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COMPANY TO WATCH:
StemCells
p. 14

Navigating
Biosimilar Regulations
p. 36

GSK's SR One
Innovation Investment
p. 30

Attack
On Medicare Part D
p. 10

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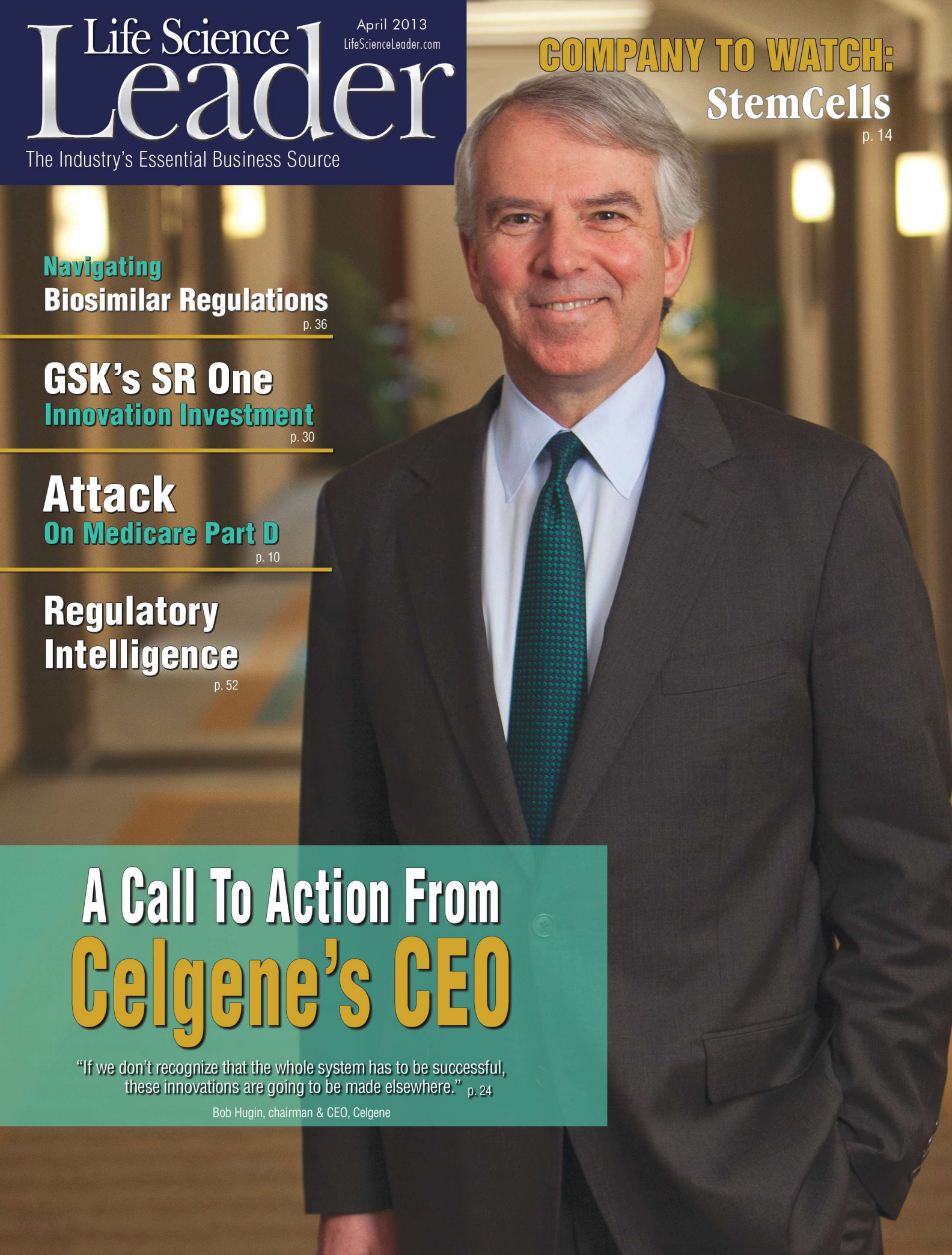

COMPANY TO WATCH: StemCells
p. 14

Navigating Biosimilar Regulations
p. 36

GSK's SR One Innovation Investment
p. 30

Attack On Medicare Part D
p. 10

Regulatory Intelligence
p. 52

A Call To Action From Celgene's CEO

"If we don't recognize that the whole system has to be successful, these innovations are going to be made elsewhere." p. 24

Bob Hugin, chairman & CEO, Celgene

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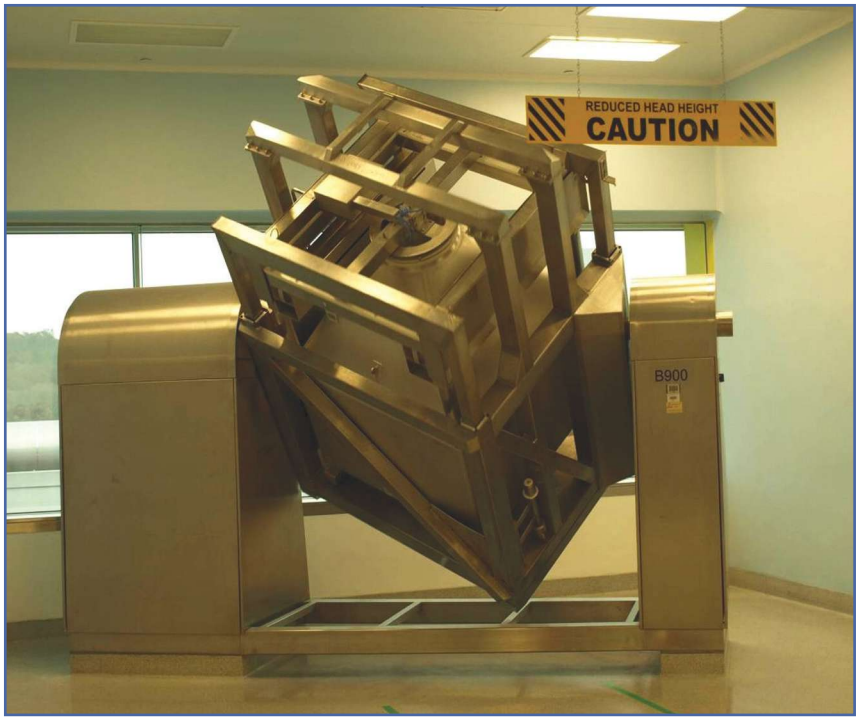

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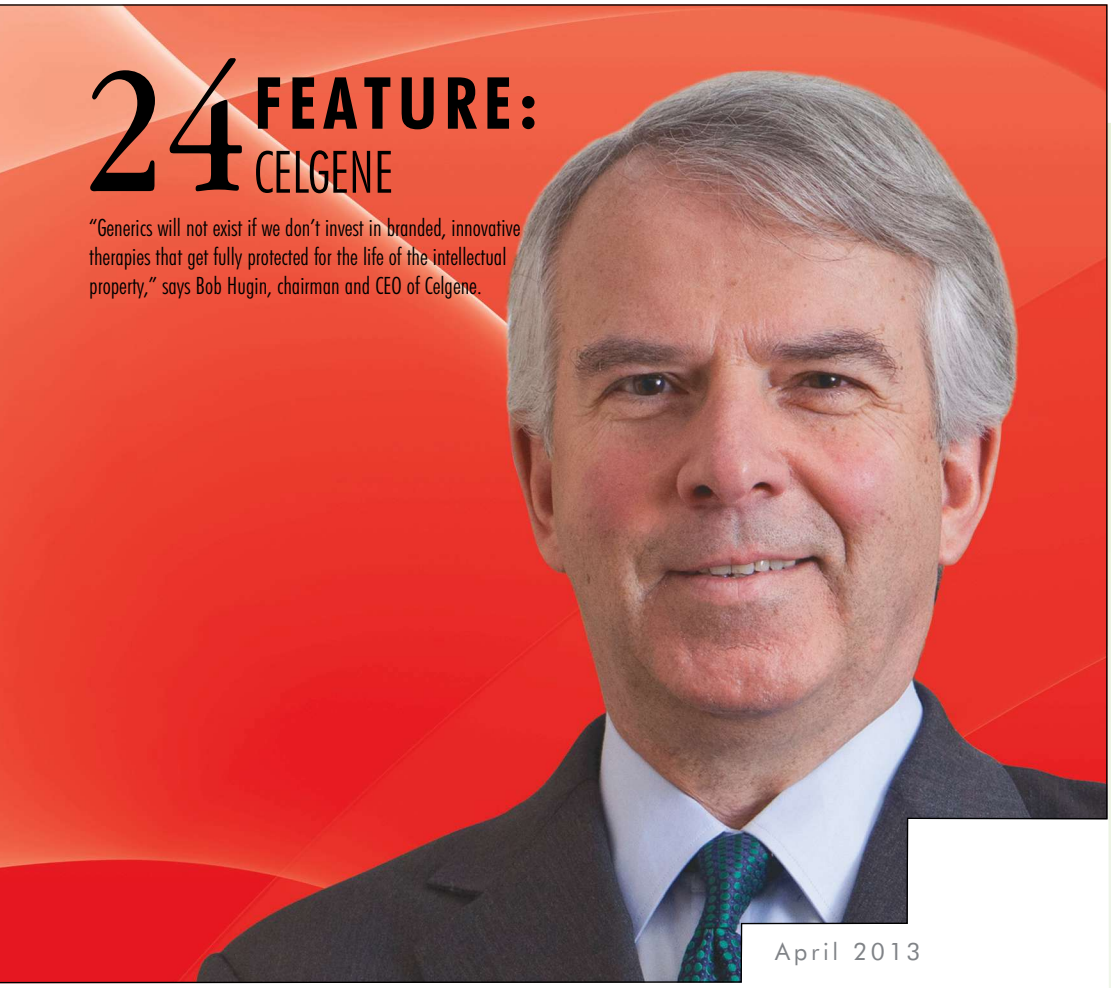

24 FEATURE: CELGENE

"Generics will not exist if we don't invest in branded, innovative therapies that get fully protected for the life of the intellectual property," says Bob Hugin, chairman and CEO of Celgene.

April 2013

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CONTENTS

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EDITOR'S NOTE

Let's Incentivize Innovation – Before It's Too Late

What do the U.S. auto and pharmaceutical industries have in common? For starters, both have traditionally held positions of world dominance. For example, after WWII the United States supplied about 75% of the world's autos. The U.S. pharmaceutical market is presently the largest market in the world at $300+ billion. Both experienced significant consolidation. Between 1896 and 1930, there were more than 1,800 automobile manufacturers. Today there are only three major manufacturers — Chrysler, Ford, and General Motors (GM). For the pharmaceutical industry, the transformation occurred between 1940 and 1950, from a collection of several hundred small, geographically based companies, the largest of which accounted for less than 3% of the total market, to fewer than 20. Both industries have become increasingly dependent upon outsourcing. Well into the 1990s, most automotive manufacturers were vertically integrated, building a majority of the components for their products in their own factories. The same could be said for pharma, which until the mid-2000s, primarily researched, developed, manufactured, and sold their own medications. Another similarity is that both have served as lightning rods for political policy, such as the 2009 federal auto bailout shepherded by President Obama or the Medicare Prescription Drug, Improvement and Modernization Act (Medicare Part D) enacted by President Bush in 2003. The two industries both face competition from emerging markets as well. However, for the automotive industry, the threat is already a reality, as the U.S. is no longer the top producing country. In the pharmaceutical industry, the U.S. is clearly the number one market, and U.S.-based Pfizer is still the largest pharmaceutical company in the world, but for how long?

China recently surpassed Japan as the third-largest pharmaceutical market. Over the next five years, China is expected to grow at a pace of more than 20% annually. At this rate, it won't take long for it to catch and surpass both the EU, growing at an anemic 1% to 3%, and the U.S., which anticipates growth of 3% to 5%. What can be done? What should be done?

In recent reports, I found it interesting that the automotive industry is taking a page out of the pharmaceutical playbook — seeking innovation. On a per-employee basis, the motor vehicles, trailers, and parts manufacturing subsectors invest $15,704 annually. The biopharmaceutical industry is the most R&D-intensive, investing $105,428 per employee annually. This has resulted in drug discovery costs rocketing past the $1 billion mark. Thus, simply investing more in innovation is not the answer. Neither is foreign policy focused on protectionism and trade restrictions. Both industries have tried these unsuccessfully. What is needed is pro-innovation political and regulatory policy making, not just for pharma, but for U.S. industry in general. If you want more innovation, more jobs, greater economic growth, and stability, implement policies which encourage U.S.-based companies to do those things. The FDA has been doing a good job, as evidenced by the implementation of FDASIA (Food and Drug Administration Safety and Innovation Act) and the tropical disease voucher program within FDAAA (Food and Drug Administration Amendments Act). But we need more. The greatest management principle in the world espoused by Michael Leboeuf is, "Things that get rewarded, get done." Let's incentivize innovation, and we can start by providing pharma with longer patent exclusivity.

Rob Wright
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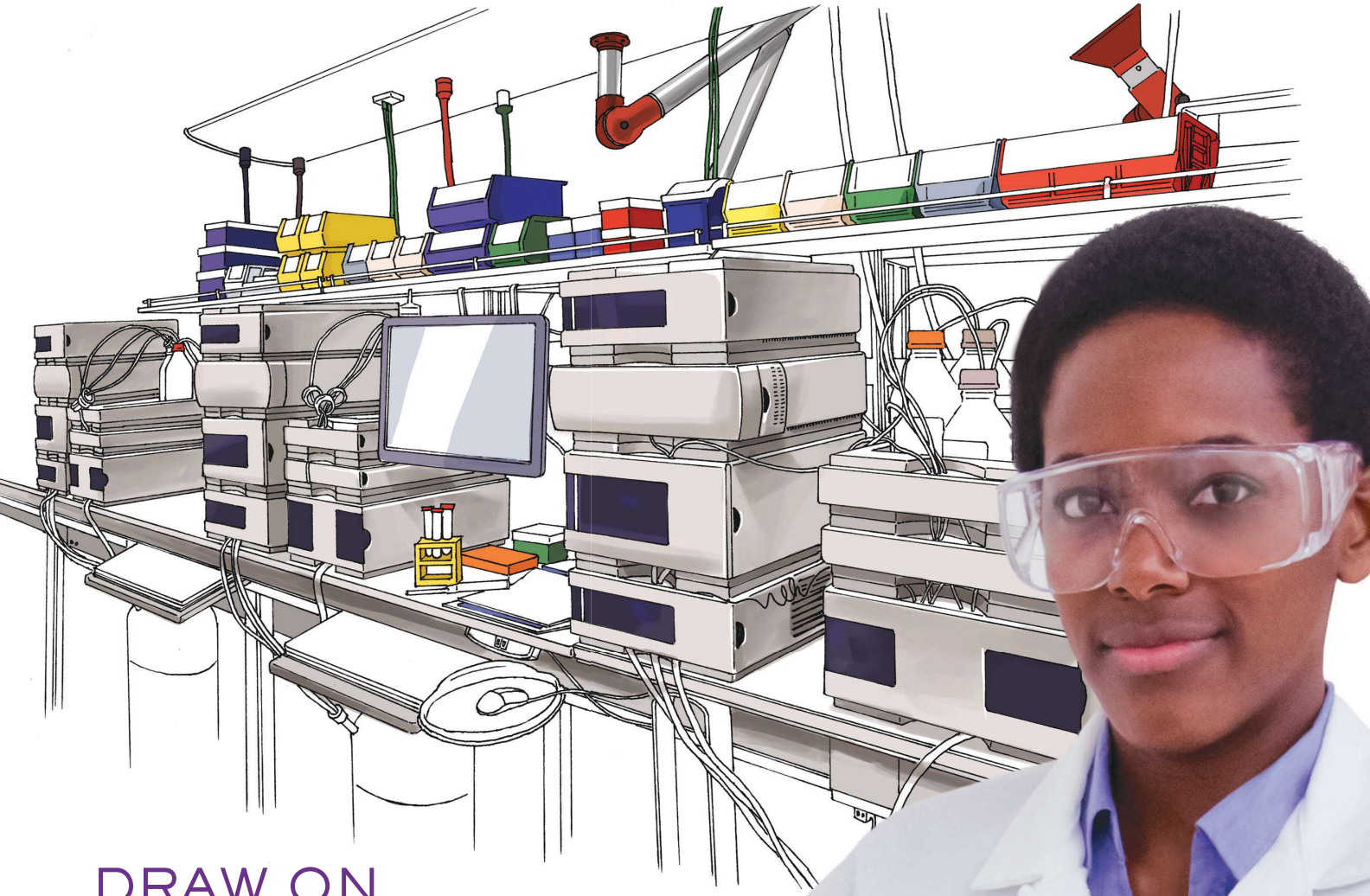
@RFWrightLSL

abbvie



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The awards at the March 13, 2013 ceremony

Congratulations to all of the winners of the CMO Leadership Awards, sponsored by *Life Science Leader* and Nice Insight. To get more information about the winners and to see photos from the CMO Leadership Awards Reception & Ceremony held on Wednesday March 13, 2013 at the W New York Hotel, go to www.CMOLeadershipAwards.com.

THE CMO LEADERSHIP AWARDS

ASK THE BOARD

Have a response to our experts' answers? Send us an email to atb@lifescienceconnect.com.

Q: What is your biggest concern with the U.S. life sciences industry, and what should be done to address it?

There are real threats to the U.S. life sciences industry, including increasing pressures on reimbursement for innovative new medicines, a scaling back of investment in early-stage biopharmaceutical companies, and a drain of scientific and entrepreneurial talent to rising powers such as China. To address these threats, we need to first educate political leadership and the public that continued medical innovation is worth the price, as innovative medicines actually reduce net healthcare costs over time. Second, we need to use the tax code more effectively, enacting laws that allow start-ups to appropriately retain and use nonoperating losses (NOLs) while providing other tax incentives. Third, we need an immigration policy that allows the brightest scientific minds to remain in the U.S., offering green cards to foreign nationals who receive an advanced U.S. degree.

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

Q: What are the top 3 challenges (and possible solutions) faced by U.S. companies outsourcing to India/China?

Ensuring product quality and consistency is, of course, an overriding objective. This requires effective technology transfer but is equally dependent on securing a reliable supply chain. It is important to recognize that there are significant differences between India and China, which will impact outsourcing decisions. The maturity of the pharma industry is quite different in each. Issues such as infrastructure and language may also play an important part in the success of an outsourcing exercise, and there will need to be work with local regulators and a focus to ensure the quality systems employed meet the high standards required. Finally, it is important to recognize that any equipment used may well be sourced locally so its suitability, integrity, and reliability all need to be considered.

Tim Freeman
Freeman is director of operations for powder characterization company Freeman Technology. He has 10 years of experience in understanding and characterizing powder behavior and works closely with the pharmaceutical and powder processing industries.

Q: Why does it seem the pharmaceutical industry is slow to adopt new technologies?

The pharmaceutical and biotechnology industries are dominated by scientists, even on the commercial side of the business. Scientists become uniquely excited and personally engaged by new technologies. Yet, the regulated nature of the industry means that scientists' personal desire to adopt better, more effective and efficient technologies are seriously hobbled by the need to consider how they will affect regulatory submissions, reviews, and ultimately revenue flow for their areas of responsibility. The hurdles to adoption are as varied as the innovations themselves, times the number of regulators potentially involved. Though scientists are attracted to new technologies, the industry is very risk-averse, and thus why you have a significant difference between what bio/pharma decision makers say they want and need and what actually gets implemented. If you want to speed up adoption, be sure to address their regulatory concerns about your new technological innovation proactively.

Eric Langer
Langer has more than 20 years of experience in biotech and life sciences international marketing, management, market assessment, and publishing. He has held senior management and marketing positions at biopharmaceutical supply companies.

"We needed a high-quality pharmaceutical checkweigher to present data sync on our demo line; we chose Thermo Scientific's Versa Rx to demonstrate this critical capability."

- Glenn R. Siegele, President
Omega Design Corporation

Scan to see what else Glenn said...

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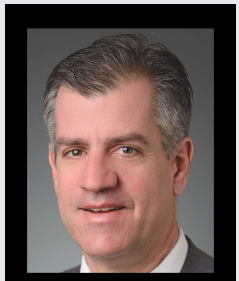
Why Is The President Attacking The Successful Medicare Part D Program?

In February, the Congressional Budget Office (CBO) released its new "baseline" projections for Medicare spending, and for the eighth time in nine years it reduced its projections for prescription drug spending under Medicare Part D. Indeed, the 2013 estimate for the next 10 years is 8.9% lower than last year's estimate and a staggering 45% less than initial estimates for the cost of the program.

Yet the Obama administration continues to advocate for the application of Medicaid rebates on low-income populations in Medicare Part D, which would slap the pharmaceutical industry with a more than $137 billion bill over 10 years for selling drugs to the program. What's going on here? Why is the administration attacking a program that is producing tremendous results for our seniors and taxpayers alike?



John McManus, The McManus Group

First, some background. In 2003, the Republican Congress enacted a market-based drug benefit that relied on competing prescription drug plans to deliver pharmaceuticals to Medicare beneficiaries. The concept was simple but revolutionary in health policy at the time — rather than establishing price controls and government formularies, trust seniors to choose the plans that suit them best and rely on the market to contain costs. Plans that were ineffective at negotiating with pharmaceutical companies and encouraging generic substitution would be priced out of the market and fail to attract seniors.

During congressional consideration of the bill, Republicans rejected an amendment that would have locked in prescription drug premiums at $35 a month for every plan — the then CBO estimate of the "average" prescription drug plan. That amendment would have destroyed the whole concept of the program by undermining any incentive of plans to aggressively contain costs in order to attract more beneficiaries. Mandated equality is antithetical to capitalism.

Thank goodness that amendment was defeated. When the program actually rolled out a few years later, the average monthly prescription drug premium was $23 or 40% cheaper than CBO's estimate. Critics dismissed these low premiums as abject attempts to nefariously gain market share in order to hike premiums in subsequent years. However, premiums actually declined in the second year of the program. While healthcare costs have increased, Medicare prescription drug premiums have remained stable at $30 for the past three years. And generic utilization — a metric for efficiency of the program — has increased from 60% in 2006 to 80% in 2011, which is substantially higher than commercial plans.

A deficiency of the drug benefit was addressed when the Affordable Care Act (ACA) required brand-name companies to provide a 50% discount for drugs dispensed in the coverage gap, i.e. the "donut hole," and also gradually eliminates this benefit gap over the next 10 years. It left the competitive market delivery of the benefits in place.

But less than a year after working with the President to enact health reform, the pharmaceutical industry was shocked that the President proposed applying Medicaid rebates to low-income individuals in the Medicare program.

The Administration's argument was that the pharmaceutical industry had received a "windfall" because dually eligible beneficiaries who formerly received their drug benefits through Medicaid were no longer paying Medicaid rebates to states. Medicaid rebates are nothing more than price controls and based on a three-pronged formula: 1) a minimum rebate of 23%, 2) best price rebate if a privately negotiated price discount exceeds the minimum rebate, 3) any price increase that exceeds inflation (measured by the consumer price index) since launch of the product. Medicaid rebates average about 45% for a typical brand-name drug, but for some products they may be as high as 70% or more because of the penalty for price increases.

The administration's argument has several fundamental flaws:

1. Medicaid is a notoriously poor payer and should not be the standard for appropriate pricing in Medicare. There's a reason why the administration supported a provision in the ACA to increase reimbursements for primary care physicians in Medicaid to the Medicare level — very few physicians accept Medicaid patients because they lose money on those patients.
2. Price controls inevitably accompany restrictions and shortages. The Veterans Administration, which administers a price control regime, covers fewer than 40% of the most commonly used drugs by seniors while the most popular Medicare prescription drug plans cover about 84% of those drugs. Medicaid is similarly restrictive; the Kaiser Family Foundation reports that 16 states limit the number of prescriptions a beneficiary may fill, which can be devastating for Medicaid beneficiaries.
3. The Medicaid rebate would be applied to not just the 6 million dually eligible Medicare beneficiaries, but another

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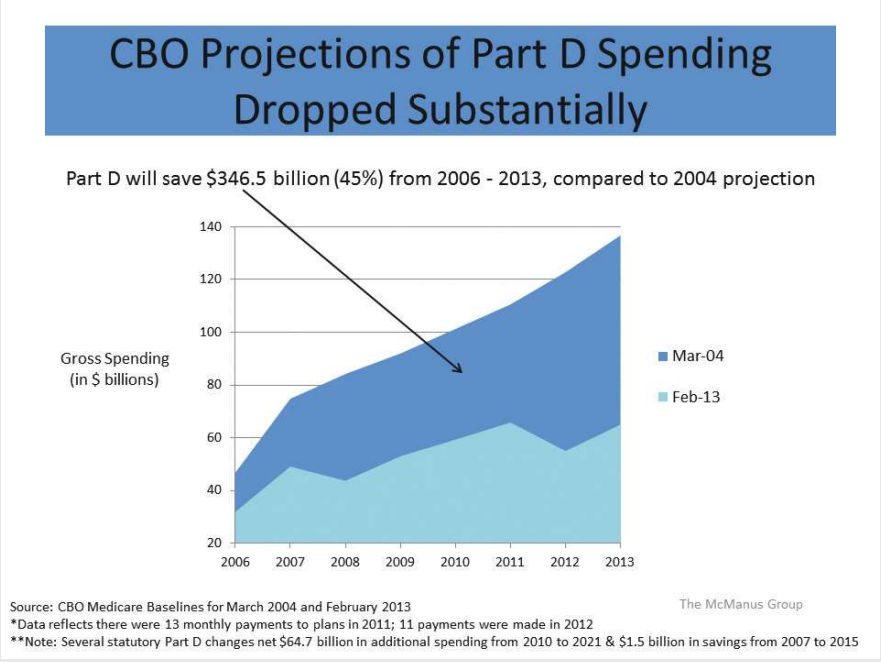
5 million low-income beneficiaries — a population that never had Medicaid coverage or its price control scheme.

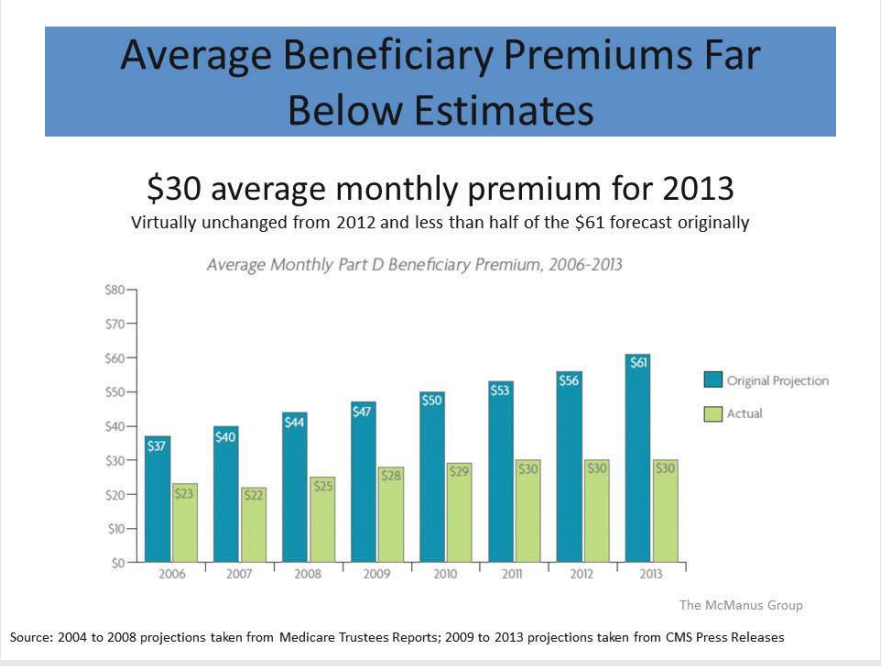
4. Numerous economic studies by government actuaries and leading academics have documented that pharmaceutical price controls will result in pricing distortions that will hike prices to employer plans, veterans, and nonlow income Medicare beneficiaries. Not everybody can get prices better than average.

So why is the administration pushing such a policy when the pharmaceutical industry already contributed more than $100 billion to healthcare reform? Answer: Expanded Medicaid rebates will substantially restrict pricing flexibility for brand-name pharmaceutical companies. Under the Administration's proposal, any cumulative price increase that exceeds the CPI since launch will be recaptured as a rebate for about half of the drug spend in the Medicare program, in which free market pricing now applies. *It wants control over pharmaceutical pricing*.

If the administration gets its way, there are only two possible outcomes: 1) substantial cuts to research and development, particularly for the more risky endeavors; and 2) job cuts to an industry that has already laid off 200,000 workers over the past several years. The Battelle Institute estimates that an impact of $10B to $20B a year on the industry, as the administration proposes, would result in 130,000 to 260,000 lost jobs in the high-wage pharmaceutical sector and the industries it supports.

I am not aware of any government program that has come in 45% below budget, is vastly popular with its customers, and yet is being targeted for a fundamental overhaul. Congress should reject such a proposal.





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

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By Wayne Koberstein

StemCells

A cautious agenda in developing tissue-derived adult stem cell therapeutics could lead to big leaps in patients' quality of life.

SNAPSHOT

StemCells supplies research materials and cell lines to laboratories, but its main purpose is to develop a pipeline of stem cell-based therapeutics for spinal cord injury, dry age-related macular degeneration (AMD), Pelizaeus-Merzbacher disease (PMD, a rare myelination disorder in the brain), and Alzheimer's disease. Although the company supplies stem cell lines from all sources, including embryonic, its therapeutic pipeline uses only tissue-derived adult stem cells, which originate from the respective organ or tissue to be treated. Tissue-derived stem cells grow reliably into the type of cells from which they were taken, so in contrast to embryonic or induced pluripotent stem (iPS) cells, no "programming" is needed. The company's stem cells are also allogeneic — derived from donors and requiring no modification — rather than autologous — derived from individual patients and potentially needing correction for damaged genes. Given such properties, StemCells asserts that its cells circumvent the high costs and technical roadblocks that have defeated commercialization of other stem cell therapeutics. In fact, the company touts its technology's potential to make "stem cells in a bottle," similar to other biotherapeutics or pharmaceuticals.

Martin McGlynn, CEO

LATEST UPDATES

• *February 2013:* Favorable 12-month data from the first patient cohort in StemCells' Phase 1/2 clinical trial of its HuCNS-SC product (purified human neural stem cells) for chronic spinal cord injury (SCI) demonstrating two of three patients had multisegment gains in sensory function following transplantation of the cells. These were first observed at 6 months and persisted after 12 months.

• *October 2012:* 1) Publication in *Science Translational Medicine* of Phase 1 clinical data showing evidence of new myelination in PMD patients following transplantation of HuCNS-SC cells; patients also had modest gains in neurological function. 2) The first patient dosed in a Phase 1/2 clinical trial of HuCNS-SC cells in patients with dry age-related macular degeneration (AMD).

WHAT'S AT STAKE

The name StemCells reflects the company's brave but cautious approach. Brave, because people have sometimes rated the prospects of stem cell technology somewhat equal to that of cold fusion. Cautious, because the company "has not taken a 'bet the house' approach to searching for new treatments for serious diseases." StemCells also hired a seasoned CEO, Martin McGlynn, a self-described veteran of the pharma industry, who cut his executive teeth at Becton Dickinson, Abbott, and Anaquest before heading into the entrepreneurial life sciences world.

What does the favorable Phase 1/2 data for its HuCNS-SC neural stem cells in SCI really mean? Recently announced one-year results from its spinal-cord injury trial showed "considerable gains in sensory function observed in two of the three patients at the six-month assessment have persisted." No one got up and walked away, like a miracle in an old-time revival — but the sensory-function gain is just what the company is aiming for among a number of defined clinical endpoints in its now-enrolling Phase 1/2 trial: changes in sensation, motor, and bowel/bladder function. This is a cautious approach, but justified based on data showing the ability of the HuCNS-SC cells to differentiate into the specialized neural cells which produce myelin, the sheathing around nerves.

The American Spinal Injury Association Impairment Scale (AIS) classifies SCI patients into groups A, B, and C, in descending order of severity in symptoms and extent of paralysis. To widen the patient base, StemCells convinced Swiss regulators to allow a three-tiered study design covering AIS A, B, and C patients. Any benefit in the AIS A group would be gravy, but a very rich one, as any treatment advances would be unexpected.

StemCells' development programs in other areas display similarly cautious approaches, and they all recognize the same principle: In severe conditions like SCI, no noticeable benefit is trivial — and some benefits, though far removed from a cure, can be profound. Perhaps if StemCells succeeds in such modest but significant aims, it will someday reach one of its longer-term goals: regenerating nerve cells to free patients from the chains we now accept as permanent.

VITAL STATISTICS

• Employees: 49; Headquarters: Newark, CA
• Finances: Public, NASDAQ; market cap $62.2M; 2012 cash burn $19.9M; cash balance $22.4M, December 2012
• Research funding: $305K grant from the National Institute of Diabetes and Digestive and Kidney Diseases (2008), $978K Federal Qualifying Therapeutic Discovery Project (QTDP) Grant (2010)

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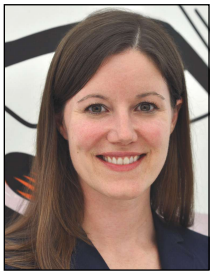

OUTSOURCING INSIGHTS

Outsourcing And The Oral Solid Dose — Will Challenges Lead To New Patterns Of Outsourcing?

By Kate Hammeke, director of marketing intelligence, Nice Insight

Historically, the prevailing dosage form for small molecule drugs has been the oral solids. They are cost-effective, have a proven safety and efficacy record over the course of more than a century, and from a consumer perspective, the familiarity of this form promotes patient compliance. But while tablets are still the most popular means for taking medicine, current industry information indicates that a significant portion of new chemical entities present solubility challenges, forcing developers to look at alternatives more frequently. As one industry observer put it, a lot of the low-hanging fruit has gone, so discovery is increasingly focused on niches and more complex approaches. So the question is how innovative dosage forms will develop, and what this means for contract manufacturers.

Nice Insight's survey asks buyers of CMO services about their practices in outsourcing solid oral-dosage forms. Responses tell us that, on average, 51% of respondents from pharmaceutical companies outsource solid dose manufacturing. Big Pharma (55%) and emerging pharma respondents (54%) skew the average higher, as they are more likely to engage a CMO for manufacturing than specialty pharma respondents (43%).

> Fewer than one in five [of survey respondents] believes that traditional tablets will meet all the delivery needs of its drug development pipeline.

However, fewer than one in five believes that traditional tablets will meet all the delivery needs of its drug development pipeline. About 85% state that innovative dosage forms — including controlled-release, fast-dissolve, or combinatorial drugs with multiple APIs — will be essential in coming years. Interestingly, almost a quarter of respondents from emerging pharma believe they can stick with the classics, but only 1 in 10 Big Pharma and specialty respondents believes traditional oral solid dose will continue to meet its needs. This may be an indication of the balance of what these companies are working on, or it could simply be indicative of experience.

THE DRIVERS THAT INFLUENCE OUTSOURCING

Differences among these three groups carry over to the drivers that influence their decisions to outsource as well. Quality and reliability consistently take the top two positions across the board, but priorities diverge from there. Big Pharma ranks productivity next, followed by regulatory, affordability, and innovation. Emerging pharma also ranks productivity third, but follows with affordability, regulatory, and innovation. Specialty Pharma bucks the trend by placing innovation third, followed by productivity, affordability, and regulatory.

PREFERRED CMOs

With diverging drivers for outsourcing, it is perhaps no surprise that they have varying preferred CMOs for oral solid-dose manufacturing. However, Next Pharma and Catalent both appear in the top three in two buyer categories. Big Pharma's descending order of preferred CMOs are Boehringer Ingelheim, Next Pharma, and AMRI. Specialty Pharma respondents identified Wellspring, Catalent, and AbbVie (formerly Abbott Contract Manufacturing) in the top spots. The top three among emerging pharma respondents are Catalent, Glatt, and Next Pharma.

There are important similarities among these CMOs — namely, that each possesses technologies and/or formulation skills focused on solving broader solubility challenges. Proprietary technologies and advanced formulation capabilities will likely cement pharmaceutical innovators into long-term relationships, and if they are seeking strategic relationships as industry trends suggest, they may be looking for CMOs that can offer the flexibility of traditional solid-dosage solutions as well as innovative dosage forms.

There is no doubt that solid dosage will remain relevant wherever it is feasible due to its cost benefit and relative lack of challenges, but innovative routes will not only address formulation challenges, they will also be relevant to other healthcare trends and future possibilities, such as efficacy breakthroughs and changes in patient expectations, behavior, and lifestyle.

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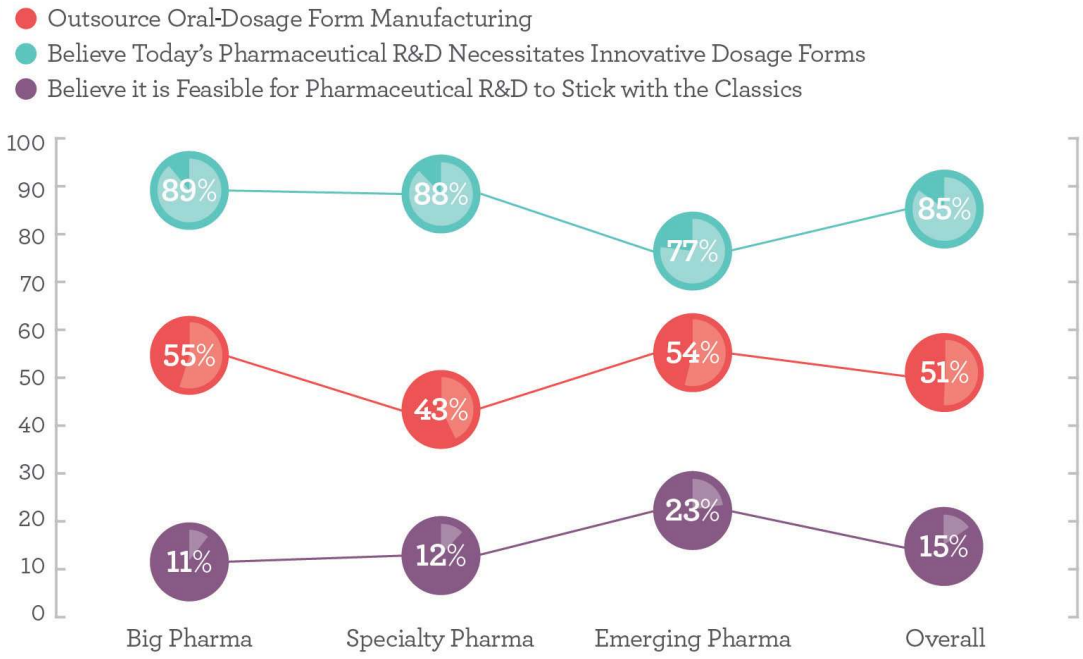
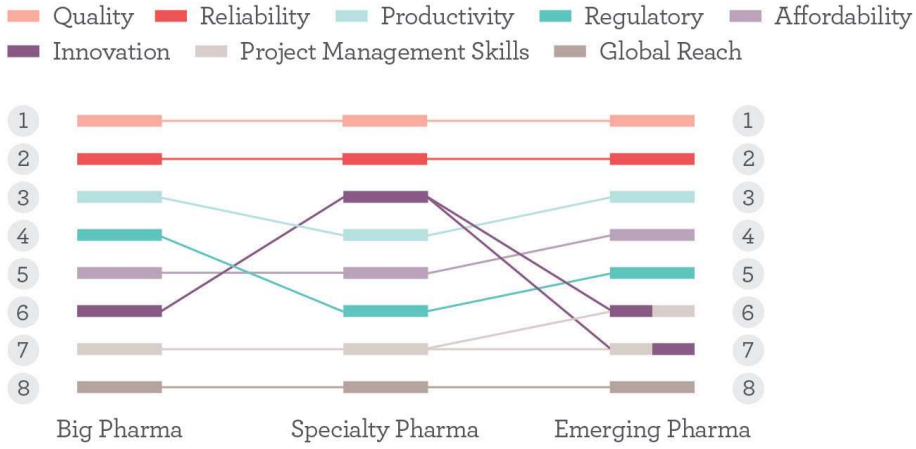
The Percentage of Respondents Who...



Outsourcing Drivers Ranked in Order of Importance



Survey Methodology: The Nice Insight Pharmaceutical and Biotechnology Survey is deployed to outsourcing-facing pharmaceutical and biotechnology executives on an annual basis. The 2012 sample size is 10,036 respondents. The survey is composed of 500+ questions and randomly presents ~30 questions to each respondent in order to collect baseline information with respect to customer awareness and customer perceptions on 170 companies that service the drug development cycle. More than 800 marketing communications, including branding, websites, print advertisements, corporate literature, and trade show booths, are reviewed by our panel of respondents. 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.


Walker

If you want to learn more about the report or about 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

Vendors Ignore Calls For Innovation In Assays

Fewer vendors committed to improved testing and assay services

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

Our column last month discussed biomanufacturers' increasing demand for better analytical-methods development for process monitoring, comparability analytics, and other critical areas associated with process improvement. More than one-fourth of respondents to our *10th Annual Report and Survey of Biopharmaceutical Manufacturers* find an urgent need for new or improved testing methods across eight assay areas (see: http://www.bioplanassociates.com/10th). This is also mirrored in the opinions of the 450 global subject matter experts and industry manufacturers on our Biotechnology Industry Council. Our council of industry experts this year identified assay development and analytical methods as one of the top critical trends for 2013.

Our studies surprisingly show a disconnect between what the industry wants and what suppliers are investing in. Today, biopharma companies are generally dissatisfied by the slow pace of innovation in assay development. In the face of these calls for greater innovation, it appears that fewer vendors are looking at improved assay-testing services this year, according to data from our industrywide global study. What's more, the lack of commitment on the part of vendors continues a trend we saw last year. Investments by suppliers into development of better assay technologies are down, possibly and simply because improvements are technically difficult. Improving assays for characterization of large molecules or developing single-use sensor technologies that work under multiple manufacturing conditions is not easy.

SURPRISINGLY LOW STATS FOR ASSAY INNOVATION

As part of our study, we asked vendors to identify the top new technologies or new product-development areas their company is working on in biomanufacturing. Of the nearly 40 areas identified, 11 pertained to assay-testing services. Discouragingly, no more than about 1 in 10 vendors we surveyed was innovating in any of those areas. By comparison, almost 4 in 10 are developing new bioprocess development/optimization services/bioprocess modeling technologies.

In addition to low investment levels, fewer vendors are developing improved assay testing across several areas. The following list captures the downward trend in interest for those testing/assay services areas:

Glycan/glycosylation analysis/characterization: 7.9% indicating some work on innovation in this area this year, down from 9.6% last year and 11.4% in 2011

Cell-line testing: 7.1% this year, compared to 8.3% in 2012 and 15.8% in 2011

GMP cell-bank development: just 3.1% this year, from 6.4% last year and 11.4% in 2011

The only areas that indicated somewhat constant levels of innovation interest this year compared to last year are impurities detection, raw-materials testing, biosimilarity testing, and structural analysis.

It is particularly interesting to see that there has been no rise in the percentage of vendors who are working on improvements to biosimilarity testing. This was one of the key subtrends identified by our council panel of experts, due to its potential to reduce the costs of biologic manufacturing. A number of respondents noted the technical and operational difficulties associated with such new assay development. For example, the fact that there does not exist today a consensus on what constitutes similarity in itself is a challenge. Further, as analytical technologies improve, so does our ability to understand structural attributes that define therapeutic protein drugs. Some see this as creating a dilemma — gaining such knowledge helps de-risk biosimilar programs, but such specific measurement capabilities may create an impossibly difficult path to biosimilar product development. Demonstrating biosimilarity on the basis of critical-product attributes will require better analytical methods. But as better information emerges, the definitions of biosimilarity may change as well, thus setting up a moving target.

WHY AREN'T SUPPLIERS INVESTING MORE IN ASSAYS?

The data paints a clear picture of declining numbers


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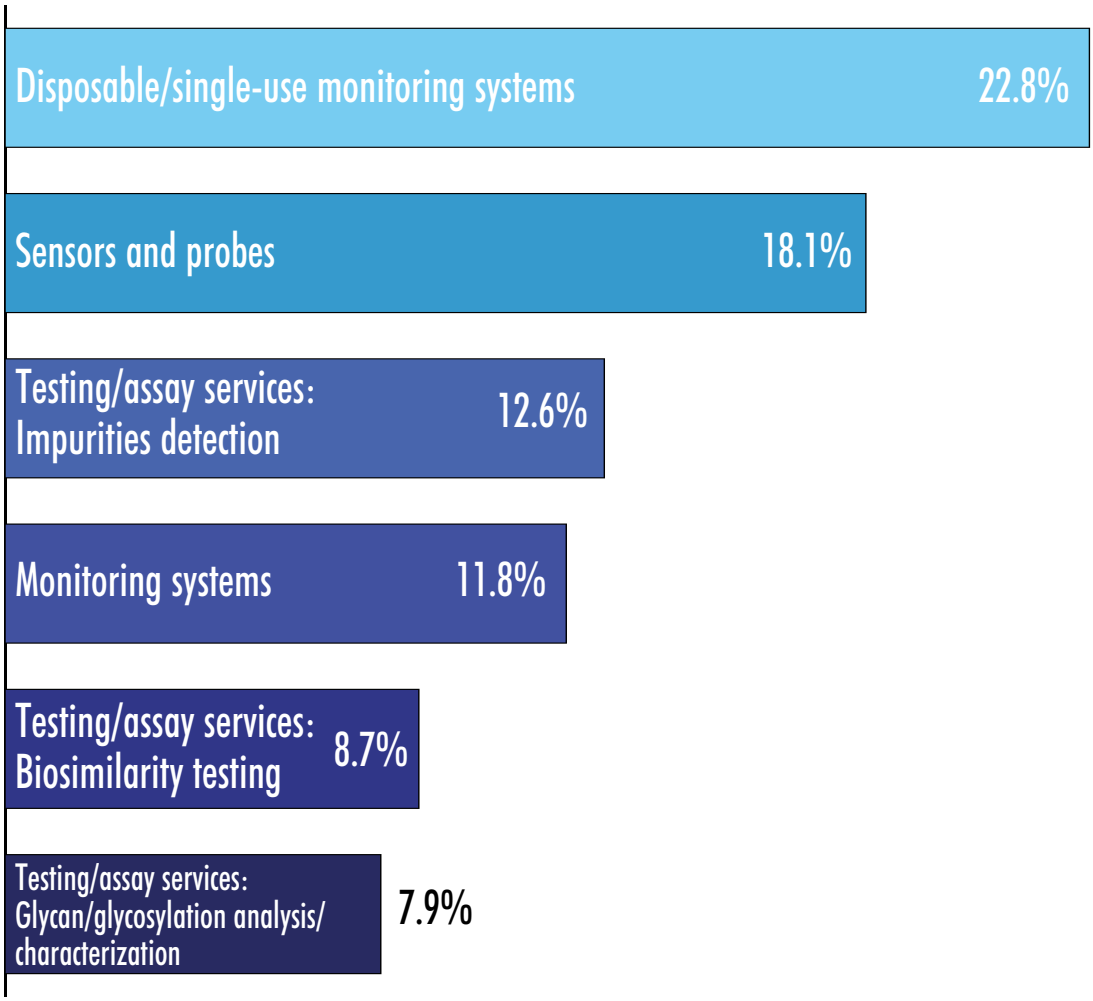
of suppliers interested in investing in challenging assay innovation. This is a curious trend, given that it counts as one of the strongest areas of opportunity we've noted this year. It could be that there is simply more low-hanging fruit in areas such as single-use devices, downstream processing, automation software, simpler sensor technologies, etc. Despite the fact that fewer vendors are investing resources into assays, the demand for solutions will continue to grow. Ultimately, solutions will be found. Whether these come from established industry suppliers or new industry entrants remains to be seen.

Figure 1: Selected Key Assays In Development By Vendors (Of ~40 Areas Evaluated)



Survey Methodology: The 2013 Tenth Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production is an evaluation by BioPlan Associates, Inc. that yields a composite view of and trend analysis from 300 to 400 responsible individuals at biopharmaceutical manufacturers and CMOs in 29 countries. The respondents also include more than 185 direct suppliers of materials, services, and equipment to this industry. Each year the study covers issues including new product needs, facility budget changes, current capacity, future capacity constraints, expansions, use of disposables, trends and budgets in disposables, trends in downstream purification, quality management and control, hiring, 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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Bob Hugin, chairman and CEO, Celgene

Protecting U.S. Medical Innovation

A Call To Action From Celgene's CEO

By Rob Wright

THERE IS A LONG HISTORY OF INNOVATION IN THE UNITED STATES. EVERYDAY PRODUCTS SUCH AS THE TELEPHONE, LIGHT BULB, MICROWAVE, AND PERSONAL COMPUTER ALL ORIGINATED IN THE STATES. THIS CULTURE OF INNOVATION HAS TRANSLATED TO HEALTHCARE AS WELL. For example, in the last 10 years the United States has been responsible for producing more than half of the world's new medicines. But the U.S. culture of medical innovation is at risk, and that risk is coming from within. Domestic regulatory and tax policies have opened the floodgates for other countries to offer various incentives to boost private investment in new medicines and medical devices in order to lure research facilities and jobs away from the United States.

This doesn't sit well with Celgene Chairman and CEO Bob Hugin, who ascribes to the notion that the ultimate value of medical innovation is derived from where discovery and development take place, not just where the resulting innovation is distributed. Take Europe as an example. "Thirty years ago Europe produced more than 50% of the intellectual property around new medical compounds," he states. Today, the EU represents less than 25%, a decline Hugin attributes to Europe's lost opportunity to aggressively support early-stage research with policies that allow for good reimbursement and a reasonable return for companies developing drugs. This failure to recognize the inextricable link between medical innovation and economic progress and prosperity has contributed in a cycle of decline that has rippled throughout the EU economy as evidenced by the European commissioner for economic and monetary affairs forecasting a weak 0.1% growth rate across the 27-member nation economy for this year.

Hugin does not want to see the same thing happen to the U.S. R&D engine of medical innovation, which supports approximately 4 million total U.S. jobs and creates an economic output in excess of $900 billion annually. "If we don't recognize that the whole system has to be successful, these innovations are going to be made elsewhere, and the economic benefit is going to accrue in other countries," he says. In order to prevent this, Hugin is asking life sciences industry leaders and constituents to take action. "We need spokespersons advocating for an environment of collaboration, pro-innovation policies and regulations, as well as IP protection laws which support the U.S. medical innovation ecosystem," he states.

LEAD BY EXAMPLE

To become a successful spokesperson or industry advocate, Hugin believes you have to speak from experience and lead by example — something which Celgene has most certainly been doing. The company has been recognized as one of the most innovative in the world by Forbes. A recent entrant into the Fortune 500, Celgene's exceptional stock performance over the past 10 years, +1,778%, is the envy of many of its peers. Some experts are predicting Celgene to be the best-performing biotech in 2013. Hugin attributes Celgene's success to a positive policy environment, collaborations with multiple constituencies, and an internal company culture he describes as entrepreneurial, challenging, and innovative. It's those success stories and industry credibility that he's bringing to his new spokesperson role as chairman of the Pharmaceutical Research and Manufacturers of America (PhRMA), a position he assumes in April, replacing Eli Lilly's John Lechleiter. But Hugin can't do it alone. He is looking to all stakeholders to step up as spokespersons for medical innovation to spread the message — a healthy U.S. medical innovation R&D engine is an integral component of a healthy U.S. economy.

"Generics are invented by branded innovative companies. They aren't invented by generic companies."

Bob Hugin, Chairman and CEO, Celgene

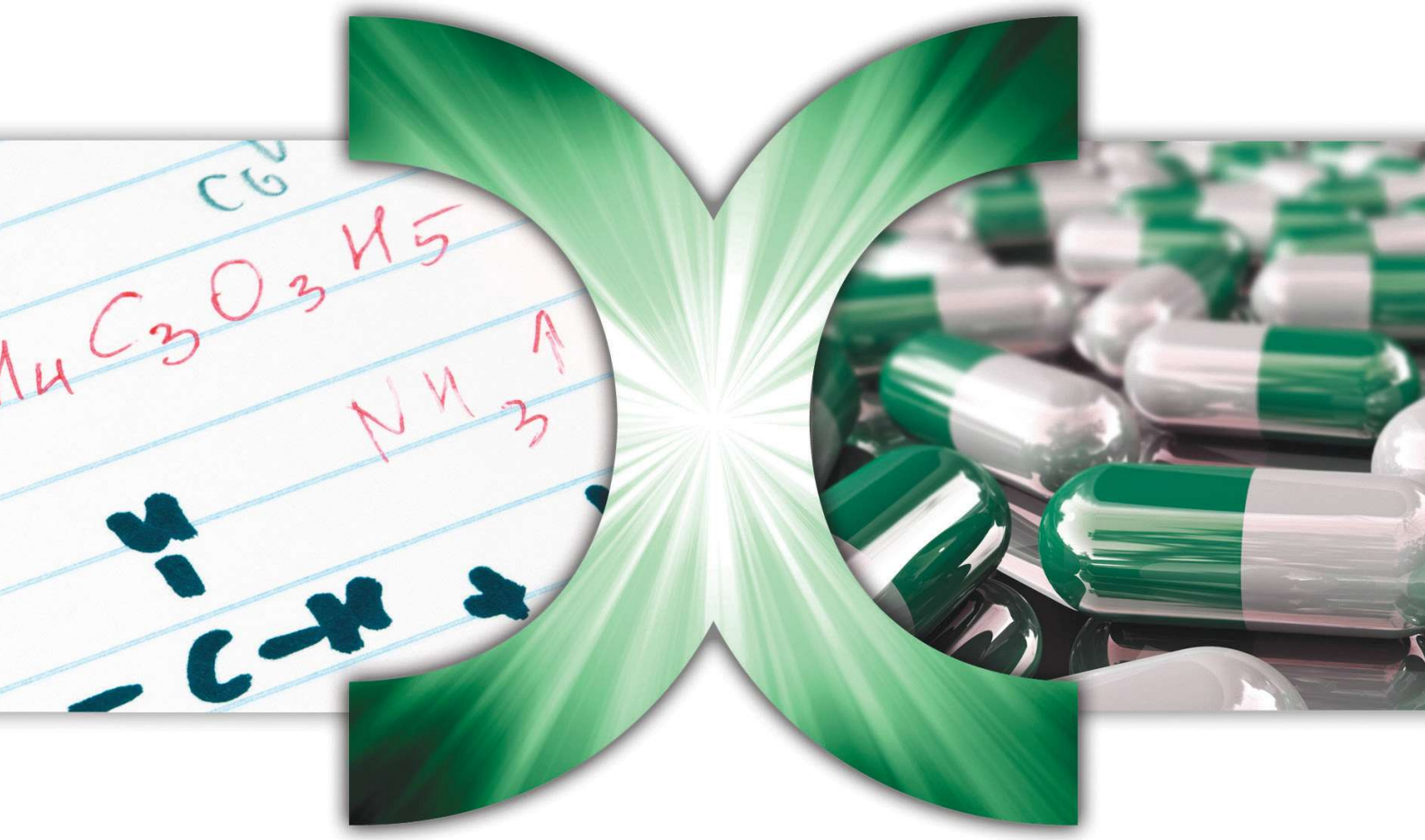
CREATE A CHALLENGING ENVIRONMENT WITHIN YOUR ORGANIZATION

When it comes to touting the importance of a healthy pharmaceutical R&D industry, Hugin suggests you first look at your own company. For instance, do you have a challenging environment internally geared toward innovation? For Celgene, the process of creating an entrepreneurial, challenging, and innovative environment all began with getting the FDA to allow the company to bring back a drug that had been withdrawn from the market over 50 years ago.

When Celgene's REVLIMID (lenalidomide) first received FDA approval in 2005 as a viable treatment for blood cancer, it was no small feat. That's because the drug is a derivative of THALOMID (thalidomide), which was withdrawn from the market in 1962 after being linked to birth defects. Given the tragic history associated with this drug, the decision to try to launch a new drug derived from it certainly created a challenging environment at Celgene. Many might think that the politically correct thing to do would have been to not even try. But would that have been the right thing to do? According to Hugin, "The drug had positive attributes which were beginning to be understood by people who had no treatment alternatives, including the AIDS community." As a result, Celgene leadership was willing to take the risk of bringing back THALOMID and developing next-generation therapies with improved features and greater clinical benefit — a challenging endeavor requiring multiple collaborations between the FDA, patient advocacy groups, and insurance payers. Facing this unique situation forced Celgene to ask the following types of questions of its leadership team that ultimately led to the evolution of a more innovative environment.

- How do we create a mindset to look at things in creative ways?
- What can we do to challenge the conventional wisdom internally?
- How can we work in areas that are going to make transformational change for patients and change the way science and medicine are practiced?
- How can we revolutionize processes so that we are looking to do things in a way that has the highest probability of creating great outcomes and doing things that have the most efficiency?
- What are we doing to focus on operational excellence internally so that every dollar saved can be put back into creating more opportunities?
- How can we improve access to drugs for patients?
- Are we really committing our resources to advance science and medicine?

Having a more innovative and challenging environment at Celgene improved R&D productivity. For example, Hugin notes that the company has nearly halved the time it takes from discovery, when a development candidate is first identified, to entering clinical trials. Since FDA approval of THALOMID in July 1998 for treatment of erythema nodosum leprosum (a severe and debilitating condition associated with leprosy), Celgene has not only gained approval of REVLIMID worldwide, which had sales of $3.77 billion in 2012, but also recently won regulatory approval for use in China. A next-generation oral immunomodulatory therapy, POMALYST (pomalidomide), was approved by the FDA in February for the treatment of relapsed or refractory multiple myeloma in the U.S. It is important to note that survival rates for patients with multiple myeloma have soared to well over 50% as a result of the introduction of novel therapies including REVLIMID and POMALYST. In addition, REVLIMID is up for FDA priority review for a new use in patients with mantle-cell lymphoma with an expected decision in June. One of the keys to Celgene's success has been its commit-



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ment to put significant financial resources into R&D — a policy Hugin believes needs to be implemented on a more macro level.

BRANDED INNOVATION BENEFITS SOCIETY THROUGH A VIRTUOUS CYCLE

Evangelizing the importance of increasing investment in medical innovation in the U.S. requires more than just a revamped culture of innovation. Namely, it requires pro-innovation policies and regulations, IP protection, and a significant financial commitment. Presently, the biopharmaceutical sector is the most R&D-intensive industry in the United States, investing more than nine times the amount of R&D on a per-employee basis when compared to manufacturing industries overall. Celgene is even higher, investing approximately $265,000 in R&D per employee. Compare that to the $7,634 per-employee average R&D expenditure for all U.S. manufacturing sectors between 2000 and 2004.

Celgene and the biopharmaceutical sector have demonstrated the financial fortitude to invest in U.S. medical innovation, which helps people live longer, better, and healthier lives and, in turn, stimulates the U.S. economy. But Hugin believes there are some big opportunities that should be mentioned and discussed frequently, for example, the facts related to the cost of drug development. "When successful drug discovery costs close to $1.2 billion and takes an average of 12+ years, that is just not sustainable if you want to provide therapies that can be cost-effective while continuing to invest in more programs to have more solutions," he states. In order to protect the U.S. medical innovation R&D engine, the effort needs to be truly collaborative, with multiple constituents, including life sciences companies, academia, patient advocates, payors, FDA, NIH, and CMS (Centers for Medicare & Medicaid Services).

Additionally, he says the fact that most drugs eventually go generic is an important consideration for all life sciences constituents. "If you want people to take risks, they have to have confidence and the certainty that if, in the rare case they are successful, they will benefit from it and be able to sustain the business model and make future investments in R&D," he notes. An integral component of the virtuous cycle of medical innovation is that new discoveries are accessed and reimbursed based on their therapeutic value. As a result, this provides both funding for future innovation and long-term benefit to society in the form of generic drugs after the original patent life has expired. As a point of reference, the innovator's discovery spends more time in the generic phase of its product life cycle than it does in the brand phase of its life cycle — an enormous societal benefit. "Generics will not exist if we don't invest in branded, innovative therapies that get fully protected for the life of the intellectual property," reminds Hugin. "Generics are invented by branded innovative companies. They aren't invented by generic companies."

SEEK OPPORTUNITY WHEN FACING ADVERSITY

Hugin is hopeful that U.S. government lawmakers heed the example of the EU's drug industry. He believes public policies which are supportive of collaboration and pro-innovation are necessary to truly protect the U.S. medical innovation R&D engine. Referencing Federal Reserve Chairman Ben Bernanke's Feb. 26, 2013 comments, Hugin advocates the need for addressing problems with a long-term approach as opposed to the EU's implementation of austerity — spending cuts and increasing taxes. Bernanke recently urged Congress to consider tax and spending policies that "increase incentives to work and save, encourage investments in workforce skills, advance private-capital formation, promote research and development, and provide necessary and productive public infrastructure." Hugin is in agreement, noting, "Often, during times of great adversity, you are presented with excellent opportunities. Seek to find the opportunities adversity presents." Not bad advice coming from the CEO of a company that overcame adversity by bringing back a once-banned drug that ignited bold pursuits in science and transformational approaches to rare, serious, and debilitating

THE ECONOMIC BENEFITS OF GOOD PUBLIC POLICY

"So few people today appreciate the improvements to the quality and length of life that medicines, devices, and medical innovations have on our society and the economy at large," states Bob Hugin, chairman and CEO of Celgene. For example, in 1900, the average U.S. life expectancy was 49 years. Today, it is 79. It is estimated by 2040 U.S. life expectancy will reach 85 years, a full 13 years more than the rest of the world. This is primarily the result of innovation in medicine and improvements to public health, which translates to U.S. economic health as well. Economists Kevin Murphy, Ph.D., and Robert Topel, Ph.D., calculated life expectancy gains from 1970 to 2000 to have added approximately $3.2 trillion per year to national wealth. They estimate a modest 1% reduction in cancer mortality would be worth $500 billion to the U.S. economy. Unfortunately, many pundits focus on prescription drug spending in a vacuum, noting increased spending on newer prescription drugs, while failing to note the overall reduction in medical spending that often results. Research conducted by Columbia University Professor Frank Lichtenberg, Ph.D., provides strong evidence to support the use of newer drugs in actually reducing total healthcare spending. For example, he estimates the use of a newer drug to treat a condition would result in an increase in prescription drug spending of $18. However, it would also result in a reduction in other medical spending by $129, with most of the savings being due to reduced hospital and physician office-visit expenditures. Hugin cites Medicare Part D as a real-world example in support of Lichtenberg's research. "In the first year, we saw a $14 billion reduction in other medical services expenditures with just the introduction of Medicare Part D – and costs 43% below forecasts," he attests. "It's only been around seven years and has nearly a 90% approval rating, which is pretty much unheard of. How can anyone not believe that Medicare Part D represents great public policy and an important social advance for America?"

diseases, including REVLIMID and POMALYST for patients with multiple myeloma.

Some pharmaceutical sector analysts estimate REVLIMID will generate sales in excess of $6.7 billion by 2018. That's good for society long term since it creates multiple opportunities for Celgene to reinvest in the next generation of life-enhancing therapies that may enable healthcare providers to turn more terminal diseases into long-term manageable ones. But if that is the only number which impresses you, then you didn't think nearly big enough nor nearly long-term enough. Big problems require long-term solutions — and spokespersons like you — to preserve the U.S. medical innovation R&D engine. Medical innovation is the crown jewel of America. It has contributed so greatly to the economic success of our country over the last 50 years, and it offers enormous potential to make a meaningful difference in the quality and length of our lives in the next 50 years. Of all the critical trends that will create a prosperous future, medical innovation will be the most important. For those of us who believe that medical innovation in a culture of change in science and medicine will be part of the solution, we must stand up and advocate for public policies and laws that support a positive environment and positive solutions to the challenges we face. Certainly, here in America, we have to believe in a positive future and be bold and courageous as we create it.

THE IMPORTANCE OF THE FDA INCENTIVIZING INNOVATION

Tropical diseases are not a prevalent problem in the United States. So why then did the FDA create a policy that incentivizes companies to develop new drugs geared toward treating these diseases? Because if you want companies to invest in developing new innovative drugs, which may not be commercially viable in the U.S. but will prove beneficial in solving global health problems, create a program that rewards these companies for their efforts. The FDA voucher program falls under the FDA Amendment Act of 2007 (FDAAA), and here is how it works. If a company develops a drug for a tropical disease treatment (e.g. TB) and receives FDA approval for it, the company is eligible to receive a transferrable voucher that allows the bearer to designate a single human drug application (i.e. another drug in the company's pipeline) submitted under section 505(b) (1) or section 351 of the PHS Act, to receive six-month priority review status. I think this is a great example of pro-innovation policy. If you want new innovative therapies that advance the treatment paradigm, stimulate the economy, and reduce the burden on our healthcare system, provide appropriate incentives. Not only is the FDA helping to treat diseases found primarily in poor and developing countries, but who knows what else might develop from this research?

Jens Eckstein, president of SR One

GSK Pushes Into Innovation Investment

By Wayne Koberstein, contributing editor

A conversation with the head of SR One reveals the evolving strategies, aggressive portfolio building, and key lessons learned by a Big Pharma's venture into the VC space.

As the funding gap for life sciences companies grows into a yawning abyss, new players enter the field to keep the flame of innovation alive: venture funds created by large pharma companies such as Novartis with Novartis Venture Fund (NVF), Pfizer with Pfizer Venture Investments (PVI), J&J with the Johnson & Johnson Development Corporation (JJDC), and GSK with SR One. Many of the pharma VCs are relatively new, although SR One launched almost 30 years ago and is the second oldest pharma venture fund after JJDC. Big Pharma's movement into the VC world belies the industry's dependence on academics and small companies for the majority of new drugs and devices and, perhaps even more important, for new directions in medicine.

Pharma VCs are often "evergreen" funds, typically investing less than $100 million per year but at a steady rate; nonevergreens are subject to funding cycles and interruptions. The steady contribution and unique assets of pharma funds, as separate but parallel units of the pharma giants, may amplify their impact on the investment scene. And in the latest twist, pharma and nonpharma funds are combining resources, as with GSK, J&J, and Index Ventures, which last year collaborated to create a new €150 million life sciences fund in Europe. Significantly, the pharma partners will sit on the new fund's scientific advisory boards, setting direction but not choosing investments.

Companies that have spawned VC units have no problem acknowledging their self-interest in helping to fill the life sciences funding gap. "In the top ten pharma companies, in-licensed products can make up 50% to 60% of their pipelines. So they know that more than half of their pipeline might not come from the inside; it will come from the outside," says Jens Eckstein, president of SR One. "So you need a window on external innovation, and you need to look out the window, find the innovators, and put money behind the ones you consider most likely to produce positive financial and medical returns."

For his company, the window Eckstein describes is venture funding. SR One gives it intense involvement in new research and related business initiatives on the ground floor of disruptive technology development. Without the potential for overturning old ways of delivering medical care, a start-up has little or no chance of landing funds from SR One.

"The biggest goal for us is innovation," Eckstein says. "We invest globally and broadly in healthcare and the life sciences, and we want to invest in technologies that will become extremely important for the whole healthcare industry within six to seven years from now — technologies that will significantly change the way medicine is done, for the better."

Investments are diverse, and candidates may include therapeutics, diagnostics, biomarkers, electronics, information technology, or materials, he says. "We are especially excited about some of the convergence areas, where you can start breaking down the old silos of therapeutics, diagnostics, and so on, and use them in a way that manages the whole patient, not just a disease."

FUNDING FOR PROFIT, INVESTING FOR INNOVATION

A "patient-centric approach to therapeutics" might once have sounded cliché, but the very real prospect of reimbursement based on patient outcomes, not product use, has apparently sharpened the industry cliché into a cutting edge. Just the fact that a venture investor in the life sciences, whether at SR One or any other experienced firm, talks about patient outcomes and integrating diverse technologies in healthcare represents a sea change.

Traditionally, many VCs put their money on products and potential markets, without much care for large-scale waves of reform in healthcare. Market share and sales projections largely rested on static assumptions about the four Ps — patients, providers, payers, and policymakers — plus the big R, regulators. The idea was to exit as early as possible and hopefully make your profit before the new tide actually washed in.

Eckstein maintains SR One operates as independently and financially driven as any other investment fund. Its funding decisions, negotiations, and contracts place no ties to GSK on the recipients, GSK obtains no special rights or access to confidential information from the deals, and the fund must ultimately base all of its invest-

ments on monetary return. But given those ground rules, SR One pursues its larger vision of supporting potential leaps in healthcare, and thus the environment in which its parent, GSK, competes. SR One's patient-centric perspective also mirrors GSK's strategic commitment to developing drug therapies that improve the full range of outcomes in patient care, using any effective supporting technology as needed.

"We want to address not only the maintenance of disease but also curative approaches. That is why we are going beyond just therapeutics. If we can find a new material or piece of electronics that could be curative, that is what interests us," Eckstein says.

FROM INVESTMENT STRATEGY DOWN TO CANDIDATE CHOICES

One principle that keeps SR One grounded in reality arises from the fundamental nature of venture funding — every investment candidate is unique and must undergo a critical evaluation based on its own merits. Philosophy becomes phylogeny as the evolutionary history of each candidate plays out in live-or-die tests of the proof of concept. The fund's investment analysts draw on experts not only in their own personal networks, as do their peers in other venture firms, but also in the vast GSK organization.

In 2012, SR One invested in almost 20 different enterprises, covering not only pharma and biotherapeutics but many other, sometimes surprising, areas of healthcare. Individual cases are informative; they show how the group translates high-minded words about true innovation into financially sound deals. Funded companies represent a single-digit percentage of all the candidates sorted through or sought out by the investor team. Eckstein highlights three deals as examples of how the fund balances prudent financials with its "revolutionary" aims:

• Auxogyn, the first deal of 2012 for SR One, is a small company developing clinical tools to improve fertility. Now in a collaboration with Merck-Serono, the company already markets the Eeva test, a visual algorithm to determine the fitness of fertilized eggs for in vitro fertilization (IVF), now available in the United States and soon in Europe. Embryo viability is the primary challenge in IVF, and a highly accurate way of measuring and boosting it could greatly raise the efficiency and effectiveness of the practice.

• PsiOxus, an oncology company featured in our September 2012 issue's "Companies to Watch," is developing a "systemically available oncolytic vaccine" that kills cancer cells like a virus, selectively — thus combining targeted and immunotherapeutic strategies. Citing a recent success by Biovex with an earlier oncolytic vaccine, Eckstein depicts the PsiOxus product as a second-generation approach that addresses first-generation issues with side effects and local administration. "That would be a fantastic breakthrough."

• IlluminOss Medical has a potentially groundbreaking bone-fracture treatment in development, which Eckstein summarizes as "No more metal, no more big plates, no more big surgery." The noninvasive procedure starts with a micro-incision and insertion of a balloon catheter that injects a monomer liquid inside the bone channel, and then a filamental light source in the catheter polymerizes the liquid into solid form inside the bone. With no cast or other supports needed, the stabilized bone retains enough flexibility to promote healing, yet patients may be load-bearing in a day, avoiding bed-ridden or hospital time and costs. Osteoporosis-related fractures may be the ideal area for such a treatment, reducing comorbidity such as with infection.

One common and important thread through many of SR One's investments is a connection, however oblique, back to the business of therapeutic drugs, drug/device combinations, diagnostics, and other supporting technologies currently in the portfolios of many "pharma" companies — including, of course, GSK. Even the bone-fracture procedure would encourage greater, and presumably more effective, use of therapeutics: "If you can get patients walking again quickly and to keep using their medicines, you have a better outcome altogether. So that reflects our view of the world — that you manage the patient, not just a single condition," says Eckstein.

PHARMA FUND PLUSES: STRATEGY, CONTINUITY, & LONGEVITY

Venture funds that look beyond the short-term financials, adopting a more environmental view of investment, rightly deserve the adjective "strategic." On a continuum, then, the other end would be the "nonstrategic" VCs, somewhat infamous for their propensity to bolt and run long before the final verdict on a product's success in the real world comes.

Eckstein observes that some institutional venture funds have pharma companies as limited partners where "strings" do exist and thus might be more affected by the pharma partner's strategy than are more independent VCs like SR One or the Novartis Venture Fund. "You have to look at the books these days to figure out what the strategy of a given venture fund really is. It's an interesting change in the world."

Strategic funds will naturally be able to pursue opportunities the less-strategic ones overlook. Does a strategic approach therefore increase the risk of investment? "There is a general rule that, if you are the only one looking at a particular investment, you are either crazy or you're a genius! Maybe sometimes we're both," jokes Eckstein. "This is an interesting time; because of the scarcity of VC money, we have a huge smorgasbord of opportunities in front of us. I like finding ones that at first may look a little bit crazy, because you have to push the envelope to change something, and we have many changes under way."

Perhaps balancing the risk of a more strategic approach is SR One's ability to rely on what Eckstein calls the "huge database" of expertise and experience in the worldwide GSK organization. "We have the freedom to pick up the phone anytime and call someone at GSK. We can conduct due diligence quickly and get a quick feel for the concept under consideration. It's all on a nonconfidential basis, of course. Collaborations and even acquisitions can and do arise for GSK from such interactions, though only incidentally to the SR One investment.

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"Most of the team have been in venture capital for some time, so we all have our personal networks and brand as well," says Eckstein. "The venture business is still very personal; some deals we're looking at specifically because someone wants to work with a certain person on my team or vice versa. In a business like this, you pick up on ideas. We always go through an exercise prior to a deal: We look at all of our projects and identify white spaces — areas with medical need not yet addressed by VCs or entrepreneurs. We also have 'holy grail' projects in areas of huge medical need without current breakthrough innovation because of risk or lack of success through traditional approaches. In those areas, as in others, we bring a broad piece of science together and envision the best development path to patients."

Eckstein marks a recent trend toward more investment at an early development stage. "More and more, we go directly to academia or the principal investigators and talk with them about the science, and if we like something, we will pay to repeat some of their experiments. We might even improve some of the critical experiments and create data sets that will help us make a decision, based on early-stage data, about whether we should go forward or invest more time on evaluation."

SUPPORTING THE SURVIVABILITY OF FUNDING RECIPIENTS

As a deal passes the selection stage and begins to coalesce into an investment relationship, Eckstein sees plenty of opportunity for reducing risk by ensuring the good health of the funded company. One of the points in his CV that helps account for his view is his membership in the Society of Kauffman Fellows. He explains, "Kauffman Fellows go about building businesses according to the old mentorship model, because venture capital is a business you cannot learn at the university; you learn by doing, by working together with people who know the business, who have been there before, and once you figure something out, you try to give back."

The mentoring often begins with a business plan, a treatment that lays out all of the potential strengths and challenges of the company and how it will deal with them. Each company in the portfolio can use SR One's resources to improve its business model and operations, but the fund is also mentoring on a wider scale. It recently launched a business-plan competition in Europe named OneStart (www.oxbridgebiotech.com/onestart), offering a top prize of £100,000, plus free lab space and IP/legal advice.

Mentoring extends beyond the business plan to help solve key challenges that are strategic, technical, and operational. For example, life sciences start-ups often run afoul of costly problems in manufacturing scale-up and supply of product for clinical trials. SR One can tap GSK's manufacturing expertise as needed to help.

A TWO-WAY WINDOW FOR INVESTOR & INVESTMENT SEEKER

Elaborating on the reasons for SR One's and other pharma funds' existence, Eckstein explains the implications of his original Big Pharma "window on innovation" analogy. "If you want to tap into the best minds, it doesn't matter where they are; you go there and try to work with them. Whatever knowledge you gain through conversation, you can pass along to someone else, and that's the best way to find what you're looking for."

At the same time, Eckstein is eager to get a message to those who are looking in through the investor's window: "If your idea is sound, and you're willing to get advice and work together with people, you will get funded. I'm very optimistic right now. There are always great ideas out there. We have learned a lot through all our pains, and it is a fantastic time right now for life sciences investment."

If nothing else, the note of optimism in an otherwise bleak VC environment might prove as stimulating to innovation as the investment itself. If the pharma-supported funds succeed in breathing new life into the industry, it will be by delivering money and mentoring where they are most lacking and needed — those brave little start-ups that could change the world.

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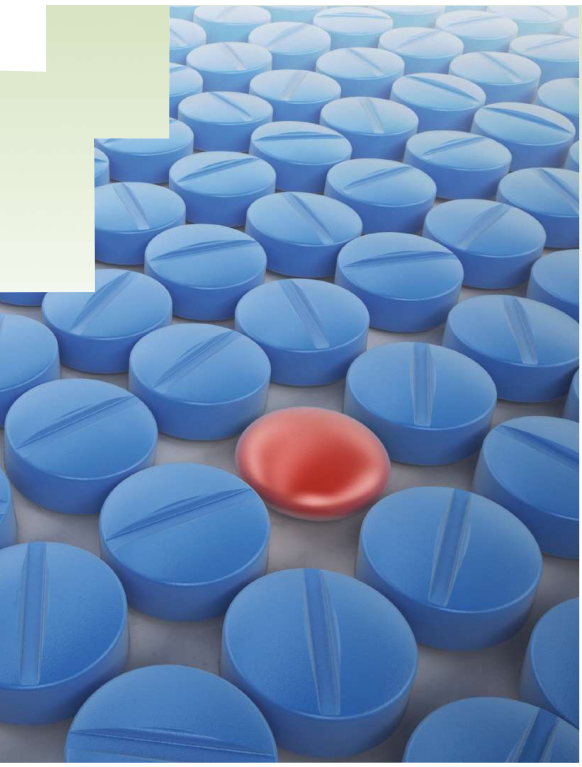

How Pfizer Navigates Changing Biosimilar Regulations

By Nick Taylor, contributing editor

The imminent loss of patent protection on blockbuster biologics is creating an interesting market opportunity — biosimilars. It is a highly lucrative opportunity too, with BCC Research predicting the global biosimilars market will swell to $3.6 billion by 2016. That figure has attracted virtual biotechs, generics giants, and the biggest of Big Pharma. Each is united in pursuit of a piece of the $3.6 billion and by a common challenge — regulations.

Diem Nguyen grapples with the challenge every day. "From a biosimilars regulatory perspective, there's still a lot of uncertainty," says Nguyen, general manager of Pfizer Biosimilars. Because biosimilars are never exact copies of the innovator medicine, establishing appropriate standards for biosimilarity remains an important area for scientific, legislative, and regulatory debate. While all regulators in established markets have created guidelines, they are still ironing out the details. The sector is too young for anyone in industry or regulation to know how things will play out. Everyone is navigating untrodden paths.

Differences in regulations across the major markets further complicate biosimilar development. Some regulators, such as the FDA, allow developers to run similarity tests against innovator drugs sourced from overseas. (The U.S. still requires an FDA-licensed reference product.) The European Medicines Agency (EMA) and other regulators want developers to source comparators, called reference products, locally. Europe plans to become more flexible, like the FDA, but global alignment is a distant dream. The variance means that even in the preclinical stage, a "one-size-fits-all" approach is impossible.

INVEST EARLY IN ROBUST PRECLINICAL DATA

Common regulatory goals and values lie behind the different biosimilar development guidelines though. Regulators are united on the value of data showing similarity between a biosimilar and reference product. They all want to see similarity shown through structural and functional characterization of a biosimilar and reference product. The biosimilar concept is based on robust evidence of similarity being demonstrated in preclinical, quality, and functional comparisons, which then allows a tailored preclinical/clinical program to be followed which does not require repetition of the entire development program of the innovator.

Money spent on generating data showing similarity can therefore save time and resources later by reducing clinical testing requirements. Still, Pfizer is committing significant resources in time, money, and intellectual expertise into clearly showing similarity and ensuring the safest and most effective biosimilars are developed. Analytical tools and cell-line development knowhow from the innovative biologics division support the effort. Backed by these resources, Nguyen thinks Pfizer has an advantage in technically demanding areas of biosimilar production.

The FDA showed just how hard it is to replicate biomanufacturing processes when it rejected a Genzyme drug in 2008. Genzyme had already won FDA approval for the Pompe disease drug, Myozyme, but a manufacturing change caused problems. The FDA said scaling up from 160L to 2,000L reactors altered the drug enough to make it a different product. Regulators accept that biosimilars will differ from innovators — small differences without clinically meaningful effects are allowed — but showing similarity is still tough. It is also just the first of many obstacles on the path to approval.

HOW TO DESIGN A GLOBAL BIOSIMILARS TRIAL

The goal when designing a global biosimilar trial is to meet the needs of as many regulators as possible. This way, a company can run one trial, instead of several smaller studies, to access multiple markets. The challenge is finding a trial design that satisfies the needs of all the major regulators.

Nguyen shares a hypothetical example to show potential global trial design pitfalls. Say Pfizer designs a trial and takes it to the European Committee for Medicinal Products for Human Use (CHMP). The CHMP likes the trial design and clears it without any alterations. But when Pfizer takes it to the FDA, the U.S. regulator asks for tweaks to the trial design. Pfizer then has to modify the trial to meet the needs of both regulators or run separate trials for the U.S. and Europe.

Matters become even more complicated when emerging markets are thrown into the mix. India, for example, largely follows the European biosimilar pathway, but requires local trials. And its guidance is short on detail

about Phase 3. "So, even though India broadly follows European standards, a product could win approval in one market, but not the other," Nguyen explains.

A flexible, creative approach is needed to navigate through the regulatory maze. For Pfizer, this means applying experience with innovator biologics, which was boosted in 2009 by its merger with Wyeth. Newcomers to biologics are partnering to gain expertise, a trend illustrated by the joint venture between Samsung, Quintiles, and Biogen. Knowing what worked in the past will only get a firm so far though. "If there's one thing about biosimilars development I'm comfortable with, it's that it will evolve," Nguyen says.

COME PREPARED TO MEETINGS WITH REGULATORS

To glimpse into the future, companies must pay attention to the utterances of regulators. Ask the right questions, and a regulator can make the path forward a little clearer. Comment periods on draft guidance documents are an agency's opportunity to listen. But meetings to discuss an individual biosimilar or indication are the best chance to talk over the fine details.

At Pfizer, the process of preparing for regulatory meetings begins by looking backwards. "We draw on our knowledge of regulatory precedents, past programs, and known issues with similar products," Nguyen explains. With few biosimilar precedents, the regulatory fate of the innovator biologic being copied is a useful guide. If side effects were a regulatory hurdle for the innovator biologic, a biosimilar will face scrutiny, too.

Pfizer feeds knowledge of what happened in the past into its models of biosimilar development pathways. Before meeting with regulators, Nguyen and her team investigate the feasibility of all credible biosimilar development options. The impact of different development choices, such as enrollment targets, is predicted. One pathway might offer the cheapest, fastest route to market but increase the likelihood of regulatory restrictions.

Regulatory meetings are particularly useful in markets that are still finalizing the details of their approval pathways. But even in Europe — which was a pioneer in biosimilars — guidance is still evolving. The EMA expects to publish a revised draft of its 2005 guidelines on biosimilars later this year. And, with several emerging markets taking their lead from Europe, the changes could have far-reaching consequences. As with much in biosimilars though, it is too early to say with total conviction. "We've not progressed far enough to know if a change in European biosimilars' guidance could trigger a shift in Brazil or India, too," Nguyen states.

All this uncertainty is a problem for developers of biosimilars. Even at this early stage in the history of biosimilars, some firms have hit development difficulties as regulatory expectations change around them. In October 2012, both Teva, which is developing biosimilars

with CMO Lonza, and Samsung independently halted trials of rituximab. Media reports linked the decisions to halt tests to doubts about regulatory situations in the U.S. and Europe.

If these companies reach the stage of submitting data to regulators, they will face a whole new set of uncertainties. The FDA is yet to accept an application under the biosimilars approval pathway, so nobody knows what will happen.

PHYSICIANS NEED TO BE EDUCATED

In small molecule generics, being the first to bring a copycat to market almost guarantees a big slice of the sector. But biosimilars, as in so many other areas, are more complicated. The path from approval to taking market share is less certain. For starters, though the U.S. law includes a definition of "interchangeability" that speaks to substitution without the intervention of the prescriber, it is a question of individual state laws whether pharmacists are permitted to switch patients from innovator drugs to biosimilars. Pfizer is of the opinion that the physician should own the decision to treat an individual patient with a biosimilar in view of the complexity of biologics in general, and, therefore, automatic substitution of biosimilars for innovator drugs without the intervention of the physician is inappropriate.

Whatever the FDA decision, biosimilars manufacturers will need to work to win market share. The price difference between biosimilars and innovator products will be less pronounced than for generics. And the complexity of the products further shifts the risk-reward balance away from the biosimilar. The challenge will be similar in scale to marketing innovator biologics. Pfizer, with its background in innovative biologics, believes this gives it an advantage. "Our relationships with physicians across multiple therapeutic areas allow us to understand what they want from data," Nguyen says.

Physicians are, along with regulators, pharmacists, and payors, one of the key stakeholders dictating how patients will access biosimilars. It is important they understand the issues. "Physicians need to be educated about differentiation, quality, and data perspectives in biosimilars," Nguyen states. With this understanding in place, physicians can make informed decisions about prescribing and help increase trusted acceptance of biosimilars.

If biosimilars take market share, patients will benefit from more affordable versions of lifesaving biologics, and payors will gain a new tool to drive down healthcare costs. There is still a long way to go until this is achieved, though, and getting there will require creative thinking. "A cookie-cutter approach to biosimilars development simply isn't going to work," Nguyen concludes.

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The Cold Chain: What You Don't Know

By Gail Dutton, contributing editor

Pharmaceutical supply chain experts are among the best at managing the cold chain, but new innovative packaging and transportation options are changing some well-established assumptions. "You have to be aware of daily conditions on the shipping lanes," says Jim Cafone, VP of supply network services at Pfizer Global Supply. "If you don't know what's happening, you can't validate the lanes."

He advocates monitoring each shipment. Analyzing that data can identify usual shipping conditions but may not reflect the extremes faced during unseasonable weather or delays. Delays are more common for containerized and palletized shipments than for small packages because of the shrinking fleet of wide-body aircraft, he adds.

At Amgen, "One of the big 'ahas!' was the need to qualify packaging systems in the same environment in which they would be packed," says Tim Valko, executive director of risk management. "Validate the packaging on the floor where products actually are packaged — not in the lab. And, ensure the process becomes an SOP (standard operating procedure) for the scientists and for the packaging line operators. Validation must not be a paper exercise."

PACKAGING EXPECTATIONS ARE CHANGING

Currently, most pharmaceutical shippers use dedicated packaging solutions for summer and winter, but universal packaging for clinical trials (where the drugs being shipped) have limited stability data. "With commercial products, the cost of universal packaging is approximately twice that of dedicated packaging. So, if you're shipping commercial products in the same climate range, is it worth the cost of universal packaging to prevent a brief excursion of perhaps 2°C?" asks Tom Pringle, principal, Pringle Consulting, LLC.

While shippers are trying to streamline their packaging options, regulators are still formulating requirements for their own countries. Currently, "Each regulatory body has different expectations. It's a complex Rubik's cube," Cafone says. For example, some products stored between 2°C and 8°C may withstand temperature excursions of a few days' duration, but some regulators allow excursions of less than three hours while others allow none. Accommodating those differences requires different package engineering and shipping solutions and, therefore, increases costs.

Ideally, pharmaceutical manufacturers would develop their products so they don't require the cold chain. As Martin VanTrieste, RPh, senior VP of quality at Amgen, elaborates, "Many biological products are much more heat stable than we originally thought. If you perform the proper studies, you can minimize cold chain needs or ensure that minor excursions are acceptable."

UNDERSTAND PACKAGING LIMITATIONS

The choice of active packaging systems (that are plugged into electrical current), passive packaging systems (that rely on insulation and coolants like liquid nitrogen or dry ice), or hybrid packaging systems (that combine active and passive systems) depends upon the stability, geographic origin, and destination of the product. "For example, Brussels to Chicago has a standard elapsed, door-to-door shipping time of about 36 hours. For that, we can use passive containers with a 120-hour hold time," Cafone says. Shipping from Brussels to an emerging market, however, is less predictable. "It may take 72 hours, or it may take 14 days. For that, we use active systems and hope handlers plug them in."

It requires more than plugging them in to ensure products arrive in good condition, though. Although properly operating containers set to 5°C typically are accurate to plus or minus 3°C, "Shippers often overlook the importance of preconditioning the operating container — not just the air inside it — and the product to the same temperature," says Karl Kussow, manager of quality at FedEx Custom Critical. Kussow, who is helping write the upcoming Parenteral Drug Association (PDA) technical report on active containers, says active containers can't truly be validated. "They're mechanical. For the report, we agreed to call the process 'qualification.'" He says the three keys to success using active containers are proper maintenance, attention to the shipping and loading process, and ensuring active control. "Having passive protection inside is a good buffer for transfers between modes," he adds.

For passive containers, tailored phase-

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change materials like dry-vapor liquid nitrogen are quite effective at maintaining temperatures for several days. Although these materials may be more expensive than the packaging they replace, they can reduce overall costs by reducing weight and, therefore, freight costs.

DEVELOP SOPs FOR COLD CHAIN HANDLING

At Pfizer, Cafone says, "We develop specific instructions regarding how shipments are loaded, transported, and received. We define who is responsible for each hand-off, when and how temperature-controlled containers must be recharged, how they are recharged, etc." The documents average 45 pages and should be available to package handlers. The objective is to ensure that carriers are capable of handling the product, understand the products' requirements, and have procedures to minimize mistakes and remediate them when they occur.

"We spend a lot of time teaching service providers and encouraging them to invest in education and equipment to maintain the cold chain, based upon the requirements of the products they handle. That includes identifying destination conditions and ensuring that customs offices and the final recipients have the equipment and procedures to protect shipments from thermal excursions. You have to examine the whole chain of custody," Cafone emphasizes.

KNOW THE SHIPPING ENVIRONMENT

Understanding the partners and their resources, as well as the product's chemistry, becomes even more critical when switching transportation modes. Some companies are moving part of their air cargo to ocean freight, reducing costs but altering risks. Logistics experts talk about reefers disconnected from ships' power and never reconnected, and about partially charged batteries that were drained during handoffs. "Ocean shippers aren't good at handoffs," Cafone says. Therefore, they prefer to avoid transporting pharmaceuticals. They are, however, doing it — particularly for products that don't require close temperature control.

"Active containers for ships may not operate within the same tolerances expected of air carriers," says Jamie Chasteen, product development manager at Cold Chain Technologies. Part of the issue relates to the larger sizes of marine containers. To help remedy this potential temperature differential, Kussow recommends loading products in active containers so air flows around the product's sides.

Active containers also are at risk when disconnected from ships' power. That risk can be mitigated by deploying passive packaging as a buffer inside the active containers. Amgen's products are shipped in intermodal reefers and lifted from trucks to the ship, where they are plugged into the ship's power. "The reefers have batteries, and all of ours have temperature indicators inside the containers. We know the key profile the product experiences and can reject it if it experienced temperature excursions," says VanTrieste. Advanced monitors incorporate wireless and radio-based communications and real-time monitoring that can alert shippers to pending excursions. Although intervention is possible, it's often impractical because the containers may be inaccessible inside the cargo bay.

COLDER ISN'T BETTER

"Distributors and wholesalers often have the mindset that colder is better. It's not," Chasteen says. Freezing substantially diminishes the efficacy of many compounds. "That concept is new to various segments of the industry."

Shipments packaged to withstand extreme heat may be damaged when they are used in less severe situations. "A very common problem we see is customers using data loggers who have had no problems with multiple shipments, but who suddenly have a cold excursion. Approximately 95% of the time, when the temperature suddenly hovers between 0° and 2°C, the package was placed in a refrigerator. Invariably, a new employee was stressed about keeping the package cool until the carrier arrived."

CONSIDER THE LAWS OF THERMODYNAMICS

Solar radiation also is just beginning to be considered in packaging. Chasteen recalls one pharmaceutical shipment that sat on a tarmac at 25°C. "The temperature monitor on the package registered more than 50°C." The differential was caused by the reusable, clear plastic covers that protect pallets from the weather and from abrasion from cargo netting. "The covers created a greenhouse effect."

Even without the covers, solar radiation has an effect. "Historically, more than 90% of temperature-sensitive boxes were white lined corrugate," Pringle says. That's changing as shippers realize that white marks packages as high value. The less expensive brown lined corrugate, however, absorbs more solar radiation than white and must be factored into cold chain decisions.

Positioning matters, too. "High-density products may exhibit the right temp on the surface but not in the center," Cafone notes. Palletized products, too, will have temperature differences between products at the center of the pallet and those along its exterior. "We conduct studies to understand how long to prechill products to achieve the correct, consistent temperature gradient throughout the pallet.

"We also work with surface carriers and airlines to ensure products are placed in the right position in cargo bays. For example, if a refrigeration unit is at the front of the truck, cargo in the front will be colder than cargo near the back. Also, it's warmer over the wheel wells," Cafone says. Aircraft have similar issues, with hot spots near heating elements and toiletry equipment. Depending upon placement, temperatures may range from 8°C to 25°C in a cargo hold. The differences vary even among the same model of plane, so no single solution is effective fleet-side. Some carriers, like FedEx Custom Critical and Panalpina, can control temperatures inside their cargo planes. But, temperature-controlled packaging is still required to ensure proper temperatures are maintained.

"The packaging environment is very dynamic, as companies validate new technologies and put them in place," Valko says. "The key is to understand the science behind the packaging, the product's sensitivity, and the complexity of moving that package, and to ensure that material handlers are qualified and understand how temperature excursions affect people's health."

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Finding The Gaps In Your Logistics Plan

By Gail Dutton, contributing editor

Supply chain gap analysis is moving from managing individual shipments to providing predictive forecasts that can improve an organization's overall supply chain performance. Gap analysis is a critical tool to assess processes throughout the supply chain, but it is only one tool needed to optimize a quality system.

Abbott, for example, has an extensive, routine monitoring program as part of its supply chain risk management activities. According to Michael Douma, divisional VP of supply chain, global pharmaceutical operations at Abbott, "One hundred percent of shipments from both of our main distribution facilities are monitored. Metrics provide an objective basis for actions. They measure general performance and are used in risk management for root-cause analyses and in process improvement/optimization projects." Specific targets for the improvements are confidential, but include reducing the annual number of exceptions and thus enabling continuous improvements and better control in the shipping process.

Monitoring is no longer focused solely on finished products. Now monitoring extends to the entire supply chain, starting with incoming ingredients and ending only when the product is in users' hands. As Douma underscores, "Managing supply chain temperature during manufacturing is a rapidly expanding area of focus by many countries' ministries of health. And, the issue of end-to-end supply chain temperature control routinely comes up during ministry of health meetings and customer audits."

KEY SUPPLY CHAIN GAPS

"Within logistics, the most frequent supply chain failures occur in transportation and customs clearance – specifically around the handoff between freight forwarders and in-country brokers," Douma says. There also is a high potential for packaging or handling mistakes that may lead to temperature excursions when products are exposed to very different external environments during shipping. "For example, shipping products from winter in Chicago to summer in South America requires very robust packaging to manage the changes in temperature and humidity." Shipping from Chicago to Berlin, by contrast, is less challenging because environmental conditions are similar.

Not surprisingly, logistics experts agree that, although all geographic areas have potential perils, the greatest risks are in developing markets. Each nation typically has different cold chain requirements and different interpretations of those requirements. Currently, for example, there are more than 30 different GDP (good distribution practices) regulations from organizations and nations, and more in development. For the same product, one country, for instance, may allow no temperature excursions while another may allow excursions of 1° to 2°C or more. Some require data loggers, while others accept indicators. There is no blanket policy for handling the same product around the globe.

Working closely with their supply chain partners, including logistics providers, not only helps organizations stay abreast of changing cold chain regulations, but also helps them identify areas needing improvement. By working together, Douma says, "We found a better definition of specific conditions during each stage of shipment and the potential risks. We also realized there is a need to educate all supply chain partners on GDPs and on supply chain temperature management."

To identify gaps in policies, procedures, and their implementation throughout the supply chain, as well as conditions that contribute to packaging failure, pharmaceutical companies need to analyze all the relevant data relating to a shipment, including time, temperature, packaging solutions, transportation mode, and the exact path it takes to reach its destination (the lane). However, "The quality of data is more important than the quantity of data," stresses Niclas Ohlsson, CEO of TSS AB (a supplier of cold chain management solutions, including temperature monitoring), speaking at the 2012 IQPC Global Cold Forum.

TEMPERATURE MONITORING EXPANDS

Acquiring temperature data is an obvious first step in any cold chain gap analysis. Although equipment and facilities — including cold rooms — have been temperature mapped for years as part of good manufacturing processes (GMPs),

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many ministries of health recently have begun requiring 100% supply chain temperature monitoring on cold chain pharmaceutical products imported into their countries. "Temperature monitoring of product in-transit and temperature mapping of facilities and/or equipment are critical to complete a comprehensive, value-added gap analysis," Douma emphasizes.

To generate temperature records throughout transit, progressive companies pack temperature monitors inside several boxes for each shipment. They monitor temperature continuously throughout the journey, and the data is uploaded once the product is received. That data provides proof of actual product temperatures throughout transit. Shippers using GPS tracking may gain deeper insight by linking any excursions to a geographic location and handler.

TEST IN THE LAB AND IN THE ENVIRONMENT

Testing packaging is also advised — and not just to ensure proper temperatures. Distribution chain studies should test products against exposure to temperature, pressure, shock, and vibration during transit so formulations may be designed to minimize the chance that proteins will denature or that aggregates will form.

Shipment routes and packaging can be tested, either through a comprehensive testing facility or through real-world shipments. In controlled surroundings, shippers have the advantage of testing extreme conditions in a repeatable environment while conserving product. In that situation, shocks, vibrations, and temperature issues should be experienced concurrently, just as in actual transit. Conversely, real-world situations don't test as broad a range of conditions, but have the additional advantage of undergoing customs clearance. If there are issues with paperwork or handling, they may be identified during a small shipment, before commercial quantities are shipped. This is particularly important in countries in which the pharmaceutical import market is not yet mature.

AstraZeneca, for example, has a well-established global presence and significant research, development, and manufacturing alliances in developing markets. When moving product, APIs, and samples throughout its networks, it knows that collaboration with its supply chain and logistics partners is vital.

Once AZ gathered comprehensive information throughout its supply chain, it shared both the data and the analyses with its carriers. "That gives our freight forwarders detailed insights on specific routes to help them identify actions they can take to mitigate risks," says Christine Foster, senior quality assurance supplier manager at AstraZeneca. The company does this without fear of breaching trade secrets or reducing its competitive advantages, understanding that sharing data on routes, temperature, vibration, and other logistics data with its logistics providers helps strengthen its network. Others are more cautious. Abbott, in contrast, keeps much of its logistics data in-house.

AUTOMATE REPORTING

In addition to changes in logistics, AstraZeneca also changed its reporting systems. Before beginning the program, "Reports were cumbersome," Foster recalls. In June 2010, it partnered with TSS to design a comprehensive distribution chain analytics system that was implemented the following spring.

This new system provides an overview of logistics throughout the company, putting nearly real-time information about routes and performance criteria at managers' fingertips, and allowing ad hoc reports for snapshots of specific concerns. The other benefit of the consolidated reporting system is that it enforces data consistency, removing site-to-site variation. "We can associate trends with cost of resources, enabling savings that can be applied to drug development," Foster says.

MANAGING NUANCES

From a logistics provider's perspective, "Managing nuances of various shipping lanes, packaging, environments, and other factors that affect the cold chain efficiently through analytics helps the logistics industry be more responsive to customers without driving up costs disproportionately," says Jerry Hammon, VP of transportation and logistics for GenPact, a business process management solutions provider, speaking during a logistics webinar. To realize efficiencies from any analytics package, however, organizations must overcome the challenges posed by operational silos, ineffective use of data, and the accumulation of meaningless metrics.

Organizations still operate in silos, with communication gaps between planning and execution that delay feedback and impair efficiency, Hammon says. The rapid proliferation of data makes sharing information across silos even more challenging. "The volume of data is growing at 40% per year, and it's difficult to discern what's relevant. More than 89% of companies don't use their data effectively to make informed decisions. Instead, the trend is to gather more data," he says.

To optimize efficiency, Hammon continues, "Identify the data sources and determine which are predictive and can affect business outcomes." Also identify useful data that may not be recorded currently but that could be captured with existing technology. "Don't be constrained by just the data that's flowing toward you."

By analyzing that data, organizations can make more informed decisions to help them select transportation modes and design logistics strategies. As Satish Armugam, assistant VP of transportation and logistics at GenPact, says, "Analysis can be used to drive efficiency in function. This results in gains of 10% to 12% in network design and optimization, 8% to 10% in carriers sourcing, and 6% in distribution center analytics." These results can be achieved through more effective consolidation, mode shifts, capacity utilization, and load planning.

The long-term objective of data analytics initiatives is to move organizations from descriptive analyses to predictive analyses so they may address challenges proactively. Like biomarkers in drug development, predictive analytics identify lead indicators that forecast performance and provide insights to further optimize operations and yield competitive advantages.

Collaborating internally across silos and externally with supply chain and logistics partners is key to achieving the most effective outcome from any supply chain gap analysis. As Hammon says, collaborating ensures "We aren't reinventing solutions."

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Parenterals, Prefills, & Purity: Are Suppliers Up To The Challenge?

By Wayne Koberstein, executive editor

Somebody better be up to this challenge, or we're all in trouble. With more and more reliance on large-molecule drugs, the injectables market has soared just as shortages due to product contamination, recalls, and plant shutdowns have plagued companies and patients. The two crises are intimately related, and only an industrywide surge in investment for facility upgrades, mainly by suppliers, will address them both.

From my earliest days in the pharmaceutical industry, production, storage, and distribution of parenterals have been the downfall of many companies. Typically, a Big Pharma will buy a smaller company with an injectables line. Boom — within a year, the inspectors descend on the acquired facilities and lock them down. Headlines declare the company's complacency toward product quality and patient safety. The company defends itself, shifting as much blame as possible to the company it acquired, as if it were just another innocent injured party in the unfortunate affair.

Eventually large companies, presumably exhausted from repeating the experience with such acquisitions, began to rely increasingly on third-party suppliers. One effect was to spread drug production globally; many of the great pharma production centers in the United States and Europe have since closed in favor of outsourced manufacturers in India and other far-flung facilities. CMOs took over some of the abandoned capacity in the West but followed the general trend toward worldwide production. One major result was that the sheer number of plants far outgrew regulators' ability to inspect and validate them. Lack of inspection is now a standard part of many suppliers' business models — and if the pendulum were to swing toward greater enforcement as the FDA threatens, it would throw those companies into a financial sandtrap.

The technologies that can ensure the purity of parenterals have existed for some time. Prefilled syringes or auto-injectors offer a general solution. One specific platform is aseptic blow-fill-seal (BFS), which I have described in the past. Avoiding microbial contamination on the shop floor by isolating the product from personnel and other sources and sealing it against exposure to further contaminants in distribution are the central challenges. But any new system that requires retrofitting or de novo construction will mean capital expenditures a given supplier may be unable to make. So the question of who is up to the challenge is more about economics and finances than technologies.

REWARDS FOR HIGH QUALITY ARE LIKELY IN THE FUTURE

Regulators may yet apply enough pressure to force widespread investment in the needed technologies. But even those who put their faith in market forces would accept the inevitability of a major shakeout among suppliers over this issue. Sooner or later, regulators and customers will find ways to punish the poor-quality producers and lax distributors responsible for adulterated or counterfeited products, or related breakdowns in supply. There will be rewards as well for the suppliers who survive by maintaining or upgrading their production lines.

One obvious reward would be entry into the burgeoning market for prefills. Prefilled injectors not only ensure sterility in manufacturing and distribution, but also cross-contamination between patients or providers at the point of care. Their ease of use, stability, and safety have created a growing demand and preference for them over traditional injectables.

Other incidental benefits may also apply with prefills. One is materials saving due to reduction or elimination of overfilling — one article I read claimed 20% more product yield because vials typically require the same percentage of overfill. Increased speed and flexibility of prefill production lines is another potential advantage. Prefill lines are also subject to greater automation, simplified cleaning, and less down time than traditional injectables.

Still, I can't help but believe that the most compelling reason to adopt prefills is to upgrade the supply chain to a higher level of cleanliness. Yes, simple cleanliness should be the hallmark of any medical

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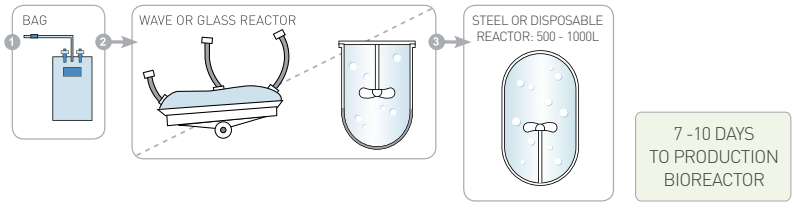

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facility or organization. The rewards thus seem identical to the solution.

IS A HIGHER STANDARD ON THE HORIZON?

Make no mistake, however — for many suppliers, low cost is their main or only selling point. Any technology that increases production costs or capital outlays pinches precious margins. To some extent, the entire existence of the generics industry depends on low-cost production and supply. But it doesn't necessarily follow that poor-quality injectables must be the norm. If suppliers that cannot manage to maintain sterility of facilities, equipment, and product drop out of the game, a higher standard will apply to all the players that remain. Prices and margins will adjust accordingly.

CHANGE MAY NOT COME SOON ENOUGH

Raising the bar for parenteral suppliers may come about without government pressure, but I doubt it. Yes, there is plenty of market pressure, but perhaps a bit too much on both sides of the issue. The recalls and drug shortages that make the news push producers toward the light of a higher standard; the economics toward the dark shadows of cut-rate production.

An echo exists in the question as well — the now age-old struggle between the innovative and the follow-on sides of the industry. Innovation may impel a more progressive approach to new technologies, on the assumption that generics inherently promote the opposite. But ours is a cut-and-paste industry; there are no longer only two distinct camps working in opposition. These days you see Big Pharmas with generics divisions, specialty pharma, new drug-delivery approaches, prospective biosimilars, and every shade in between — all arguably favoring widespread adoption of technologies that ensure purity of parenterals.

If you doubt my argument, or indeed accept it, a reliable test for it exists: time. Time will speak the final word on whether suppliers move widely to raise the standards for parenterals, spending what is necessary for prefill and other technologies to ensure sterility and supply from production to point of injection. My somewhat educated guess is that the change will not come soon enough or spread widely enough to save a great number of suppliers from a degraded fate. To the extent such a fallout occurs, we all stand the chance of suffering the consequences, as professionals or as patients.

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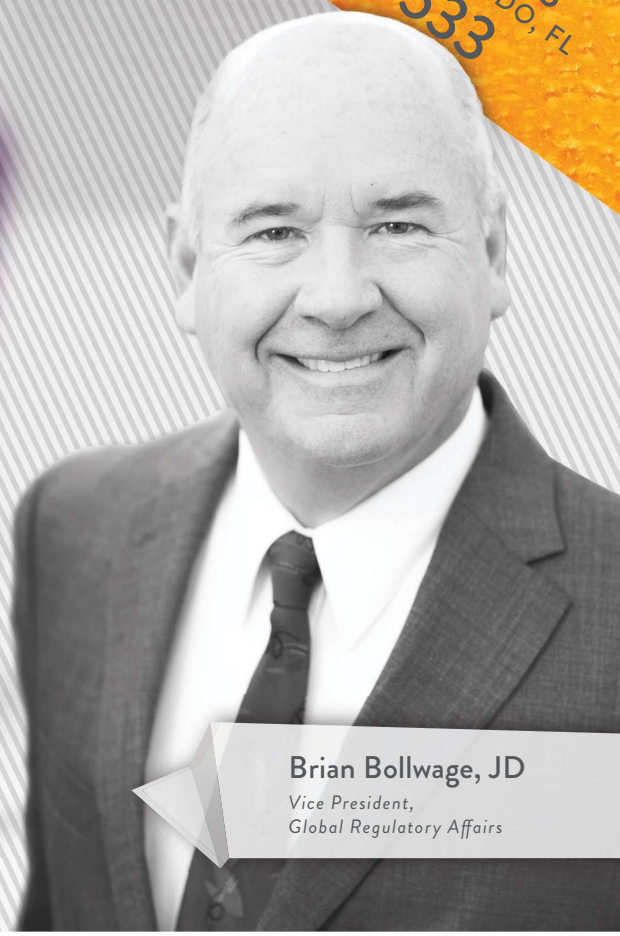

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Why Regulatory Intelligence Is More Important Than Ever

By Cathy Yarbrough, contributing editor

When FDA official Robert Temple, M.D., speaks at the agency's open-to-the-public workshops and other meetings, Gary Buehler, VP of global regulatory intelligence and policy at Teva Pharmaceuticals, listens. "Remember the old TV commercial about the stock brokerage company, 'When E. F. Hutton talks, people listen?'" Buehler asks. Dr. Temple, deputy center director for clinical science at CDER (Center for Drug Evaluation and Research), is an FDA "thought leader," to whom regulatory intelligence officials should listen during public meetings, Buehler said.

"Dr. Temple's comments often provide insight about how FDA officials are thinking, what they are planning to do, and what is on the horizon regarding new policies, regulations, and guidelines," he said. "I take that information and assess how it applies to Teva," added Buehler, who formerly headed the FDA's office of generic drugs. He joined the company in 2010 after 24 years at the agency.

Regulatory intelligence (RI), which made its first appearance about 15 years ago at the large biopharmaceutical companies, is a relatively new arm of global regulatory affairs (RA) at Teva, Buehler said. RI typically is part of a biopharmaceutical company's RA department and broadens the traditional regulatory affairs function beyond preparing and submitting applications to the FDA and the regulatory agencies of Europe and Asia. RI officials keep the company's leadership up-to-date about current regulations affecting the development, approval, and maintenance of products, as well any changes to the regulations and/or regulatory landscape that may impact their efforts.

"RI focuses on the regulatory pathways associated with the drug development and approval process, often using historic decisions of regulatory agencies as a lens for potential future decisions," he said. According to Buehler, RI contributes to every biopharmaceutical company's bottom line by helping the RA teams provide the highest quality submissions to agencies. If the FDA or EMEA (European Medicines Agency) delays approval of a regulatory submission because of a flaw in the application, the long-term sales of the new compound could be significantly affected, particularly if the company aims to be first-to-market in a specific drug class.

"Global regulatory drug development is more complex than ever before," because of the globalization of the life sciences industry, Buehler noted. "Today's regulatory professionals must understand not only the regulatory guidances for each geographical market in the world, but also the hot button issues that affect the review of new drug applications in these regions. That's because those issues also may influence the FDA's evaluation of the compounds," he said.

RI AND THE REGULATORS

Today's RI professionals also must shape the global regulatory landscape. "By proactively participating in the drafting of legislation and guidance documents and providing input to questions regulatory agencies have in formulating their perspectives we are ultimately helping the regulatory agencies have the information they need to review and approve medicines," he said. By submitting comments about the FDA's draft proposals, the company's RI staff can influence whether the proposed regulation or guidance will be adopted entirely, in part, or at all.

In assessing a regulatory agency's guidance documents and other statements, Buehler said that RI officials "often have to read between the lines," because the agency's expectations and requirements are not always clear. For example, the FDA has issued three draft guidance documents on biosimilar product development, in response to the 2010 Patient Protection and Affordable Care Act that amended the Public Health Service Act to create an abbreviated approval pathway for biosimilar products. Despite these guidance documents, the FDA is being "coy," Buehler said. "The FDA has stated that the process for approving certain follow-on protein products is likely to be complex. There are a number of factors that will influence development and eventual approval, and the FDA would like to comment on them in the early stages. For this reason, the agency is advising manufacturers to meet with the agency to present their

product and clinical development plans."

THE VAST ROLES OF RI

If a company plans to submit an application to the FDA for marketing approval of a biosimilar, the RI staff members' job would be to provide the agency with detailed information about the safety and efficacy of the biosimilar products that have been on the market in Europe. "The FDA loves data," Buehler noted. The EMEA, which has given marketing approval for biosimilar products since 2006, is now the largest biosimilar market worldwide.

Biopharmaceutical companies also love data, particularly when considering in-licensing a new compound, a merger and acquisition, or a strategic alliance and partnership with another company. "RI is often employed as part of a due diligence team in looking at existing and/or emerging products that a company may want to partner on or acquire," he said. "The RI team will review the potential asset to help formulate a regulatory benefit/risk that is factored into the comprehensive due diligence efforts."

> "Global regulatory drug development is more complex than ever before."
>
> Gary Buehler, VP of global regulatory intelligence and policy, Teva Pharmaceuticals

RI is typically separate from but collaborative with the competitive intelligence (CI) function at biopharmaceutical companies. "CI focuses more on the financial side of the business, looking at market shares, sales, and pricing," he said. There are points of overlap, for example in claims and promotion, in which RI and CI should work together to provide a comprehensive picture to guide the company.

To guide the regulatory decisions of the company's leaders, RI staff must develop systematic procedures to review, document, and summarize massive amounts of data. "The leaders of all affected functions at the company should be trained or informed in a timely manner," Buehler said.

Biopharmaceutical companies often turn to specialized external consultants to supplement the work of RI staff. But, even if consultants are hired, RI leaders should continue to keep abreast of regulatory agencies by, for example, attending open-to-the-public FDA sessions. Attending these meetings and paying attention to thought leaders such as Dr. Temple are among the best of the "best practices" to impact the company's bottom line.

Steps To Get Your Life Sciences Company In Shape In 2013

By Cindy Dubin, contributing editor

While Moody's Corp. has stated that a credit downgrade for the U.S. is looming, Moody's Investor Services has actually revised its outlook for the global pharma industry.

According to *Forbes*, the ratings agency believes earnings should rebound next year as the deluge of patent expirations on big sellers finally slows down. Since 2007, Moody's has, in fact, maintained a negative credit rating on the industry but now believes the worst is over.

"The stable outlook reflects our view that the worst of the industry's blockbuster patent expirations has passed," says Moody's Senior VP Michael Levesque. "Although industry earnings will still be affected by very recent patent expirations, earnings for large, branded (drug makers) will … rebound in 2013."

But while the worst may be over, *Forbes* reports that Levesque believes the industry "remains challenged by a difficult regulatory approval environment for new products and by areas of research that are still seeing limited success." A new report from global consulting firm Booz & Co. points out that successful life science leaders (LSLs) will need to take action in several areas in 2013 and beyond. They will need to identify untapped growth opportunities, focus on core capabilities, analyze operating models, collaborate with the payor/provider community, and trim more fat from the bottom line.

FIND THE MISSING "HEADROOM"

The study authors define headroom as the market share you don't have less the market share your company will never get; it represents the missing sales already available to you for any particular product. Knowing your headroom helps determine whether a brand is worth further investment.

"Finding headroom should be done as part of the strategic planning process for any product," says Greg Rotz, partner with Booz & Co. "To do this, every life science leader should ask the following of its brand teams and commercial teams: Where is the headroom for growth with this product? That is a different question than where is the biggest untapped part of the market because it might be that the biggest untapped part of the market may not actually be accessible to you."

The equivalent here is in politics: Some states will always vote Republican, some always Democrat, and there are those swing states that can actually be persuaded to change their behavior. Headroom is all about getting a sharper view of the equivalent of the swing states. Find the patients and physicians that have a propensity to value what you are offering and therefore a propensity to change their behavior in your favor. "Headroom brings a level of sophistication and surgical precision to finding those pockets of growth and opportunity where you have a reasonable chance to change behaviors," says Rotz.

FOCUS ON DISTINCTIVE CAPABILITIES

A capability is the capacity to reliably and consistently deliver a specified outcome through a combination of processes, knowledge, and skills within the organization. Only a few of the capabilities have core strategic value that help differentiate one company from its competitors. As defined in the Booz & Co. report, differentiating capabilities could include personalized medicine, digital patient engagement, or expertise in a particular type of treatment. "Just looking at a few critical capabilities across your product portfolio will make a big difference," says Rick Edmunds, senior partner, Booz & Co.

Some of the biggest names in Big Pharma did just that in 2012, with many pharma executives taking pen-

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"There's a lot that can undermine the operating model, but there is a lot of value in getting an operating model lean, efficient, and effective, especially during these challenging times in life sciences." Greg Rotz, partner with Booz & Co.

cil to paper to slash costs unrelated to core capabilities. For some, the price cutting was public, like Pfizer, which publically announced it would slash 30% of its research budget as part of a plan to focus on only the most promising areas, like cancer and Alzheimer's disease. For others, it was more a quiet battening down of the hatches that involved less visible reductions in budgets and headcount. "Many execs feel like they've been at this cost cutting for a long period of time in an industry that's historically been a growth industry. And now many are asking, 'What's next?' and 'How can I regenerate growth?' while still maintaining cost fitness," says Edmunds.

The answer is that it requires identifying the capabilities that are most critical to the company's growth. "Reduce investment in the less critical capabilities so that you can fully fund building the muscles that will drive your differentiation," says Rotz.

WHAT YOU CAN GLEAN FROM LAST YEAR'S DRUG APPROVALS

U.S. drug approvals in 2012 reached a 15-year high with regulators giving the thumbs up to 39 new drugs. Of the 39, 11 were for cancer treatments and almost 20 were designated orphan drug status.

"The sheer number validates the shift of pharmaceutical companies over the last number of years focusing on more oncology drugs and developing drugs that meet unmet medical needs," says Rick Edmunds, a senior partner at Booz & Co. "The increase is suggestive of the future growth potential of the industry."

Edmunds adds that these are the efforts of an industry that has spent the last 5 to 10 years pruning its portfolios to focus on unmet medical needs, areas that are attractive to payers, providers, and the FDA. This shows, he says, that receiving FDA approval is less than half the battle of bringing a drug to market. It is also about how the market — opinion leaders, physicians, payers, and institutional providers — perceive the value of the drug. "While we think the increase of approvals is great, LSLs should not be naïve to think that it's a panacea," says Edmunds.

Greg Rotz, a partner with Booz & Co., adds that, "While the number of approvals has been going up over the last few years, the thing that keeps life science leaders awake at night is the number of drug launches that have missed their expectations; their uptake and adoption in the market is much less than any of us would like to see."

So, while we may have more success moving through the regulatory hurdle, the point is that the commercial hurdle is vexing because studies suggest that between 2/3 and 3/4 of launches going back to 2009 to 2010 are underperforming expectations. "LSLs should be encouraged by the uptick in approvals from the FDA and learn lessons of past launch disappointments to make sure that these 39 molecules that we'll take to market this year are actually outperforming expectations as opposed to contributing to the disappointing skeletons along the road," says Rotz.

HOLD UP A MIRROR TO THE OPERATING MODEL

To stay focused on the key capabilities discussed above, Rotz and Edmunds say it is critical to have the right organizational design (e.g. how the company organizes and runs itself, how it structures itself, how many layers of decision making there are, how quickly decisions get made, how the company compensates and incentivizes to get things done on a daily basis). And once decisions are made, is there follow through, and are people held accountable?

"Holding up a mirror to your model means taking a critical look at how you make decisions and run a life sciences organization," says Rotz. "There's a lot that can undermine the operating model, but there is a lot of value in getting an operating model lean, efficient, and effective, especially during these challenging times in life sciences."

One of those challenges, as Edmunds points out, is that large pharma companies with large product portfolios across the globe can face difficult decisions regarding how they spread out the dollars they invest and the capital in which they invest. "As a senior management team, these multitude of trade-offs can be very hard to make, whereas operating where the senior team stays primarily focused on the critical capabilities to drive success across the portfolio/markets enables a more streamlined concentration of management focus and true investment (versus just operating expense) prioritization," says Edmunds.

PARTNER WITH PAYORS

In the past, pharmaceutical manufacturers would negotiate with a payor to determine how much discount or rebate would be given for a particular drug based on that plan's membership. "We want and need to move from that transactional and contractual type of interaction with the large payors and hospital systems to a more collaborative dialogue about where the unmet need is in a certain population of patients," Rotz says. "That would be quite a fundamental shift on both the payor and pharma sides of the equation because that's not historically how they've done business."

These partnership migrations are evidenced with the one-year research partnership between Humana and Novo Nordisk,

whereby they will work together to explore diabetes treatment and care. A similar move was made by Geisinger Health System and Merck, which recently embarked on a multi-year collaboration designed to improve patient health outcomes by focusing on solutions that facilitate shared decision making between patients and physicians and improve adherence to treatment plans and clinical care processes. Teams from Geisinger and Merck will work together to improve patient adherence, increase the role of patients in making decisions to help manage their conditions, share information among extended care teams, and improve clinical care processes. The first tool being developed is an interactive web application designed to help primary care clinicians assess and engage patients at risk for cardiometabolic syndrome — the risk factors that put an individual at risk of developing Type 2 diabetes and cardiovascular disease.

"It has been slow, but that equation is changing considerably with payors and providers opening to collaboration, but the process is being initiated by the pharmaceutical companies, and smart industry executives understand which payors and providers are willing to engage in this different model," says Edmunds. "When we see the partnership work, it's because both sides are jointly developing solutions rather than a pharma company developing a solution and trying to push it or the payor/provider asking for something and shopping around to see what pharma company can satisfy its request. This collaborative model takes investment and the mindset from both sides to build successfully."

Successfully fulfilling the resolution to get in shape this year will leave many LSLs struggling with the realization that they have to change how they operate and not be afraid to risk moving too far away from current business models.

One-On-One With The Industry's Players At JPMHC

By Wayne Koberstein, contributing editor

On the train from the airport to downtown San Francisco, the people were friendly and helpful. But a harder reality awaited me when I departed my station; a young street woman offered to carry my briefcase by grabbing it off my roller bag, only letting go when I finally said "Stop!"

Soon I was making my way on foot up familiar Powell Street, dodging a roughly equal number of surly businessmen and street types as I climbed the steep sidewalk toward my hotel. The experience proved to be a small precursor to my following four-day marathon — the JP Morgan Healthcare Conference (JPMHC).

Our Chief Editor Rob Wright and I worked together at this year's event, attending sessions, meeting on- and off-site with company CEOs and others, and bumping shoulders with the crush of people climbing up and down the St. Francis hotel staircases and surrounding San Francisco hills. As Rob observed in his blog (14 January 2013, "Why J.P. Morgan Healthcare Conference Remains Relevant"), JPMHC is the hub of countless interactions for investors and business developers, with Big Pharma companies and C-Level execs serving up the main action. A concentric circle of smaller-company players also attracts packed crowds because folks generally know that if you have finally made it into the elite squadron of presenters, you must have something going on.

The third circle, bigger by far than the first two, consists mainly of start-up enterprises that can't wait for presenter status; they must act now to raise money, find partners, and otherwise spread their message in meetings off site. JPMHC is invitation only, two-person max per company, plus some media and analysts. Normally, it takes years as a JPM client to wangle an invitation, easily leaving most of those who flock to the scene on the outside looking in.

Despite the mass movement of participants here, the investment game is — as one VC leader remarked — a personal, one-to-one business. Individuals confer across tables, randomly in sessions, and throughout the hallways. Professional relationships begin, develop, and sometimes end in personal interactions that occur at the event but, often, also extend far beyond it.

Befitting the event's personal basis, I offer my observations in the first person, as one witness among many, following an ambitious schedule but in no way covering every significant moment. JPMHC forces choices; its five tracks and breakout format ensure no single observer sees it all. If you plan carefully, however, you will survey a large sample of Big Pharma announcements, mid- to small-company pronouncements, and start-up proclamations that may presage momentous developments.

Large companies mainly use the platform for updates on their finances and pipelines, but offer little content unavailable through public sources. In fact, at least two companies saved their biggest news for after the event: Novartis replaced its Chairman/CEO and AstraZeneca moved in a new head of R&D a week later. Breakout sessions reveal some interesting details but nothing earth-shaking in most cases.

SEE THE COMPANIES, ALL IN A ROW

The following are brief accounts describing examples of my company meetings and attended presentations at JPMHC, with some thoughts about the companies' potential contributions, likely hurdles to overcome, and state of progress toward their elected goals. Most often, the information exchanged offers important implications for the life sciences industry and its people.

Alkermes

Much of Alkermes' pipeline is aimed at indications that accompany CNS conditions or their treatments. One candidate is an oral antipsychotic without the usual side effects of weight gain oft-linked to diabetes. Alkermes has both commercial and development portfolios, along with Big Pharma partnerships. It doubled annual revenue in fiscal 2012 to almost $400 million and expects to nearly double it again this year, so it can

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afford to finance its own R&D and believes it will launch at least one blockbuster drug: a long-acting antipsychotic (with J&J), treatments for alcoholism and MS, or a monthly Diabetes 2 drug. For all the start-ups with big dreams, this company offers plenty of inspiration.

Rib-X

We visited off-site with this nonpresenting company, one of the few players in ribosomal drugs. Rib-X uses rational drug design (remember that?) based on crystallography, computation, and other new tools to construct small-molecule antibiotics that target bacterial ribosomes and thereby impede drug resistance. Just to be a player in antibiotics these days is to belong in an elite group, following major retreats from the field by the likes of Roche and Lilly. That any new antibiotic must employ a novel drug mechanism is a given, but less obvious is how long it will take for the bacteria to adapt. We will be following the progress of Rib-X and will return to it as it reaches future milestones.

Bayer Healthcare

A major division of the now diverse and global corporation, presenting company Bayer Healthcare had a good year financially with 4% overall growth and 6% in EBITA, led by its pharma business. Single-digit growth was once nothing to crow about, but nowadays, growth is growth. It is intriguing that Bayer's top-selling product is Betaseron, an early biotech product that goes back to Schering AG and mighty little Triton Biosciences of the Bay Area in the 1980s. Primary care is a shrinking business in the West, however; Bayer is moving its PC headquarters from Berlin to Beijing because China bucks the trend. It is also ending further contraception and Betaseron research, expecting sales declines. The future apparently belongs to the now-booming cardiology and oncology areas, with remaining areas following along opportunistically. Watch Bayer in OTCs, where emerging markets are now one-third of its business vs. one-fourth in the U.S.

Metabolon

Another nonpresenting company, Metabolon, met with us to describe how its end product — metabolic biomarkers for drug discovery and manufacturing — demands a deep understanding of therapeutic areas where biomarkers play a growing role, such as obesity, diabetes, and cancer. The company serves a base of 500 customers, including most top pharmas and biopharmas, all aiming at new treatments. It uses multivariate analysis and biochemistry, not genomic tools, to identify biomarkers and evaluate biochemical for potential therapeutic safety and efficacy.

Lilly

Expiration of top-product Zyprexa in 2009 has dominated Lilly's strategy, as well as external comment, since well before then. The goal was to replace the lost multibillion-dollar revenue mainly by maximizing existing-product sales, increasing productivity, maintaining the stock dividend, and funding pipeline development, according to Chairman John Lechleiter. The first steps began in 2004: reducing the workforce, expanding in emerging markets, and replenishing the pipeline. 2008 brought a large acquisition of ImClone, restructuring into five business areas, and creation of Lilly's Center of Excellence research arm. A major collaboration with Genzyme came in 2010. The pipeline now has 13 products in Phase 3 and 20 in Phase 2. Lechleiter argues that existing products have now achieved double-digit growth, workforce is down 16%, and the company will meet or exceed financial goals in 2014. Such performance may yet vindicate Lilly's spending "at an appropriate level" for R&D, though higher than its peer companies with deflating research budgets.

AstraZeneca

Not that I was prescient at this presentation — AstraZeneca replaced its head of discovery a few days later — but I did sense an uneasiness in the CFO's discussion of the company's pipeline as he spoke about the "opportunity to replenish" the Phase 3 stage of its platform from the ample stable of candidates in Phase 2. He also emphasized the company's "sustainable base" of off-patent products such the "resilient" Zoladex and Synagis/Flumist. AZ places much hope for new products in its Medimmune division and in an aggressive partnership program seeking "scale and reach" in R&D (40% of its pipeline is partnered, and at least eight of its partners are Big Pharmas). But a lot appears to be on the line with its decision to realign its discovery organization.

LEAVING FOR THE FUTURE

Numerous companies and individuals deserve mention here, though most will have to wait for another day. Meetings and presentations produced fuel for much future editorial coverage. Among all the stories I heard, however, I noticed a few general trends:

- Cancer remained the dominant area of development this year, but targeted therapies seemed to give some ground to immunotherapeutic approaches in the proportion of total company programs presented.
- More companies, big and small, mentioned manufacturing as a key strategic concern and the target of efficiency and optimization initiatives.
- Companies seemed to widen the practice of branding clinical trials, not only with acronyms but with word-play collages and colorful logos. Why?

By the end of the meeting, I had composed the following tweet to sum up this year's event but decided to save it for this report — "JPMHC: A 4-day nonstop steep-hill trek for body and mind." Most people who braved it would likely agree, but I bet they would also say it was well worth the journey.

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Biotechnology In The U.K.: Growing And Changing

Suzanne Elvidge, contributing editor

The U.K. has a long and deep-rooted heritage in life sciences and medicine, and a history of breakthroughs from Alexander Fleming's discovery of penicillin to Watson and Crick's elucidation of DNA. Today the U.K.'s biotech sector is still growing despite the current economic climate. As an example, in 2012 the turnover of the U.K. medical biotech sector increased 5% to almost £4 billion ($6 billion), as Steve Bates, CEO of the BioIndustry Association (the U.K. biotech industry's trade association), explained.

"The U.K. has an established pharma industry with a long history, which includes large and small companies, and a CRO sector that is growing in response to increased outsourcing and risk sharing in the pharmaceutical industry," says Mark Treherne, CEO, Life Science Investment Organization (LSIO), a U.K. Trade and Industry (UKTI) initiative to promote investment in the U.K. life sciences industry.

GROWING FROM STRENGTH TO STRENGTH

Biotech and medical research in the U.K. has a global reputation. In a recent report in the British Medical Journal (BMJ), the U.K. is second only to the United States as a source of new drug development, generating more than 10% of all new therapeutics worldwide.

"The U.K. has a number of key strengths — it has a strong and supported ecosystem, well-established strengths in science, a good clinical community, and entrepreneurial people. We are well-connected globally," says Bates.

A number of subsectors are performing well in the U.K. life sciences; for example, the specialty pharma companies and the medtech sector. Also on the up is the relatively new field of cell therapy.

"Specialty pharma companies are often small and low-profile, but they are growing and building sustainable value through development and marketing. The U.K. also has a growing medtech sector, particularly in combination therapies and companion diagnostics, together with pharma services," says Steven Powell, CEO, Virttu Biologics, a clinical stage U.K. biotech company pioneering the development of viruses to treat cancer.

One of the strategically important, though still relatively young, subsectors in the U.K. is that of stem cell science, including cell therapy and regenerative medicine, explains Michael Hunt, CEO, ReNeuron, a clinical-stage stem cell company. "The U.K. has always been one of the forerunners in cell therapy, but now more emphasis is being put on translation, moving projects into the clinic and beyond. However, regenerative medicine lacks a credible investor base in the U.K. — it's novel, which can scare investors off."

The Cell Therapy Catapult, a London-based technology center, has been created to help very early-stage companies in this field. Its aim is to provide access to finance and expertise, and help to move products into clinical trials. Programs like this will help to build confidence and reduce risk in new areas.

DRIVEN FROM ABOVE: NATIONAL SUPPORT FOR U.K. BIOTECH

The U.K. government is behind biotech, and in December 2011, it launched the Strategy for U.K. Life Sciences, which made a commitment to improving the translation of scientific invention and innovation into products and services. The government's commitments include tax relief programs to support both large and small companies, such as the "Patent Box" (see "Innovation In The U.K. Biopharma Industry," *Life Science Leader* March 2010), and R&D tax credits.

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Proposed by the U.K. Chancellor in March 2009, the Patent Box cuts corporate tax on income from patents originating in the U.K. for both U.K. and non-U.K. companies. It comes into effect in April of 2013. Companies carrying out research in the U.K. also qualify for R&D tax credits at a rate of 130% of qualifying expenses for large companies and 200% of qualifying expenses for small companies. This "superdeduction" effectively reduces companies' taxable profits.

From April 2013, large companies will have the option to claim "above-the-line" R&D tax credits instead, which are applied to the company's profit–and-loss account rather than its taxable income.

Support from the U.K. government also includes funding streams. The Medical Research Council and the Technology Strategy Board (the U.K.'s innovations agency) run the £180 million Biomedical Catalyst, which provides funding for life sciences' small and medium enterprises (SMEs) in the U.K., supporting opportunities with both scientific and commercial potential. This support has the potential to bridge the funding gap for early-stage research, as well as encourage academia and industry to work together. The National Health Service's (NHS) National Institute for Health Research provides research awards for collaborations between U.K. healthcare academics, clinicians, and industry that focus on developing patient-focused innovative medical technologies.

In the U.K. there are government-backed regional funds. Scottish Enterprise provides grants for projects up to early-stage clinical trials; Invest Northern Ireland backs bench-to-bedside research; and the Life Sciences Investment Fund supports the Welsh life sciences sector.

The headquarters of Powell's company, Virttu, are in Glasgow, Scotland, and it has historically received support from regional funding. As Powell explains, "There is a significant level of regional support for Scottish companies, helping with growth, development, and infrastructure."

"The Biomedical Catalyst, changes to R&D tax credits, and the Patent Box have been well received and are leveraging additional private financing, helping biotech companies grow faster," says Bates.

THE CHANGING FINANCIAL CLIMATE: FINDING FURTHER FUNDING

Like all economies around the world, the U.K.'s has been hit by the financial downturn. The dearth of traditional VC funding for early-stage companies has led to a need for alternative forms of funding, in addition to that provided by the U.K. Government.

"The U.K. biotech sector has moved on since the boom of the early 1990s. We now have a better understanding of risks and opportunities. The nature of funding and collaborations has also changed, with less traditional funders becoming more important," says Bates.

Alternative sources of venture capital include Big Pharma companies, universities, and charitable trusts. For example, SR One, GlaxoSmithKline's independent corporate healthcare venture capital fund, has invested over $680 million in biotech since 1985. Rock Spring Ventures EU's backers include Glasgow, Edinburgh, and Aberdeen universities, and it focuses on supporting early-stage life science and technology companies. Syncona Partners, which launched in January 2013 and is wholly owned by the Wellcome Trust, has been created to help both early- and late-stage companies. Its first deal was for seed funding for Cambridge EpiGenetix, an early-stage epigenetics spin-out from Cambridge University.

> "Because funding became tighter earlier in the U.K. than in the United States, we have had to think smarter. As a result, we are leaner and less reliant on traditional funding than some of the other biotech regions."
>
> Steve Bates, CEO, BioIndustry Association

Early-stage companies are also increasingly being supported by private investor syndicates and corporate investors, rather than by venture capital companies with life sciences experience. This has broadened the scope for available funding, but means that it is increasingly important to demonstrate the value of the sector in terms of both business potential and impact on society.

The BIA is calling for the introduction of Citizen's Innovation Funds, a form of crowdfunding (see "Crowdfunding In Life Sciences: A New Route To Finance," *Life Science Leader* December 2012) that allows private individuals to invest small amounts in biotech research and innovation. This mode of funding has been very successful in France, where the Fonds Communs de Placements dans l'Innovation (FCPI) has raised more than €6.5 billion since 1997, supporting over 1,000 companies.

Financing remains a challenge for many in the U.K. biotech sector, according to Powell, who says that it's not always clear why

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some are getting access to money and others are not. However, clouds can have silver linings, and these challenges may prove to be beneficial to the industry, as Bates explains: "Because funding became tighter earlier in the U.K. than in the United States, we have had to think smarter. As a result, we are leaner and less reliant on traditional funding than some of the other biotech regions. I believe that this shows the business model is now adapting to the science and the economic climate."

POTENTIAL FOR GROWTH

Although the U.K. biotech industry is moving forward, there is still room for further growth. "We are good at creating small biotech companies. However, these then tend to license out their technologies or go to a merger or trade sale before the full value of the pipeline is realized, and the money goes elsewhere," says Hunt. "Holding onto the assets for longer would retain more value in the U.K., but these companies need more investment, as well as investors that don't look to exit early. I'm not sure whether this is a financial or a cultural issue, or just a result of the size of the economy. It's not wrong; it just doesn't sustain a broader industry."

The U.K. can learn from other biotech regions, according to Treherne: "The U.S. biotech sector is good at building medium-tier companies, which may be because they have investors that are more willing to back high-risk endeavors."

Powell sums up the status of the industry in positive terms but with a word of advice relevant to all life science companies worldwide: "The building blocks are in place for a successful biotech sector, and there are definitely some exciting things happening at the university level across the U.K. The U.K. has also increased its skills base in clinical development with translational medicine being one of the new key themes. However, the financial media still tend to focus on the negative, for example, on drug development companies where there continues to be a high attrition rate in clinical development. We need to promote the success stories and emphasize why the life sciences are important."

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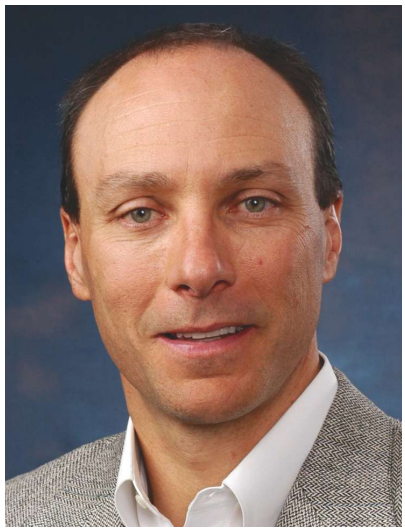
A Successful Externalization Strategy Demands Modernized Informatics

In an effort to cut costs, take advantage of specialized expertise, or conduct key stages of drug development closer to emerging markets, pharma companies are increasingly outsourcing more activities to an extensive array of contractors. This complexity opens the door to errors, rework, product delays, and compliance issues.

As externalization impacts more tasks across the drug development value chain, will the benefits gained continue to outweigh the risks? Maximizing the opportunities presented by the practice while also maintaining high levels of product innovation, quality, and safety is closely linked to smart management of a project's most valuable commodity: its data. This demands a modern, flexible, and holistic approach to the capture, control, and sharing of information that drives innovation. Here are three objectives that should be on your company's data management short list:

1. Integrated informatics. Bringing a new drug to market is a complex undertaking, more so when several contract partners and collaborators are involved. It's important that the flow of information across the entire "scientific innovation life cycle" (from lead discovery and early-stage research at the front end, all the way through safety testing, QA/QC, and production scale-up) be well-coordinated, efficient, and also closely linked with the systems and stakeholders responsible for later stage manufacturing and distribution. The problem is that, all too often, the data technologies and process management procedures used by various stakeholders (from business execs, to CRO and CMO partners, to individual scientists, engineers, lab technicians, and other experts) are disjointed and disconnected — separated by system, organizational, disciplinary, and geographic boundaries. This reality leads to information visibility "gaps" that can cause product development delays, invite errors, and impede collaboration. To close these gaps, an informatics approach that prioritizes the integration of data and processes across the end-to-end scientific innovation life cycle (and beyond) is critical. It is no longer acceptable to allow needed information to remain hidden away in "silos."

2. Consistent data capture. In an environment where a single incorrectly reported balance measure can result in a compliance violation or production shutdown, the adage "garbage in/garbage out" is apt. Companies must ensure that all project data is captured in a consistent, transparent, and traceable manner, regardless of whether it was generated by an in-house scientist, a CRO chemist, or a processing engineer working for a manufacturing partner. Weeding out paper-based and manual data entry practices is an essential first step. When possible, data should be captured automatically and electronically, direct from the lab instruments and other equipment used to conduct research. Maintaining standards for naming and tracking intellectual property is also important. This means registering and assigning unique identifiers to every molecule, chemical ingredient, formulation, cell line, and so on, so that information relevant to project progress, regulatory compliance, patent filing, and more can be found quickly and easily, wherever it is located.



Matt Hahn, Ph.D.

Dr. Matt Hahn is senior VP and CTO at Accelrys, a provider of scientific innovation life cycle management software for the life sciences, energy, chemicals, aerospace, and consumer products industries.

3. Simple, affordable, and secure collaboration. There are considerations that take on added importance when informatics technologies are extended beyond the corporate firewall. These include cost, ease of use, and security, as well as the interests of specific in-house stakeholders. An open collaborative solution championed by end users and IT groups (because of the productivity improvements or cost savings that could be gained) may not be OK with the legal department, if it is believed that the integrity of competitive corporate data may be compromised. On the other hand, a tightly controlled approach (such as deploying redundant information systems at outsourcers' physical sites) may be too costly, cumbersome, and inefficient. When it comes to collaborative technologies, flexibility is key. This is where cloud-based solutions offer a compelling opportunity: Organizations can create hosted data-exchange portals in the cloud that are easy to access via a Web browser from multiple locations. They must be simple and affordable to scale as new partners come online and are flexible enough to set up varying degrees of data access. The attractive part of this approach is that organizations can keep their sensitive data secure on-premise, while using the cloud to collaborate.

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New Approaches To Improve Vaccine Manufacturing

Vaccines have the potential to transform health outcomes on a global scale. Because of this promise, the World Health Organization and biopharmaceutical manufacturers are predicting major growth in the global demand for vaccines over the next decade. Meeting this rising demand for vaccines while simultaneously ensuring a safe and reliable supply of affordable product, produced in an environmentally responsible manner, presents the industry with a number of challenges. Indeed, many manufacturers are beginning to look closely at their production processes, and, as a consequence, we are observing an industry shift away from traditional manufacturing techniques and increased adoption of newer technologies for culture and purification, which can bring significant benefits.

According to Kalorama Information Market Intelligence (*Vaccine Production*, February 2012), the global vaccine market was approaching U.S. $30 billion in 2012 and is forecast to reach U.S. $35 billion by 2015. While the five top vaccine manufacturers account for more than 80% of global market share, the landscape is changing rapidly. China, with a quarter of the world's population, is the world's largest vaccine manufacturer by dose and the fourth largest vaccine market in the world.

WHY CHROMATOGRAPHY IS ESSENTIAL TO VACCINE MANUFACTURING

Historically, the vaccine industry has tended not to see chromatography, which is widely used in the production of recombinant protein drugs, as playing a key role in vaccine manufacturing. This is partially due to the success of vaccines using whole cells, acellular fraction, or whole virus and partially due to concerns that antigenicity of purified components might be lost. However, scientific studies have indicated that purified vaccine components are not only effective, but can also be safer with fewer side effects. For example, the pertussis vaccine, which was originally produced using whole cell technology, was initially only reluctantly accepted in spite of its efficacy because of rare but intense adverse reactions caused by toxic components remaining from production. Because of these adverse reactions, the acceptance rate of pertussis vaccine greatly decreased in the early 1970s, leading to many vaccine manufacturers making great efforts to modernize their production methods to include purification and produce a safer vaccine.

Furthermore, many vaccine manufacturing processes involve organic solvent extraction, salt precipitation, and high-speed centrifugation. In addition to the potential negative environmental impact, such processes can result in low efficiency and low consistency in the quality of vaccines. For example, conventional preparation of polysaccharide vaccines for Meningococcus and Pneumococcus uses ethanol precipitation and phenol extraction. The introduction of membrane and chromatography separation technologies can eliminate these steps, resulting in a more efficient and environmentally favorable manufacturing process, as well as higher quality vaccine. This new approach also removed the need for high-speed centrifugation, which is both expensive and inefficient at removing unwanted toxins.

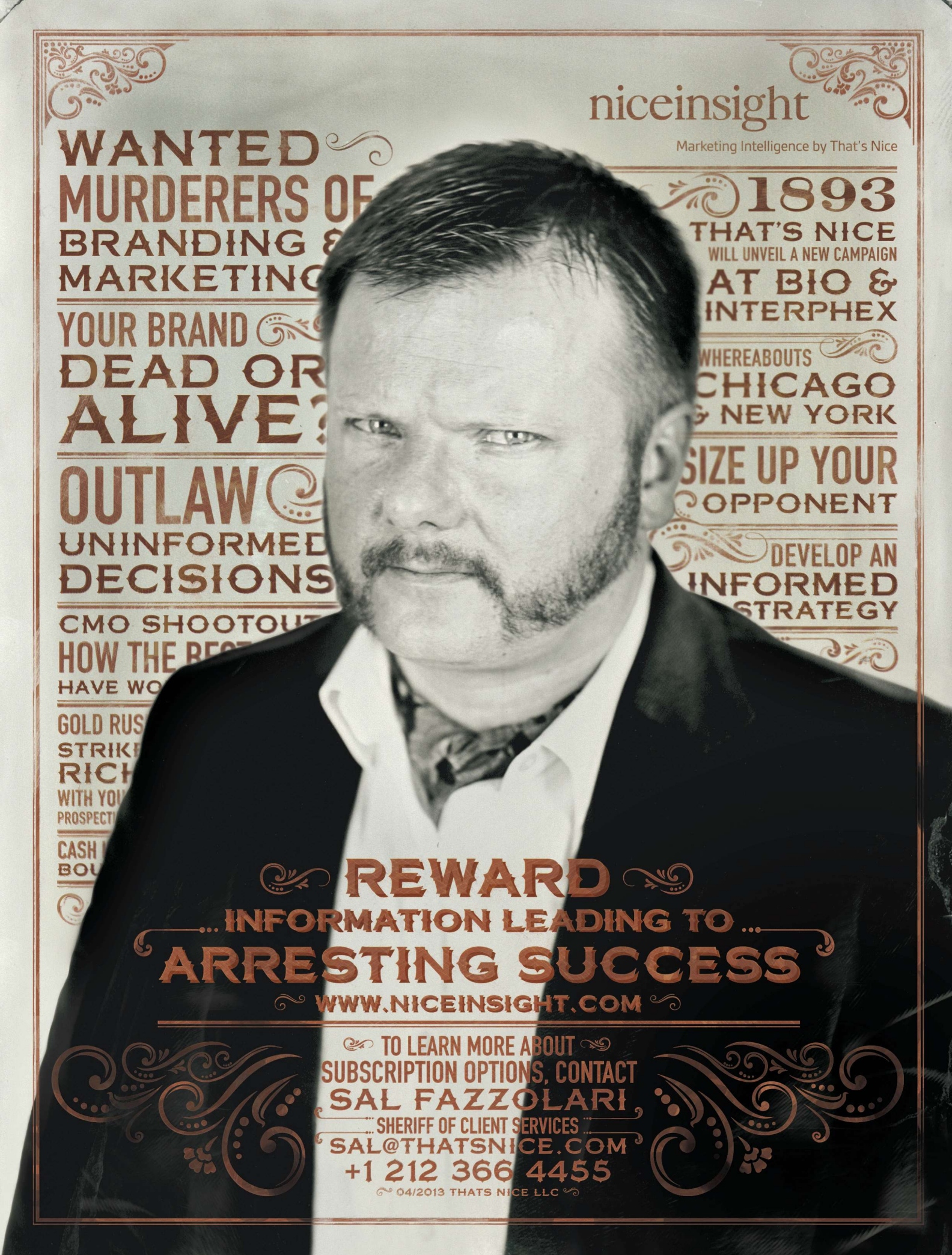
IMPROVED YIELD, SHORTENED PRODUCTION TIMES

Another major challenge for many countries globally is that domestic vaccine production cannot meet demand. In China, this is true for many vaccines, including several in the national mandatory immunization program. The annual shortfall for pertussis vaccine, for example, is estimated at 46 million doses. Enhancing the efficiency of the traditional biomanufacturing processes offers the potential to contribute to overcoming this shortage. By switching to purification of acellular components with chromatography, the need for salt precipitation and high-speed centrifugation steps is eliminated, resulting in improved yield and purity, with the added benefit of shortened production times.

New manufacturing technologies and approaches are giving the Chinese vaccine industry the opportunity to improve the efficiency of their manufacturing processes. Such improvements will help China meet vaccine demand, with the added benefit of greater manufacturing efficiency and lower environmental impact. More importantly, the benefits observed in China are likely to be applicable in any country where vaccine manufacturers are still taking a more traditional approach.

Olivier Loeillot

Loeillot is general manager of enterprise solutions at GE Healthcare Life Sciences. He has more than 15 years of experience in the global life sciences and pharmaceutical industry. He joined GE Healthcare in 2010 from Lonza where he held a series of senior leadership roles in general management, business development, and sales.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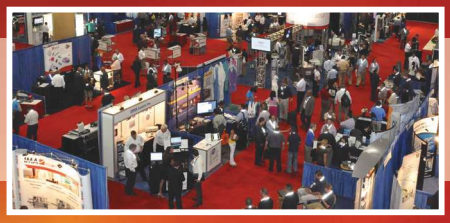

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Yes, But Do They Trust You?

Chris Hitch, Ph.D.

As a leader in today's global, around-the-clock business world, you must align people, processes, and projects to help achieve your organization's goals and objectives. Yet, simply announcing the financial and operational targets is insufficient. Do you find yourself asking one or more of these questions?

- How can I gain greater commitment from my team members?
- How can I create a culture of innovation and trust?
- How can I align my teams to increase bottom-line results?

Earning your team's trust is one critical factor to aligning your team and driving for results. One of my colleagues, Dr. Roger Mayer, at North Carolina State University has focused his research on growing trust within organizations. He's found the following three key trust factors that can increase your organizational velocity and improve bottom-line results.

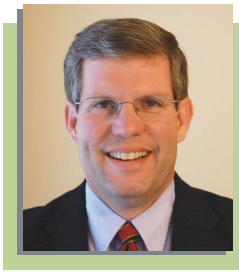
Ability: Ability focuses on one's critical job-related skills. As you start your career, these are your technical skills (degrees, patents, articles, or industry certifications). The higher you go in the organization, however, you must develop other skills as well. If you focus solely upon growing and maintaining your technical skills as you lead others, you will derail. You must shift from purely technical to a blend of technical and interpersonal abilities.

Benevolence: Benevolence relies upon empathy and selflessness. Empathy is intensely personal. Empathy focuses upon the relationship between you and the other person. If your interaction with another person is short-term and fragmented, you don't get the chance to know and learn about the other person, as well as their interests, needs, and desires. This focus upon empathy illustrates one of the challenges of virtual and far-flung teams. It is difficult to begin to grow a relationship through email. In many cases, phone calls, video chats, and face-to-face meetings provide a richer environment to grow the relationships.

Selflessness focuses upon one's intentions and motives. We all have a mental checklist running in the background when we work with other people. For instance, we ask ourselves, "What are this person's motives? Are they in it for their personal glory and advancement, or are they focused upon me and my needs and desires?" When you have worked with your team over time, they have evidence upon which to determine whether you are selfless or selfish.

Integrity: Integrity focuses upon dependability and consistency with values and principles that others find important. Dependability is neither exciting nor glamorous. It's easy to shuffle off something you said you were going to do to a later time. Yet, others are expecting you to deliver what you have committed to deliver. You grow your "dependability index" by repeatedly and successfully completing these three-point landings.

By recognizing these factors before you start with a new team, you can focus upon these areas to help grow trust, increase the velocity of decision making, execute your plan, and increase bottom-line results.



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