessary and not just a luxury.

> Between January 2010 and June 2013, the FDA issued 67 warning letters about cGMP compliance.

SYSTEMATIC VETTING IS NEEDED

The areas of greatest regulatory risks often are the areas outside the developer's immediate control — suppliers or contract service providers, according to Ian Markwell, VP of quality and "qualified person" (his real title) at Almac Pharma Services Business Unit. "It's not the use of the contract service providers, per se, which has fuelled this increase in GMP issues, but rather variation in the application of GMP standards at the contract service providers, which are then identified as significant GMP issues during regulatory inspections and result in warning letters or critical deficiencies being raised." To combat those variations, Markwell says, companies need to develop a systematic approach to select contract service providers. This should include assessing the provider's regulatory history and quality standards as well as contractual and financial considerations.

Additionally, Dick says, "Companies should have a well-structured process for identifying, documenting, and assessing quality risks associated with manufacturing activities, facilities, and systems, and have an achievable plan to mitigate those risks." This points to the need for risk-based analyses that factor experience with the compound into the product's risk profile.

Dick also points to the rise in aseptic and parenteral therapeutics as an area of potential cGMP concern. "Because they have limited manufacturing options, there is concern those facilities are being overloaded." Aging facilities and equipment pose another potential risk.

Assessments should go beyond manufacturing to include a comprehensive supply chain risk assessment that fully documents the shipping route and handoffs to identify and prioritize potential risks. Because materials typically pass through several locations and multiple parties before reaching their destination, there is ample opportunity for contamination.

API identity testing typically is performed with chemical tests. To that, Stumpff adds, "Consider additional tests, such as checking the specific packaging format used for the API and the use of numbered security seals on drums, which help confirm the API has not been tampered with prior to receipt."

"Regulators don't spend much time evaluating clinical batches," Stumpff continues. "Clinical batches tend to fly under the radar. Therefore, process issues may slip through to manufacturing. Humidity control is an example. A company may make a product for clinical trials without realizing they need humidity controls until they are making commercial batches, and the validation batch fails for lack of potency."

ATTITUDE CHANGES NEEDED

According to Dick, manufacturers need to accept that investing in both people and facilities will have long term benefits for all stakeholders. Shah expressed that sentiment in the CPhI report, writing, "The growing trend toward zero tolerance will necessitate changes in attitude and culture across an organization." In an interview for this article, he added, "What is needed is not more controls. Regulators can no longer be just inspectors or forensic auditors."

Instead, he advocates expanding regulators' advisory roles, using them as guides to train managers, who then train workers who are "engaged, directly or indirectly, in manufacturing and testing products for export to the U.S. The industry puts more emphasis on process and hardware compliance than on explaining the issues to employees and ensuring they understand their rationale."

Unless employees understand the rationale for specific procedures, asking them to follow those procedures may not produce the best results in compliance. Horstman advises writing clear standard operating procedures that are heavy on visuals — for local as well as international facilities. Often regulatory specialists write the SOPs from a technical perspective, making them hard for workers to understand. To compound the matter, the SOPs may not address the rationale for the procedures. Explaining the reasons for certain procedures provides context and allows employees to think critically. "Think from the user's perspective," Horstman says. "The best solutions often are the simplest."

Many Big Pharma companies are outsourcing manufacturing, regulatory compliance, and other functions as they downsize. That means there are fewer people in-house to focus on any given area, Flynn points out. "The most successful companies face the challenges head on," she says. "They bring their knowledge and experience as a large company to bear, partnering with their CMOs, working as a team."

Despite Challenging Economic Environment, Biotechs Are Booming

By Aftab Jamil and Ryan Starkes

The U.S. economy has been unstable for many years now, and this year, the U.S. experienced the first government shutdown since late 1995, causing many investors to become wary of the market. In spite of economic uncertainty over the budget deficit, biotechs remained a "safe haven," according to CNBC.

The biotech industry experienced tremendous growth in 2013, and amid this robust period, BDO studied the most recent 10-K filings of publicly traded companies listed on the NASDAQ Biotechnology Index to examine common trends. The 2013 study split the companies into two categories: small biotechs with revenues under $50 million and large biotechs with revenues over $50 million. Companies reporting more than $300 million in revenue were excluded to ensure findings are representative of the vast majority of companies included in the NASDAQ index.

Our analysis found that biotech companies overall are increasing their number of employees, delivering strong shareholder return, and continuing to remain committed to R&D efforts, which reinforces the biotech boom we are currently experiencing.

BIOTECH INDUSTRY SPURS JOB GROWTH

Notwithstanding the current economic environment, the number of employees at biotechs increased 13 percent from 2011 to 2012. According to EP Vantage's recent report, some companies reported staff increases of over 60 percent between 2007 and 2010. Compared to a 2.9 percent decline in overall U.S. private-sector jobs, U.S. employment in the biotech sector grew by 6.4 percent, or more than 96,000 jobs between 2001 and 2010, cites the Battelle/BIO State Bioscience Industry Development report. Of the companies on the biotech index, large biotechs were the big job creators in 2012, with overall headcount up a notable 23 percent and a 7 percent growth in R&D professionals.

In 2014, we expect to see R&D spending and employment levels remain in an upward trend in the biotech industry. With a strong pipeline of products in development and M&A activity continuing throughout the industry, the need for and ability to identify talent will remain.

BIOTECH IPO MARKET THRIVES

Biotech companies reported very strong total shareholder return (TSR) in 2012. Average TSR for all companies in BDO's study was 39 percent with smaller biotechs generating even larger increases. Positive returns have continued in 2013, contributing to significant interest among investors and a notable rise in initial public offerings. According to Forbes, the biotech sector saw over 30 new biotech offerings this year and more than $2.5 billion raised, making 2013 the best IPO market since 2000.

One important factor contributing to this growth is the enactment of the JOBs Act on April 5, 2012. Many small biotechs took advantage of the JOBs Act's reduced reporting requirements and found success and capital in the public markets. According to Biotech Now, a total of 34 domestic biotech companies have gone public in the 16 months since the act was signed into law, constituting a 79 percent increase in the number of biotech IPOs since the JOBs Act took effect.

While the increase of offerings is a great sign for companies, newly listed public companies have a challenging road ahead as they work to navigate clinical trials, FDA approvals, and increased demand following healthcare reform — all under the watchful eye of investors.

BIOTECHS REMAIN COMMITTED TO R&D

Although pharmaceutical companies have held off and sometimes even cut R&D spending for years, biotechs are committed to R&D efforts, spending an average of $54 million in 2012. Smaller biotechs led the charge despite seeing a decline in revenue last year. Small companies saw a 9 percent increase in average R&D spending overall and spent more on R&D per employee. In 2012, they spent $342,000 per employee, 42 percent more than the overall average in the

study, and 90 percent more than larger companies spent per employee in 2012.

The results of this increased R&D effort were recently identified in a report from the Pharmaceutical Research and Manufacturers of America (PhRMA), which noted that U.S. biopharmaceutical research companies are currently developing 452 new medicines and vaccines for the treatment of rare diseases, all of which are now in human clinical trials or under review by the FDA.

As biotechs continue to prioritize prudent cash management, companies reported $134 million in liquid assets in 2012, up 7 percent from 2011. This allowed biotechs to hold on average an equivalent of 2.49 years of R&D spending in 2012.

This September, the NASDAQ Biotechnology Index hit a record high, up over 46 percent. Big biotechs are attracting more investors in light of new drug approvals, positive data, and growth in sales and earnings. Heavy merger and acquisition activity continues, but at some point the increase in valuations may slow down the pace of M&A activity. As we enter 2014, we expect investor appetite for the biotech sector will remain very strong and companies will continue to pursue the public markets as a vehicle for obtaining the capital needed to continue product development. The challenge for these new public companies will now include meeting the expectations of their new investors and operating under the scrutiny of public markets.

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Competitors Collaborate To Train Asian Workers

By Cathy Yarbrough, contributing editor

Competing pharmaceutical companies typically don't share with each other. An exception is the Asia Training Consortium (ATC), whose members share their best practices in employee training to address a common challenge: preparing their Asian workers to manage the clinical trials that the companies plan to sponsor in the part of the world that is widely regarded as having the greatest potential for economic growth for the pharmaceutical industry.

By sharing resources and expertise, Merck, AstraZeneca, Novartis, Pfizer, and the other multinational ATC member companies are not only cutting their costs for training workers but also are standardizing the knowledge and skillset required for clinical trial associates, clinical project managers, and clinical research managers in Asia.

The collaboration extends from the design of the curricula to teaching the courses. In Shanghai, China, a recent ATC class on the *Foundations of Clinical Project Management* was attended by Astellas Pharma employees, taught by a Merck trainer and held at a Novartis facility.

Frequently the attendees at an ATC class represent multiple companies. This nonproprietary approach to training achieves the economies of scale that reduce each company's training cost per employee, said John Constantine, chairman of the board of ATC and executive director & dean of the Merck Polytechnic Institute, the pharmaceutical company's training and development program for R&D staff.

The ATC was founded in 2012 because Constantine and his counterparts at other major pharmaceutical companies and multinational CROs had something in common: each was paying 20 times more for training a new employee in Asia than for training a new recruit in North America and Western Europe.

Because the companies viewed their curricula as proprietary, they had to pay the total cost for each class, from the trainer's salary to the rental of the classroom and audiovisual equipment. "Even if the company had only five employees to train, it was paying the same amount of money that it would have spent if the classroom was full with 25 people," said Constantine.

GOAL: REDUCE TRAINING COSTS

The excessive costs of training Asian employees clashed with the belt-tightening occurring industrywide. To avoid less than optimal class sizes, some of the companies were infrequently holding training classes. As a result, some employees were not quickly trained to work in clinical trial management.

When Merck, other companies, and CROs began to establish footholds in China and other Asian countries, they soon found that the region, unlike North America and Western Europe, did not have a large cadre of professionals experienced in clinical trial management.

"The basic skills of clinical trial management are not taught at universities in Asia," said Constantine. "Most of the people whom we are hiring in Asia are straight out of university. They are very eager to learn, very education-oriented, and ambitious. But they don't know basic good clinical practice (GCP)."

Constantine helped establish ATC after joining Merck in 2008 to head the company's then new R&D staff training institute. "Soon after I arrived, Merck announced it would focus its growth in clinical trials primarily in the Asian market," he said. As a result, Constantine changed his focus from North America and Western Europe to China, India, Indonesia, Japan, Malaysia, the Philippines, South Korea, Singapore, Thailand, and Vietnam.

During his first trip to China, whose large population has made it the primary market in Asia for the pharmaceutical industry, Constantine discovered that the CROs and other pharma companies that also were building a presence in the region shared Merck's lack of economies of scale in the training of Chinese workers to help manage clinical trials.

Constantine took advantage of the

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then upcoming IBC-Asia 3rd Annual Partnerships in Clinical Trials Asia Conference in Shanghai to invite his counterparts at pharma companies and CROs to a two-day meeting to discuss common training challenges in Asia. The result was the incorporation of ATC in Singapore as a legal entity in June 2012. ATC subsequently won the endorsement of the China Council for International Investment Promotion.

At the Shanghai conference and subsequent meetings, Constantine and his industry colleagues decided that the consortium should address not only employee training but also their shared goal of ensuring that clinical research conducted in Asia meets the highest standards of quality.

The Asia Training Consortium was designed to prepare Asian pharma company workers to manage the clinical trials in the area of the world that is widely regarded as having the greatest potential for economic growth for the pharmaceutical industry.

CLASSES TAUGHT IN ENGLISH AND MANDARIN

At its first meeting, the ATC board identified clinical trial investigators and clinical trial management staff as the target audiences for training. However, the priority would be clinical trial associates, clinical project managers, and clinical research managers.

To design the curricula for ATC's courses, the board appointed a committee whose members shared nonproprietary training guides, content outlines, scripts, and related materials. "We found that the curricula of the various member companies were very similar," said Constantine.

Thus far, 900 days of ATC courses have been taught in classrooms throughout Asia. The ATC's *Foundations of Clinical Project Management* class now occurs quarterly in Shanghai. The course is available online in both English and Mandarin. ATC plans to create online versions of the other courses, which include *Principles of GCP*, *Presentation and Assertiveness Workshops*, *Building Performance Teams*, and *Leading Without Authority*.

Today ATC members total 17 companies, each of which annually pays $2,500 to participate in the consortium. "We decided to keep the entry fee as low as possible," Constantine said. In addition to pharma companies and CROs, ATC members include specialists in designing and packaging course content for the classroom and online.

Constantine invites other pharma companies as well as CROs to join ATC when he speaks about the consortium at life sciences conferences in the U.S., Europe, and Asia. "The more members we have, the more we can do," he said.

The ATC model for clinical trial management staff could be adapted to the training of pharmaceutical manufacturing and other workers in Asia, he added. The government of China expects that the global pharmaceutical industry's foothold in the country must include more than the sale and marketing of drugs. As a result, the multinational companies are establishing R&D and manufacturing facilities in China as well as conducting clinical trials there.

Latin America and Africa are the new emerging markets for the global pharmaceutical and CRO industries. Versions of ATC may be created for those areas, Constantine said.

ATC benefits not only its member companies but also the students trained in the consortium's courses. Because the courses follow standardized curricula, Asian workers who earn ATC certifications by completing the classes likely will be highly employable in the region, Constantine said. "If they are hired by another pharmaceutical company or CRO that is an ATC member, their new employer likely will not have to re-train them."

Asia is already proving to be a major engine of economic growth for the life sciences industry. According to the *Economist* magazine's intelligence unit, pharmaceutical sales in Asia almost doubled in the first decade of this century, and by 2016, the average annual growth rate in pharmaceutical sales will be over 13 percent.

"Type 3" Diabetes Back On Trial

Alvaro Arjona

Arjona is the editorial director for drug development at Thomson Reuters. He has authored several book chapters and over 25 peer-reviewed articles.

The underlying relationship between insulin resistance and dementia has compelled some researchers to label Alzheimer's disease (AD) as "diabetes of the brain." Although this characterization isn't widely recognized in the general public, the concept of "type 3" diabetes isn't new — it's been around for several years and is supported by some genetic and molecular research.

Several studies have shown that people with type 2 diabetes are at a higher risk of developing AD, and plausible genetic links have been discovered. As research stones are overturned, growing potential for therapeutic development rises to the surface.

EXPLORING THE RESEARCH

In July 2013, results were presented to the Alzheimer's Association International Conference showing that insulin detemir (a long-acting human insulin analogue for maintaining the basal level of insulin) was associated with improved working memory. The study involved 20 people with Alzheimer's and 38 with mild cognitive impairment, all of whom were given the intervention (Hanson, A. et al. AAIC July 13-18, Boston, 2013, Abst P3-276). In 2009, liraglutide, a commonly prescribed GLP-1 agonist for diabetics, was found to rescue memory loss and decrease the build-up of brain plaques in a mouse model of AD (McClean, P.L. et al. *Neuropharmacology 2013*, advanced publication). Results from the study conducted at Lancaster University suggest that liraglutide may be able to reverse some of the damage caused by AD in patients in the later stages of the condition.

There's more. In 2013, researchers reported that the long-lasting glucose-dependent insulinotropic polypeptide (GIP) analogue D-Ala2-GIP demonstrated effects on memory and synaptic neurotransmission in mice; when further evaluated in the APP/PS1 mouse model, it was able to rescue synapse numbers and decrease beta-amyloid plaque buildup in the cortex (Faivre, E. et al. *Alzheimers Res Ther* 2013, 5(2): 20).

These and other recent results have prompted pharmaceutical developers to examine — or, in some cases, reexamine — the potential of approved and investigational antidiabetic drugs for treating Alzheimer's disease.

EXAMINING THE CLINICAL TRIALS

However, is this renewed interest reflected in the clinical arena? What does the current clinical development landscape look like for this so-called "type 3" diabetes? In screening Cortellis Clinical Trials Intelligence for instances including antidiabetic agents in AD subjects, 10 active clinical trials involving more than 900 overall subjects were found. The trials are mostly Phase 2 studies initiated in the last 12 months that are recruiting subjects with probable diagnosis of AD and subjects with mild AD. The most common endpoints under assessment are: global and functional assessment of cognition, PET, and MRI findings, as well as regional cerebral glucose metabolic rates. There are several different interventions under evaluation: insulin, exenatide, bexarotene, tesofensine, DSP-8658 (a novel PPARα/γ agonist that penetrates the brain better than thiazolidinediones), and the aforementioned liraglutide. Liraglutide will be evaluated in the ELAD study, a randomized, double-blind, placebo-controlled Phase 2 trial that is about to initiate recruitment. This clinical trial is led by Dr. Paul Edison of Imperial College London and is partly funded by the U.K. (United Kingdom) Alzheimer's Society.

As more progress is made in understanding the link between diabetes and AD, and more light shed on whether these interventions mediate their efficacy by modulating brain glucose homeostasis or via anti-inflammatory mechanisms, it will be exciting to follow the outcomes of the trials. The research community can then reassess whether there is an actual therapeutic advantage in exploiting the AD-diabetes link. Long-sought disease-modifying AD therapies may come through the repositioning of some of these drug approaches or via novel therapeutics targeting repurposed pathways exposed by epidemiologic, experimental, or computational evidence.

The lessons learned from these trials could potentially be applied to other therapeutic areas, providing a wealth of new information for the pharmaceutical industry.

Effective Leaders Need Differing Methods Of Communicating

By Tim Moore

Good leaders know we're all more comfortable working with people of our own age and background. Generational peers are likely to "speak the same language." Sending the wrong generational signals creates a generation gap. Today there are four major generations in the workplace: Matures (born before 1946), Baby Boomers (born between 1946 and 1964), Generation X (born between 1965 and 1979), and Millennials (born between 1980 and 1997).

Connecting With Matures

Duty and sacrifice are at the heart of the Mature mindset. Matures usually do not have inflated egos or a sense of self-importance, and they don't expect special treatment, but they do believe they have earned a certain amount of deference and respect for all that they have accomplished.

- Clearly communicate to Matures what is needed from them and their teammates.
- Matures prefer to communicate face-to-face, by telephone, and by mail.
- Matures prefer to read documents on paper not on a screen.

Connecting With Baby Boomers

Boomers have a work ethic measured in face time. Commitment to "team" is paramount, and face-to-face skills are critical to success. The Boomers tend to be optimists. Boomers have two opinions on technology; they recognize technology is now ubiquitous, but a good number aren't convinced it has made things better.

- Face to face or phone call are the preferred ways to communicate.
- Focus on team goals — work in individual recognition.
- Assume that even older Boomers think of themselves as young, fit, and active.

Connecting With Generation X

Gen Xers have learned to be skeptical of just about everything. Address their innate cynicism with back-up plans for the inevitable time when a problem arises. Gen Xers dislike hierarchy, prefer transparent communication, and value efficiency. They embrace technology and use it in most aspects of their lives.

- Get straight to the point.
- They probably will prefer email updates.
- They are likely to let your calls go to voice mail.
- They dislike face-to-face communication. They will not want to make hard decisions face-to-face.

Connecting With Millennials

Build rapport with Millennials by recognizing their individuality and accomplishments. They live in a digital world – texting, email, and social media are musts. This generation regards personal information much differently than older generations. They share info more freely and may know the details of friends' and business associates' lives.

- Be authentic – don't try to fake youth or be cool.
- Recognize individuality and uniqueness.
- Texting is OK. Preferred! Do it.

Tim Moore is an accomplished author and speaker. At Generational Insights, Moore is part of a team that has become the leading voice on the impact of generational differences in the workplace.

To comment on this article, send an email to rob.wright@lifescienceconnect.com.

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