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Refusing to Play It Safe at Merck Serono

President & CEO Belén Garijo takes a risk-sharing approach to developing people **p. 24**

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Are You Embracing The New Innovation Ecosystem?

ROB WRIGHT Chief Editor

At this year's BIO CEO and Investor Conference in New York, I had the opportunity to meet Annalisa Jenkins, EVP and head of global R&D, Merck Serono. Jenkins has been busy working on a game-changing, single-source CRO collaboration model with Quintiles. Understanding how and why she did it first requires insight into the leadership approach of her risk-enabling CEO, Belén Garijo (see page 24), followed by Jenkins' detailed explanation of creating the model, along with some pretty good advice on building game-changing collaborations (see page 30). Finalizing this collaboration model won't make her schedule any less busy; in fact, it just got busier.

On the day of our meeting, the Healthcare Businesswomen's Association (HBA) publicized Jenkins as a 2014 Woman Of The Year (WOTY). Just two weeks later, TransCelerate BioPharma announced Jenkins as the new chairwoman of its board of directors. When you combine her positions with TransCelerate and HBA along with her advisory roles with the Center for Talent Innovation (CTI) and PhRMA, you get a sense for her willingness to engage outside her own company. This is a pivotal first step toward embracing one of our industry's major trends — the new innovation ecosystem, which is where Jenkins anticipates the next wave of life sciences industry R&D innovations will come from. She is not alone in her opinion.

Her vision of this new ecosystem is similar to what EY (Ernst & Young) Global Life Science referred to as "Pharma 3.0" back in 2010. It is described as collaborating in radically different ways with very dissimilar partners. For example, consider how pharma companies could collaborate with Google to incorporate Google Glass into QA/QC monitoring of a manufacturing process. Or, how about a pharma company partnering with Verizon — which already has an FDA-approved remote monitoring software platform — for a clinical trial? Essentially, engaging this new innovation ecosystem requires going well beyond the traditional partnerships the industry is accustomed to.

Perhaps an example will help.

In 2012, Coca-Cola established a partnership with DEKA R&D to bring DEKA's "Slingshot" water purification system to communities where potable water access is limited. This is a real game-changer when you consider the Slingshot's distribution is not money motivated and the potential impact for the nearly 1.8 million children who die annually from diseases caused by unclean water and poor sanitation.

Since the initial announcement, the collaboration has expanded to include IBM, Inter-American Development Bank, McCann Health, NRG Energy, Qualcomm Technologies, and UPS. Its mission has expanded as well, now including the planned delivery of EKOCENTER — a kiosk designed to improve the well-being of communities — to 20 countries by the end of 2015. The collaboration intends to place between 1,500 and 2,000 EKOCENTERs, offering a locally tailored mix of products, services, and resources to jump-start entrepreneurship opportunities and community development, along with the Slingshot water purification system.

The original collaboration simply was designed to provide pure water, yet it has evolved to providing opportunities. I wonder what new innovation ecosystem opportunities Annalisa Jenkins might discover through her external engagements. If you want to embrace the new innovation ecosystem, start interacting outside of your company's ecosystem. Networking opportunities can evolve into trusting relationships — the foundation for establishing any successful collaboration or partnership.

Life Science Leader

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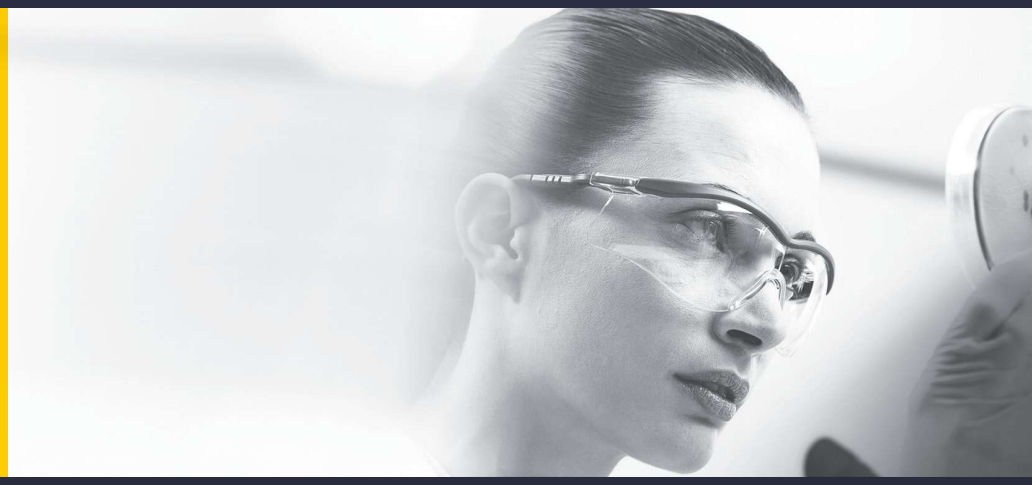

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Q In large pharma companies, which organization typically makes decisions about brand protection investments?

A THERE ARE MANY ORGANIZATIONS THAT HAVE PRIMARY BRAND PROTECTION (BP) RESPONSIBILITY or share it cross-functionally. The BP discipline is still new and maturing. Originating out of the legal/corporate security ranks, where incidents were addressed tactically, BP professionals tend to now focus on preventive measures. Supply chain leaders are logical decision makers of BP programs. The supply chain functions have the best perspective from which to evaluate supply risks, and BP solutions are often included in the cost-of-goods-sold. Brand managers should be accountable as well, especially investing in BP during the pre-launch phases of drug development, but ongoing brand management is usually decentralized regionally. Ideally, brand protection should reside as a separate, enterprisewide function.

RON GUIDO
Ron Guido is the president of Lifecare Services, LLC, a management consulting firm specializing in healthcare marketing, brand protection, and strategic planning.

Q What is a common mentoring mistake and how can it be avoided?

A A COMMENTORING MISTAKE IS WHEN THE MENTOR BECOMES MORE DIRECTIVE RATHER THAN FACILITATING IN THE MENTEE'S DEVELOPMENT. A mentor's impact can be accomplished by listening carefully to the situation the mentee is facing and then sharing relevant life experiences, providing anecdotes, and simply asking a lot of questions.

For mentees, a common mistake is to not follow through, e.g., be a no-show for meetings, not complete actions, or not get back to the mentor with information. A mentor values a mentee's follow-through because it demonstrates dedication and desire to succeed. This means learning something from your mentor, trying it out as soon as possible, and reporting back to your mentor about what happened, what worked, what you still need to learn, etc.

LAURIE COOKE
Laurie Cooke, BS, RPh, PGDip, CAE, is the CEO of the Healthcare Businesswomen's Association (HBA).

Q What advice do you have for executives seeking to incorporate single-use manufacturing technologies into their operations?

A FOCUS ON YOUR OPERATION'S VALUE DRIVERS. Beyond cost, other drivers such as flexibility and risk should also be considered. For firms that have sufficient scale to dedicate capacity to single products, more traditional approaches may be more appropriate. Where flexibility is of greater importance, a risk/benefit analysis may lead a firm to pursue single-use.

The technologies are usually positioned as significantly more economical, but this may not be the case. For instance, there are limitations of scale that should be considered when demand forecasts have significant upside. Capital investment is often less, but operating cost savings may be partially offset by the cost of the consumables. Similarly, cleaning validation savings are reduced by some additional leachables and extractables costs. So, the number of products and the attendant multiproduct risks will drive the risk/benefit outcomes.

WILLIAM F. CIAMBRONE
Bill Ciambrone is currently the executive VP of global technical operations at Shire, where he led a $470M capital expansion that included a $200M manufacturing facility centered around single-use cell culture technology.

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Partisanship Scuttles Bipartisan Reform of SGR

JOHN McMANUS The McManus Group

March 15 — Something extraordinary has occurred in Washington: The three healthcare committees of jurisdiction quietly collaborated on a bipartisan basis to develop a replacement for the dysfunctional "Sustainable Growth Rate" (SGR) payment formula that dictates Medicare payments to physicians. Unfortunately, it was not to last. This substantial bipartisan achievement was soon scuttled and overtaken by the partisan bickering over the healthcare issue that has consumed the country for the past five years: implementation of Obamacare.

The SGR has vexed policymakers for more than a decade. Enacted as part of the Balanced Budget Act of 1997, the SGR requires payment cuts to physicians and other practitioners when cumulative Medicare spending on those providers exceeds GDP per capita growth. The formula worked for a few years in the late 1990s when a growing economy fueled by the dot-com bubble allowed for modest pay increases that approximated physician practice cost increases.

But that bubble burst, and the more typical trajectories of healthcare costs outpacing the economy resumed. As a result, the SGR called for payment cuts. Congress allowed a 5 percent cut to occur in 2002 but has legislatively intervened more than a dozen times since then to override scheduled payment cuts. The "SGR fix" has become an annual ritual in Washington, creating a legislative vehicle that policymakers have often used to cut other providers or tack on other unrelated health items.

Congress funded the initial SGR fixes by steepening physician payment cuts in the "out years," kicking the can to a future Congress. We are living in those out years now. Result: Physicians across America now confront a 23 percent cut for the care they provide Medicare beneficiaries. Cuts of that magnitude would have a cataclysmic impact on healthcare and make patient access for Medicare beneficiaries more akin to Medicaid.

Just as troubling, these constantly looming cuts have restrained physician practice investments in new technology and spurred thousands of physicians to exit independent practice entirely by becoming employees of hospitals. How can any business operate with a threat of possibly losing nearly a quarter of its revenue from its major customer base if Congress fails to enact a law?

LOWER SCORE = OPPORTUNITY FOR REFORM

Congress and the physician community caught a break last year when the Congressional Budget Office (CBO) finally acknowledged that six years of steadily declining physician volume growth per capita constituted a trend (see chart on page 12). Policy makers were shocked when the CBO cut the cost of repealing SGR by 60 percent — dropping it from about $300 billion over 10 years to $117 billion.

That reduced score spurred Congressional action to develop a program that would replace the SGR, as policymakers did not want to simply write doctors a blank check or create a new formula that would come back to bite them a few years later as SGR had.

The Energy and Commerce Committee was first out of the box in July of 2013 with a bill developed by the bipartisan staff with substantial input by Rep. Burgess (R-TX) and the House Physician Caucus. The Senate Finance Committee and House Ways and Means Committee worked in bipartisan, bicameral collaboration throughout the autumn to develop legislation that not only repealed and replaced SGR but also consolidated the disparate incentive programs on quality reporting, electronic health records, and value-based modifiers that were enacted over the past decade. Those bills were voted out of committee on a bipartisan basis in December.

After six more weeks of negotiation and hard work, the three committees introduced bicameral, bipartisan consensus legislation that would repeal and replace SGR. The bill encourages physician practices to strive to deliver higher quality and become more conscious of the resources physicians prescribe in all sectors of healthcare by eventually putting 9 percent of their payments at risk. Physicians will be judged on metrics that specialties develop based on how they compare to their peers. The bill encourages value over volume by enabling practices to develop alternative payment models that could include capitation and bundled payments.

OFFSETS: STILL FUNDAMENTAL IMPEDIMENT

Of course, the fundamental impediment to enactment — how to finance the bill — had been mitigated by the lower CBO score but remained fundamentally unsolved. Interest groups assailed Congress, making the case that they should not be a focus of the savings. AARP threatened retribution on any member that voted for Medicare reforms that result in higher beneficiary costs. The American Hospital Association, nursing homes, pharmaceutical companies, and other sectors initiated all-out lobbying campaigns to convince Congress that they had paid enough for the Affordable Care Act and could not absorb additional cuts.

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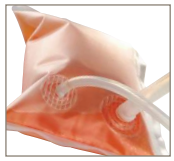

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SciLog

"The Republican leadership had selected the most controversial provision in Obamacare."

The House leadership's clever way to finance the bill dissolved the bipartisan comity: Repeal Obamacare's individual mandate to purchase health insurance. The CBO estimated this would save hundreds of billions of dollars because fewer individuals would be coerced into buying highly subsidized coverage. Republicans argued that the Obama administration had waived scores of provisions of Obamacare that helped businesses, insurance companies, hospitals, and others. Why not delay the provision most onerous to the individual — the mandate to purchase coverage?

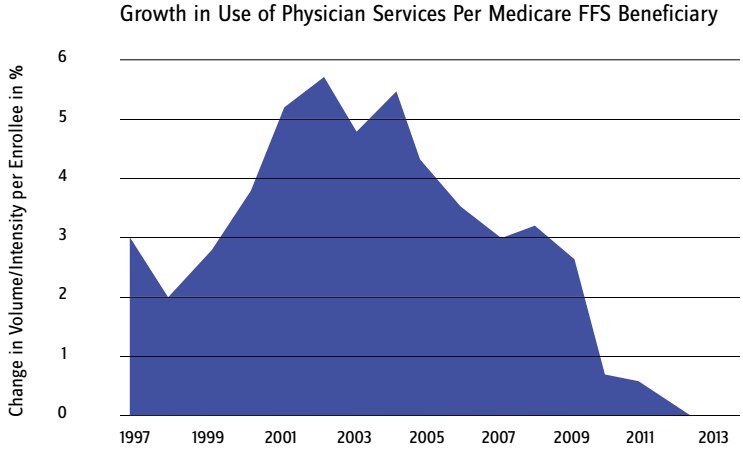
The Republican leadership had selected the most controversial provision in Obamacare. It was the basis for the Supreme Court review of the law and the administration viewed it as critical to a functioning healthcare marketplace, arguing that it would deter adverse selection. But the Republicans felt that the administration would waive this provision in essence anyway by making so many hardship exceptions that it would be a mandate in name only. Why not capture the savings and solve the SGR at the same time? The bill passed with a dozen Democrats joining a unified Republican conference.

The Senate quickly announced that it would call up the SGR reform legislation with no offset whatsoever — the one approach the House could not accept. Newly installed Finance Chairman Wyden introduced new legislation without notifying his Republican counterpart and partisan acrimony deepened. A temporary patch now looks likely, and the sword of Damocles will continue to hang over physicians' heads. Congressional paralysis continues ...

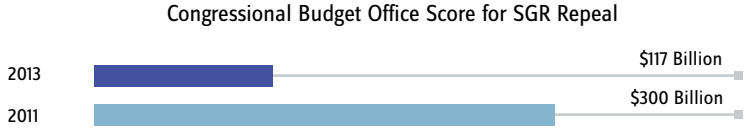
UPDATE ON PART D RULE

In February's issue, I reported on the controversial proposed rule CMS (Center of Medicare and Medicaid Services) issued that would have gutted patient access protections in Medicare Part D. The agency encountered withering push back from 371 organizations representing millions of patients, seniors, and multiple healthcare stakeholders, as well as bipartisan opposition from the finance committee. But it took the scheduling of a vote in the House of Representatives to strike the regulation that forced CMS to summarily withdraw the proposal the morning of the vote. An important victory for a program that is working!

Physician Utilization of Services Plummets



Dramatically Reduced Cost to Repeal the SGR



Source: The McManus Group

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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SYNTHETIC BIOLOGICS

Following a failed drug, a company retrenches and reinvents itself as a developer of new biologics with novel mechanisms focused on serious infections and other diseases.

WAYNE KOBERSTEIN Executive Editor

SNAPSHOT

A company reborn — that is Synthetic Biologics. Starting with a specialty-pharma model, failing a key Phase 3 trial, hitting the skids, and repurposing itself under new management as a novel biologics company focused primarily on infection, Synthetic Biologics has built a new pipeline with at least one potential blockbuster. Its oral enzyme for preventing *C. difficile* infection could be used along with every IV antibiotic. Its preclinical mAb (monoclonal antibodies) designed to clear pertussis toxin could treat a large population of infected newborns. The *C. diff* drug is approaching Phase 2 this year, and another in MS is in Phase 2.

WHAT'S AT STAKE

The value of a company — and how failure and rebirth affect it — is the theme that drew me to Synthetic Biologics. This company's corporate lineage of more than a decade is still intact; it never actually went out of business, but it did take an unexpected turn or two. The company was born as Pipex Therapeutics in 2001 to develop Coprexa (tetrathiomolybdate) for Wilson's disease, a rare brain disorder. Pipex went public through a reverse merger in 2006, but in 2008 the FDA rejected Coprexa's Phase 3 trial, and the company quickly fell to nano-cap, penny-stock status. Renamed as Adeona, the company continued to languish at a valuation too low to power much progress in the clinic with its special formulations of existing drugs. Finally, in 2012, a new management team replaced the old, quickly reshaping the company and reselling it to investors to raise its value.

"We came in and ended up doing a deal with R.J. Kirk, who is CEO of Intrexon Corp. and one of the most prolific entrepreneur investors in the biotech industry," says current CEO Jeffrey Riley. "The deal jump-started the company and enabled us to raise capital." He says "repurposing" the company required choosing a new product focus and building a pipeline to pursue it. The new team selected the anti-infectives space, with a mission to develop novel biologics to treat or prevent serious problems in antibiotic therapy. SB's lead product is meant to avoid the typical complications that arise when broad-spectrum antibiotics attack the microbiome in the colon as collateral damage and allow the notorious *C. diff* bacteria to flourish there.

"We chose something that was counter-cyclical; the big guys were no longer playing in the antibiotic space, and there's a great need from both a humanity perspective and an economic perspective," Riley says. Forming a collaboration with Intrexon to work on early-stage infectious disease candidates, the new team also searched for and acquired other pathogen-specific pipeline products and retained a legacy drug it is developing for MS whose short-term prospects outweighed its strategic fit.

Although the repurposing and new investment have pulled the company out of the nano-cap depths, going from a $15 million to a $156 million market cap in the past two years, Riley believes it will remain significantly undervalued until it achieves visible results.

"If we were private and we did an IPO today, we would be about a $350 million market cap, because we would have the visibility, and people would value us accordingly. Companies with recent IPOs are probably more accurately valued than a company like ours that has started over from zero. But if I were an investor, I would go with a company like ours because there's a built-in positive upside — our experience and skills in addition to the real assets we've built."

Riley says the company will avoid further discovery-stage partnerships if possible, except perhaps for a single drug or indication, he says. Valuation will rise, he asserts, only when good clinical data begins to arrive, as hoped for later this year. L

JEFFREY RILEY
CEO

Vital Statistics

14
Employees (9 full-time)

Headquarters
Rockville, MD

Finances

$25M
Gross raised since 2012 refocusing

Current ownership:
RJ Kirk affiliates (21%), e.g., Intrexon and Third Security; MSDC Management (5%); Belmont Global Advisors (2%)

Research Partnership Funding

National Multiple Sclerosis Society (NMSS) and NIH grants exceeding
$8M
support Phase 2 MS trial of Trimesta

Other Partners

Intrexon

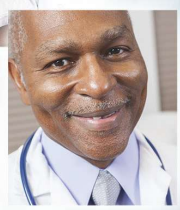
Cedars-Sinai Medical Center (Mark Pimentel, M.D.)

University of Texas at Austin (Jennifer A. Maynard, Ph.D.)

UCLA (Rhonda Voskuhl, M.D.)

Clinical Research

Health Care Providers



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New Technologies In Fill-Finish May Bring Brand Loyalty Along With Improved Patient Safety

In January 2014, Senator Charles Schumer (D-NY) called on drug makers, the FDA, and the Consumer Product Safety Commission to help reduce the number of emergency room visits among children who are accidentally given the wrong dosage. He argues that implementing flow-restricting devices on liquid formulations could prevent approximately 10,000 emergency room visits each year and would cost only a matter of cents per bottle.

KATE HAMMEKE
Director of Marketing Intelligence
Nice Insight

"Offering new technologies that are consumer-friendly and ensure accurate dosing is a way for both brands (sponsor and CMO) to gain customer loyalty."

While Schumer is pushing for the legislature to mandate further measures to protect children, kids are not the only population that would benefit from improved delivery methods aimed at precise doses. A recent survey among biopharmaceutical companies that engage CMO services showed that 73 percent of these businesses offer formulations for special needs patients, 53 percent offer pediatric formulations, and 50 percent offer geriatric formulations. Each of these populations is at risk for inaccurate dosing, and while a flow restrictor is a prospective means to reduce medicating inaccuracies, there are better technologies becoming available.

Packaging medications in a unit-dose format has been popular in Europe and Japan for some time, and has been widely embraced in the U.S. in the food and beverage market — just think of the little packets of flavoring one can add to bottled water or the tubes of yogurt to take on the go. These convenient little packages are known as stick-packs and may be filled with powders or liquids. Not only are they premeasured to ensure accurate quantities — providing an advantage over the flow restrictor — the format reduces the likelihood of spilling the spoonful of medication while trying to gain a child's compliance. Further, the packaging is travel-friendly, and stick-packs can accommodate a wider variety of medications than liquids that would benefit from a flow restrictor, including powders and drugs that require sterile processing.

CONSUMER-FOCUSED PRODUCT DEVELOPMENT

As pharmaceutical companies, especially those with OTC products, become more consumer focused — 44 percent of respondents to the same survey stated their company is very consumer focused, meaning they actively seek out information on the buyers of their products and use that information to shape product development — finding delivery and packaging methods that appeal directly to buyers helps to ensure brand loyalty. In fact, nearly two-thirds of respondents (62 percent) stated it is important for a CMO to provide proprietary technology to offer marketing differentiation. At present, there is some disconnect between showing strong consumer interest and understanding what strongly appeals to consumers. This presented itself in the research when interest levels in products specifically designed to be consumer-friendly lagged behind traditional pharmaceutical formats among

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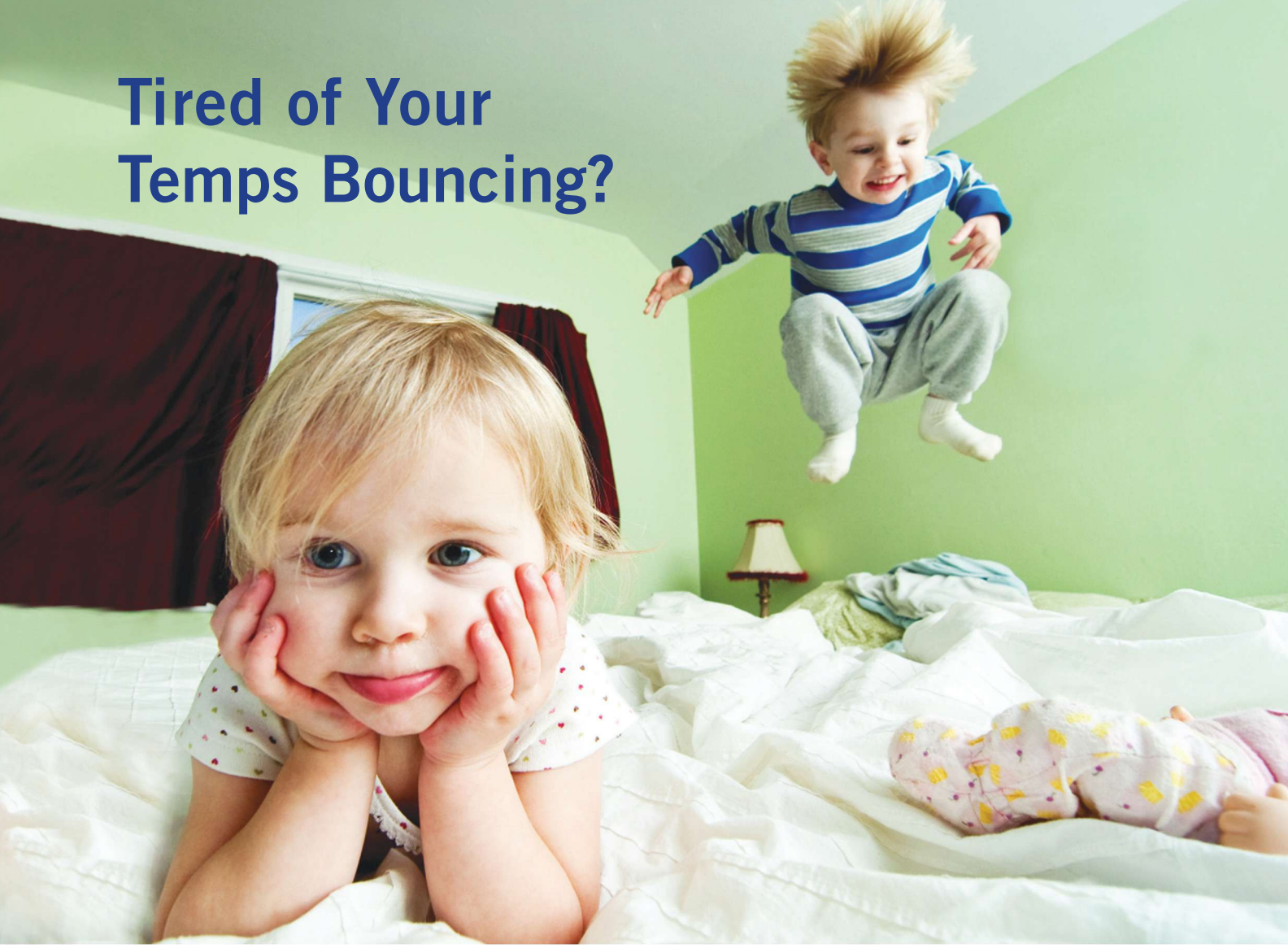

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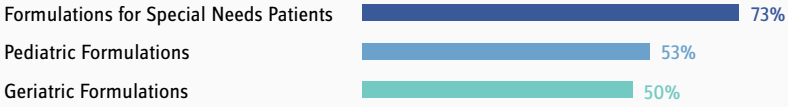
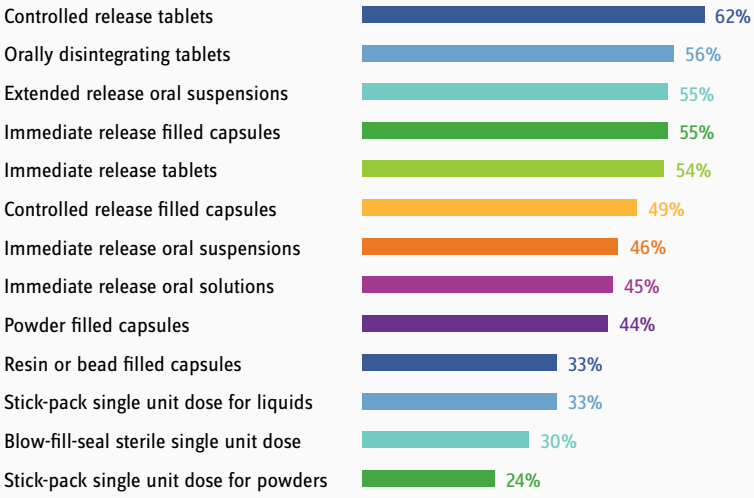
Does the company you work for offer any of the following specialized formulations?



Please select the answer below that best fits your company's level of consumer focus with regards to its drug development efforts.

44%	Very consumer focused / Our company actively seeks information on the buyers of our products and it heavily influences our product development
39%	Somewhat consumer focused / Our company knows a fair amount about the buyers of our products and that information has some influence on our product development
14%	Neither consumer focused nor nonconsumer focused / Our company knows some information about the buyers of our products, but it does not influence our product development
3%	Not at all consumer focused / Our company knows very little, if anything, about the buyers of our products

When engaging a CMO for fill-finish, which of the following types of products is your company interested in producing?



Survey Methodology: Nice Insight CMO Strategy surveys are deployed on behalf of Nice Insight clients to a targeted group of outsourcing decision makers. The surveys comprise of ~40 questions geared toward understanding current outsourcing practices, present and future expectations from outsourcing partners, and which traits contribute to successful partnerships. [n=200]

the 42 percent who will outsource fill-finish projects in the coming year.

When it comes to the product types of interest, there is a demand for advanced functionality, such as controlled or extended release, but survey respondents agreed their company's product focus still leans toward tablets and capsules. This isn't too surprising considering stick-pack technology is relatively new to the U.S. market, especially when it comes to prescription drugs. However, as outsourcing models evolve toward partnerships where biopharmaceutical companies expect CMOs to add value beyond reducing fixed costs, offering new technologies that are consumer-friendly and ensure accurate dosing is a way for both brands (sponsor and CMO) to gain customer loyalty. Specialized delivery technology can cement biopharmaceutical customers into long-term relationships with their contract manufacturer, and user-friendly packaging that facilitates accurate dosing strongly appeals to consumers. These methods will aid in capturing market share as well as building brand loyalty among consumers.

The good news is that drug makers in North America will soon have wider access to manufacturers of medications in stick-pack format, which will in turn increase availability to consumers. An established European leader in unit-dose manufacturing, Unither, has plans to open the first liquid stick-pack line in the U.S. this summer, which will join Ropack and PNP Pharmaceuticals (part of NSF), both based out of Canada, to further serve the market. L

N. WALKER

S.FAZZOLARI

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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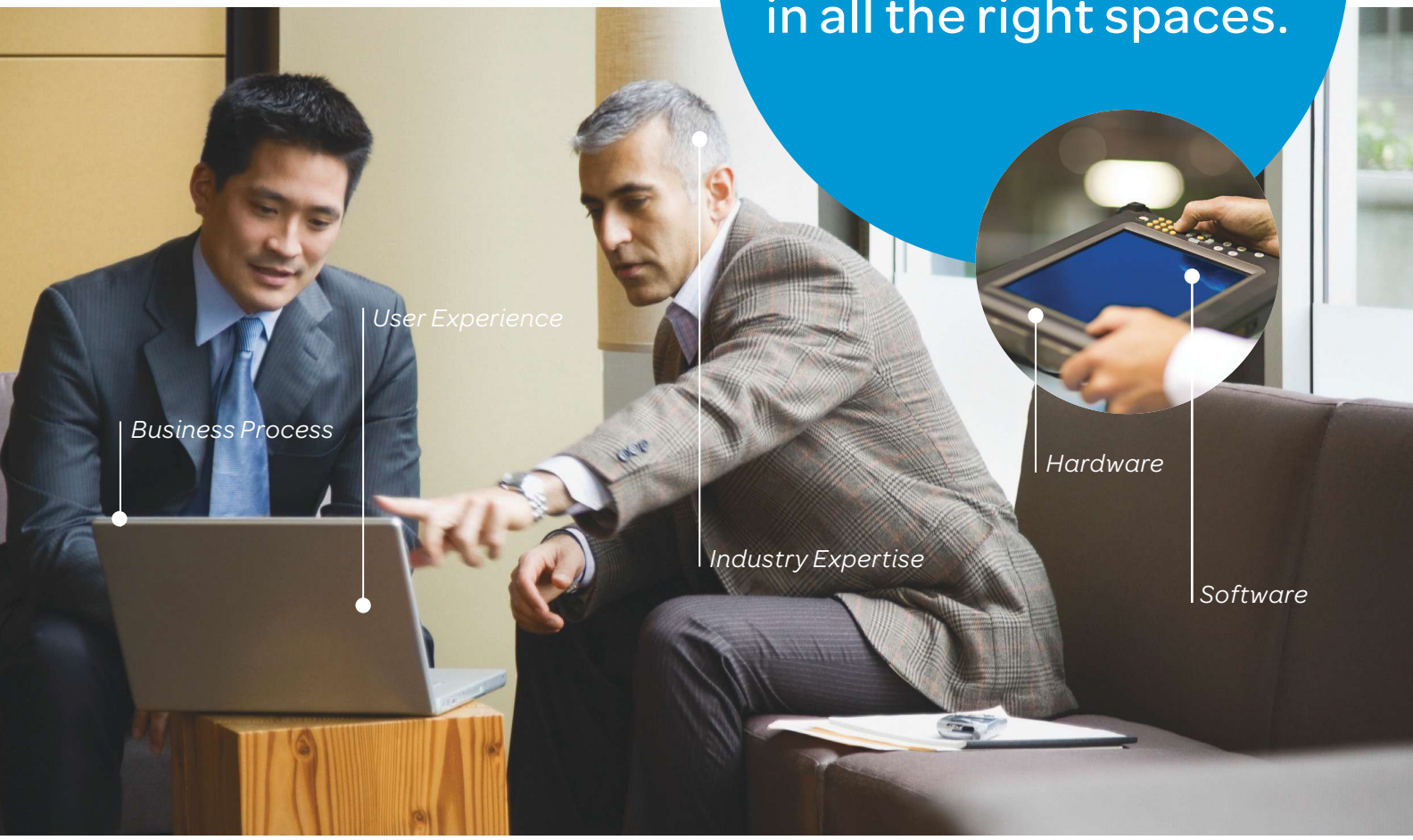

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Best Practices In Quality Management: Industry's Approach To Quality Initiatives

ERIC LANGER
President and Managing Partner
BioPlan Associates, Inc.

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

"Many firms have already implemented a range of initiatives, from QbD to process modeling."

Quality management is an increasingly important focus for biopharmaceutical manufacturers looking to avoid production problems and failures. And it's increasingly becoming a multifaceted, industrywide concern as regulators take a closer look. With this in mind, it's useful to see how the industry is approaching quality management in terms of the initiatives being pursued.

BEST PRACTICES IN COMBATING BATCH FAILURE

Preliminary results from our latest industry survey (11th Annual Report and Survey of Biopharmaceutical Manufacturers) indicate that for roughly four in 10 respondents the most recent batch failure occurred during the previous six months. That includes more than one in 10 saying it occurred within the prior month. On average, overall batch failures occurred once every 59.7 weeks. This compares to one failure every 53.3 weeks in 2013 and one every 51.1 weeks in 2009. So improvements are clearly being made at extending the industry's average time between batch failures.

To tackle batch failures, companies are taking steps such as:

- improving their process design and reducing process steps
- using improved, more robust, equipment
- adopting training programs for implementing single-use equipment
- resolving supply chain issues
- using process monitoring and process analytical technology (PAT)
- gaining experience in preventing contamination
- adopting newer cell lines and genetic engineering technologies.

FUTURE INITIATIVES

We also sought to quantify some of these efforts by presenting respondents with a list of 12 quality initiatives, asking them to identify 1) which they are currently implementing and 2) which they are planning to implement within the next 12 months. Our preliminary results indicate that among the 12 relevant quality initiatives the industry is primarily focused on:

- risk management/analysis (64.5 percent currently implementing)
- risk analysis/failure mode effects analysis (FMEA) (65.8 percent)
- platform manufacturing processes (64.4 percent)

These are similar to the rates we found in last year's study for what's currently being implemented. That plateauing may suggest these initiatives are now broadly implemented, and fewer facilities are in the planning stages of implementation, compared with last year's survey.

So far this year, we are also seeing an uptick in implementation of initiatives such as design space/DOE (design of experiment) (58.9 percent, from 52.1 percent in 2013) and QbD (quality by design) (52.1 percent, from 43.7 percent in 2013). However, most of the other initiatives we measured have remained relatively steady compared to last year.

As more facilities actually implement these initiatives, of course, fewer will

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be in the planning stages. And it seems likely that some who were planning to implement various initiatives last year are now following through. For example, in our latest survey, when we identified companies in the earlier planning stages, we found that 12.3 percent said they planned to implement QbD within the next 12 months, down from 19.7 percent last year. That was one of the larger swings, and for the most part there wasn't a marked increase in planned implementation to go along with the rise in actual adoption. PAT (process analytical technology) did rise somewhat in terms of those entering the planning stage (vs. actual implementation stage) — some 21.9 percent of respondents to this year's survey said they planned to adopt it in the next 12 months, up a few points from last year's 18.3 percent.

The data indicates that many firms have already implemented a range of initiatives, from QbD to process modeling. Those companies that have yet to implement will likely do so in the coming years. The data regarding quality initiatives being implemented in the next year shows that 10 of the 12 different types of quality-related analytical programs we identified are each expected to be implemented by around 10 to 25 percent of respondents, so one or more of these specific initiatives are likely to be implemented by the majority of facilities.

Much of the motivation influencing companies to implement these programs involves keeping up (or catching up) with regulatory expectations and industry best practices. More developers are now filing applications developed using these quantitative quality-related programs, and the inclusion of this data in regulatory filings is ultimately going to be expected by regulators.

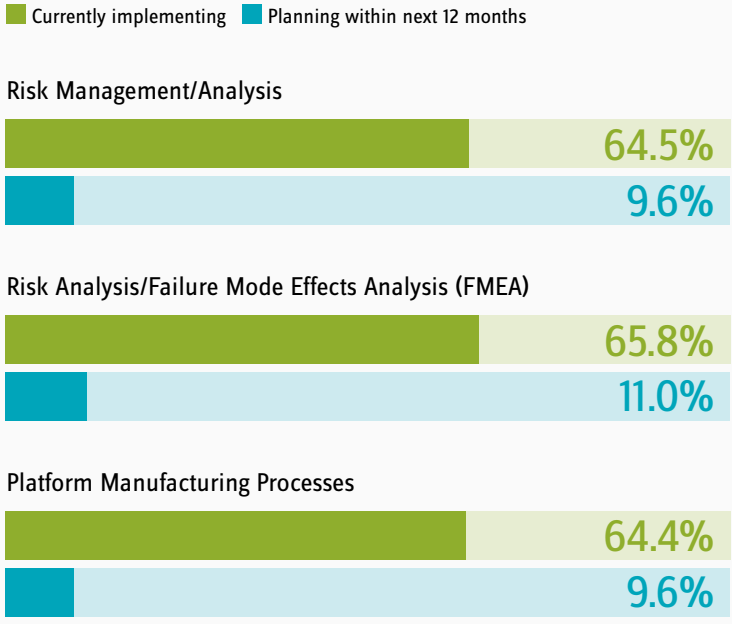
The industry can expect other benefits from adopting these quality initiatives. These include manufacturing higher-quality products through better designed and optimized bioprocessing, likely along with considerable savings as problems are avoided and processes are further optimized for increased efficiency. The use of quantitative bioprocessing data management and processing for the purpose of more fully understanding and improving products is now an established part of the biopharmaceutical industry — and is expected by regulators.

It's likely that cost-saving programs such as PAT and QbD will be adopted by the majority of developers and manufacturers in coming years. Between current and planned adoption of the various initiatives we listed, the majority could see adoption rates of at least 60 percent by the end of this year, if respondents follow through with their expectations (admittedly, a big "if").

One challenge that must be addressed is integrating quality initiatives such as QbD into existing working quality and manufacturing systems. And ultimately, the success of initiatives such as PAT and QbD in biopharmaceuticals will depend on better sensors and analytical software. Computing power is now adequate. Better analytical data and analyses can allow biomanufacturers to make a strong business case for wider adoption of these tools to maximize yields, obtain purer product, and minimize quality defects. L

FIGURE 1

Quality Initiatives Currently Being Implemented or are Planned for Implementation Within the Next 12 Months



Source: 11th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production, BioPlan Associates, Inc.

Survey Methodology: The BioPlan annual survey of biopharmaceutical manufacturers yields a composite view and trend analysis from more than 300 responsible individuals at biopharmaceutical manufacturers and CMOs in 29 countries. The survey included more than 150 direct suppliers of materials, services, and equipment to this industry. This year's study covers such issues as new product needs, facility budget changes, current capacity, future capacity constraints, expansions, use of disposables, budgets in disposables, trends in downstream purification, quality management and control, hiring issues, and employment. The quantitative trend analysis provides details and comparisons of production by biotherapeutic developers and CMOs. It also evaluates trends over time and assesses differences in the world's major markets in the U.S. and Europe.

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MERCK SERONO'S PRESIDENT & CEO BELÉN GARIJO – ENABLING RISK AND REFUSING TO PLAY IT SAFE | By R. Wright

Merck Serono's president & CEO Belén Garijo

ENABLING RISK & REFUSING TO PLAY IT SAFE

ROB WRIGHT Chief Editor

Sitting on the second-level balcony of the grand ballroom in the historic New York Waldorf-Astoria, my vantage point provides a bird's-eye view of the floor below. Today, the room serves as a central meeting place for attendees of the sixteenth BIO CEO and Investor Conference. I wonder aloud to my table guest, Belén Garijo, M.D., as to the uniqueness of being interviewed in this venue. Garijo, president and CEO of Merck Serono, the biopharmaceutical division of Merck KGaA, leans forward and peers over the railing — taking a moment to survey her surroundings. Laughing, she replies, "It's a theater, right?" in English adorned with a Spanish accent. Gesturing expansively with her hands, she says, "Why do you think this — unique?" revealing a witty side to a personality I would soon discover to be as dynamic as the company she leads. Leaning back in her chair, she smiles, declaring, "It's fantastic! Probably the most beautiful place I have ever been interviewed."

A 25+ year industry veteran, Dr. Garijo joined Merck Serono as its COO in 2011. Just two years later she was named president and CEO — an unprecedented move by the $6 billion entity. Despite having more than 15,000 employees and operating in 66 countries, no woman had ever held this high a position of leadership within Merck Serono or even Merck KGaA — the world's oldest pharmaceutical and chemical company. I asked Garijo to describe how it felt being named CEO. "I feel the responsibility on my shoulders," she states. "My challenge is to build a team under the new leadership. Make sure they understand the expectations and how we are going to work together." What about being the first woman CEO at Merck Serono? "I never felt I was developing in any role because I am a woman," she replies. "I don't believe in that. I don't practice that. I prioritize talent versus any other force that may come from politically led initiatives, and expect to be treated the same way." Her answer is bold. Yet it aligns with the company's recent penchant for embracing new ways of thinking and making game-changing decisions (e.g., announcing plans to build a new pharmaceutical plant, its second-largest, in Nantong Economical Technological Development Area of Greater Shanghai). Garijo's approach to changing Merck Serono starts with developing people, enabling risk, leading by example, and most interestingly — refusing to play it safe.

A RISK-SHARING APPROACH TO DEVELOPING PEOPLE

When asked what best prepared her for taking on the position of CEO, Garijo shares a variety of experiences, such as relocating to different areas of the globe or taking responsibility for different therapeutic areas. "At one point I made a firm, irrevocable decision that I wanted to get commercial experience," she reveals. "But I had no track record. Someone had to give me the chance to show that I could be successful." In 2002, Garijo was given the chance, or should I say, earned the opportunity, and was appointed Spain's general manager at Aventis Pharma. However, it is neither the commercial exposure nor the diversity of other experiences to which she attributes being prepared as a leader. Rather, it was the experiences of leaders being willing to take risks on her throughout her career. "There are a number of leaders who are able to trust you more than you trust yourself," she explains. "When you are given the confidence and realize some leaders are ready to take risks to develop you and help you succeed, you learn this is something you must do if you want the organization to succeed." This realization resulted in a new philosophy for her as a leader, and it has served as a guide throughout her career. She says if you want to become a better leader, take a risk-sharing approach to developing people.

Such an approach requires being innovative in how you assess talent profiles. For example, don't get overly enamored of a person's experience or lack thereof. Instead, Garijo advises to assess potential, as experience can be learned. She uses multiple means to determine potential. The first is what she describes as having a real "gut feeling" for assessing people, the result of her physician training. Another way she assesses potential is through performance. This requires three things — a willingness to take risks, a readiness to share risk, and preparedness to actively mentor. Garijo explains it this way, "When I see potential in leaders lacking experience, I try to see how much responsibility and accountability I can put on them. In this way, I become a mentor." According to Garijo, the combination of potential and mentoring is extremely powerful, because it creates shared responsibility and shared risk. "In my most recent experience at Merck Serono, I had a person in mind I wanted to serve as the president of Merck Serono Japan." Garijo is referring to Paris Panayiotopoulos, who at the time did not have any previous Japanese in-country market experience. This fact did not prevent her from seizing the opportunity to implement her risk-sharing approach to developing people. Garijo admits making the move required more than just a willingness to take a risk. It also required trust on the part of company leadership. Panayiotopoulos spent 18 months as the president of Merck Serono Japan. This past November, he was appointed president and managing director of EMD Serono, and will be responsible for driving the strategic direction of the company's commercial organization in the largest pharmaceutical market it the world — the United States. Garijo is energized by successes such as Panayiotopoulos, and believes others are as well. "When the

organization and teams realize how committed you are to giving opportunities for developing people internally, you become much more effective in retaining talent, as well as recruiting people who aspire to really develop and change organizations," she affirms.

Merck Serono's CEO leads by example when it comes to developing people. But she can't do it alone. To make real, lasting, organizational change requires more than championing a philosophy and practicing what you preach. To Garijo, it requires every member of the executive committee being willing to implement a risk-sharing approach of developing people consistently across the organization. "It's about how much of your own risk you are willing to put in the game," she says. How do you get people to be willing to take risks? Garijo says stop playing it safe.

ENABLING RISK REQUIRES NOT PLAYING IT SAFE

As Garijo explains her leadership philosophy, she places herself within examples of what not to do and why. For example, "If I position myself in such a way that, no matter what, I have to be safe, protecting and managing my image in such a way that people believe I never make a mistake, then they [members of her leadership team] will never take a risk. This is not how I operate organizations, and this is not the way I want my executive committee to operate this company." She continues, "It is only through giving opportunities and being prepared to give support, rather than focusing exclusively on yourself, that you succeed in being convincing, succeed in enabling risk, but most importantly, you succeed in making people successful."

> *"My aspiration is to have an organization that is functioning by itself without the leaders having to intervene in each and every decision-making step."*

Garijo's approach to being an enabler of risk starts with active mentoring. This involves more than providing guidance, support, and coaching, but a willingness to recognize your own areas of improvement in front of your employees. For example, Garijo admits one of her developmental opportunities involved communication. "I used to be very aggressive, maybe a bit

abrasive at times." While speaking, she drives her index finger into the table on every other word. The gesture makes an audible "thump" — exemplifying her point. "I saw this in myself. This style doesn't work when you intend to really influence and build a network." Garijo recommends when you see someone struggling with something you yourself struggled to overcome, share your past weaknesses and challenges. "This creates credibility," she affirms. "Which you need to have if you actually want to be listened to."

But don't simply operate with reckless abandon. Garijo advises gaining a deep understanding of the level of risk to the organization, as well as the consequences of failing. "You have to find a way to give responsibility and accountability, not be invasive of their space, yet position yourself to challenge the head of R&D or manufacturing as you would any business unit in your organization," she explains. "To be able to engage in very constructive and active dialogue with diverse business unit leaders, you have to put forth the effort to be educated and have a deep understanding of each business unit, so you can challenge at the required level." The process does not involve coming to Garijo with a project or problem and expecting her to make the decision. When this has happened she is quick to point out, "This is not the way we work. First, I don't have all the answers. Second, you are the experts. You have to take me through this." Garijo's challenging approach involves asking three questions: What are the scenarios? What are the options? What are your recommendations and why? She advises to keep the conversation going until you feel fully satisfied that you understand what is going to happen beyond just a financial perspective. The process of challenging has multiple benefits beyond just staying educated on the various aspects of your business. It helps everyone anticipate the various risks and understand the consequences of failure. "Once you understand the consequences of failing, you become an active participant in setting that person up for success," she explains. In addition, Garijo believes this process translates to people having higher accountability. "My aspiration is to have an organization that is functioning by itself without the leaders having to intervene in each and every decision-making step." Another key to enabling risk — make sure there is alignment between encouraging the risk-taking behavior you want and how employees are assessed.

> *"When I see potential in leaders lacking experience, I try to see how much responsibility and accountability I can put on them. In this way, I become a mentor."*

FEELING RISK-ENABLED LEADS TO CEO SHARING HER PASSION FOR LEADERSHIP

Weeks prior to my meeting with Garijo, I had put together a list of interview questions. However, none of those questions had anything to do with leadership, enabling risk, or developing people; instead, they focused on executing operational excellence in emerging markets. As it turned out, I didn't ask even one of my preplanned questions.

Instead, our conversation evolved out of some unscripted "ice breaker" questions around what it feels like to be the first woman to hold such a high position of leadership in this company. I knew this pinnacle might still be fresh in her memory, and frankly, I was curious. I asked similar questions such as, "What's it feel like becoming a CEO?"

She was plainspoken and candid with her answers, sharing her experiences of first arriving at Merck Serono and implementing the necessary operational initiatives of organizational restructuring, creating strategies, improving financials, and accelerating R&D. Throughout our conversation, though, one underlying theme emerged — people make the difference in how you execute as a leader.

The second part of this story (on page 30) is about one of those people who was fully risk-enabled by Garijo — Annalisa Jenkins, EVP and global head of R&D for Merck Serono. L

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Basem Gerges

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A Game-Changing Approach To CRO Collaboration

ROB WRIGHT Chief Editor

During my face-to-face meeting with Merck Serono's EVP and global head of R&D, Annalisa Jenkins, I was pleasantly surprised at her candor. She shared with me her opinion as to the state of Merck Serono when she joined the company in 2011, which I found to be most interesting: It was an organization that took a decidedly Euro-centric approach to manufacturing, R&D, and business in general. She said that despite the company conducting business in 60+ countries, the owners and leaders of Merck KGaA recognized that for Merck Serono to truly be a global R&D player it needed more access to global talent and R&D innovation. That would require Jenkins to be willing to make some game-changing decisions. But she also needed a CRO willing to help rewrite the rules of collaboration.

REDESIGNING THE SPONSOR/CRO MODEL

In April 2012, Merck Serono announced it was closing the Geneva headquarters of its pharma unit. Jenkins says, "It wasn't a cost thing, because we placed resources elsewhere," citing the company now operating four R&D centers — one in each of the four largest global pharmaceutical markets (i.e., Beijing, Boston, EU's Darmstadt, Tokyo). "It was more about achieving a cultural shift and becoming more of a global, cultural-embracing type of company." Around the same time, Jenkins had what some might describe as an "aha" moment. "We had no new drugs from the pipeline for years, we were closing a major R&D hub where many of the company's studies were being run, and we had a major restructuring and a failing model," she says. In other words, it was the perfect time for new leadership to do something really innovative and interesting.

The company was working with a multitude of suppliers and providers. According to Jenkins, "We had not applied any good managerial business processes and approaches to clinical study, design, and execution." At a previous company, she had experienced going from multiple CROs down to three. But questions always lingered as to if that number should be even smaller. With that experience, as well as the belief that the company's current CRO partnering model was not working, Jenkins decided to change the game. She redesigned the CRO model to be more of a biotech partnership rather than a basic client/service provider relationship. And most surprisingly, she created a model that included only one CRO. But to do so required a different approach and a new set of rules.

CHANGING THE CRO COLLABORATION GAME

Before this plan could be implemented, Jenkins needed buy-in from her team. She started by challenging them to look closely at their assumptions about CROs. "Let's assume the ideal CRO has data, information, and knowledge we do not have. It brings specific skill sets to the table that we don't possess, and it is operating at above traditional benchmarks," she states. "Then why would we feel we couldn't construct a partnership with this CRO with a common vision, purpose, and shared goals?" According to Jenkins, when developing this type of collaboration, you also would want to make sure the CRO has a seat at the decision-making table. After gaining inter-

> "We were building an innovation model, so we also needed to take feedback from the CROs on how they would build this model."

ANNALISA JENKINS
EVP & Global Head of R&D at Merck Serono

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> "Don't try to take a service model and apply it to a partnership model. It won't work."

nal agreement, her next step was to find a CRO willing to participate in such a different type of collaboration.

After speaking with some CEOs of pharma companies and CROs, she was convinced that her idea could be the future model of CRO-sponsor relationships. "Many of them were also looking at their own business models and finding much of their work was becoming extremely commoditized, renting CRAs or just data management," she recalls. In fact, many of the people Jenkins spoke with believe the current service-provider model might not be sustainable for the next 10 to 15 years.

NOT YOUR TYPICAL RFP PROCESS

Her next step was to scope out an RFP, inviting all the big companies to bid for a single-source model that would be end-to-end — starting at protocol concept all the way through to filing and registration. "The CRO would have to set up its own unit to manage our portfolio," Jenkins explains. "There would be very high-level governance from the most senior levels of the CRO, and the financial model would incentivize both parties around the common goal."

The RFP process lasted six months and involved many major outsourcing players. Eventually, two full-day, off-site meetings in Paris were scheduled for the final four potential CROs. According to Jenkins, this was not your typical RFP process. "We wanted it to be collaborative," she says. "We were building an innovation model, so we also needed to take feedback from the CROs on how they would build this model." In fact, during the discussions, the CROs frequently needed to be reminded of being willing to share their opinions. But Jenkins says on the Merck Serono side, they too had to change their thinking regarding how an RFP process was supposed to transpire. They had to forget about the traditional "just tell them what to do" model and the notion that there was a hierarchical order. When creating this type of collaboration, Jenkins advises, first and foremost, to ask questions of your CRO partner to find out what they think — don't just tell them what you know or want.

AND THE STRATEGIC PARTNER IS?

On May 15, 2013, Merck Serono announced it had selected Quintiles as its single-source CRO strategic partner. According to Jenkins, Quintiles was selected for three attributes. "Their scale and scope will give us geographic flexibility. Second, we felt they had a broad volume of experience in the areas in which we are interested — MS, oncology, and immunology. And the third reason was their sophisticated IT informatics systems." Of course, Quintiles' willingness to develop a very innovative financial model also played into this decision.

When making such a game-changing move, expect a lengthy transition phase, the result of long industry cycle times and previously signed deals. You'll need to operate in both the old and new models, which can be difficult since people tend to revert to what is familiar. Jenkins stresses patience during this phase, and to expect that, at first, not everyone (on either side) will fully understand how to operate in the new model.

MEASURING THE NEW MODEL

From the beginning of the collaboration process, both companies agreed on the need for a governance structure equivalent to the type Merck Serono would have with any other pharma or biotech company. To achieve this, Quintiles established a Merck Serono business unit. Merck Serono established a similar unit dedicated to Quintiles. These operating units handle the day-to-day management of the partnership. Above that sits a joint steering committee. "Kathy Ford, who's my global head of clinical operation, is always on the phone to Paula Brown-Stafford of Quintiles," Jenkins shares. The final level of the governance involves direct communication between herself and Quintiles CEO, Tom Pike.

In addition to having the right governance, Jenkins has the following advice if you create this type of collaboration. Put the work in up front to set a clear, shared vision, as this will be used by both companies to engage and energize people as to why the new model makes sense. Make sure the company cultures have the potential to come together. According to Jenkins, "Cultures eat strategy for breakfast." Be brave on the financial incentives between organizations. "I can't share with you the details of the financial model," she states, "but both parties are highly incentivized to achieve the common goal." Set the right expectations internally with your management team using language they understand — don't give them the expectation that just because a deal has been done everything is going to be nirvana in six months or so. Her final tip: "Don't try to take a service model and apply it to a partnership model. It won't work."

To measure the implementation of this new model, Jenkins has "three biomarkers of success" — operational, people, and financial. "With operational, make sure you measure cycle times throughout the process," she states. "Start from the beginning protocol concept, to the final stamped protocol, to first patient in, first visit, 30 percent of your sites opened, and so on." These should be at or above industry benchmarks, and if not, be sure you understand why. "You've got to measure the basics," she says. Jenkins admits the people biomarker of success is more difficult to measure. "We conducted an employee survey at both companies, beginning with the people most heavily engaged in the new model," she states. This survey focused on employee feelings, behaviors, and culture. Jenkins intends to repeat the survey so they can track this metric throughout the partnership. For the final biomarker, she stresses that you understand the financials of your old model so you can benchmark your starting point. "For example, we have a good understanding of per-patient costs in the old model. Looking at these up front, we can get a pretty good sense if our per-patient costs in the new model look competitive, better, or worse than in the old model," she explains. But she counsels not to focus too much on costs. "I'm far more interested in timelines and quality."

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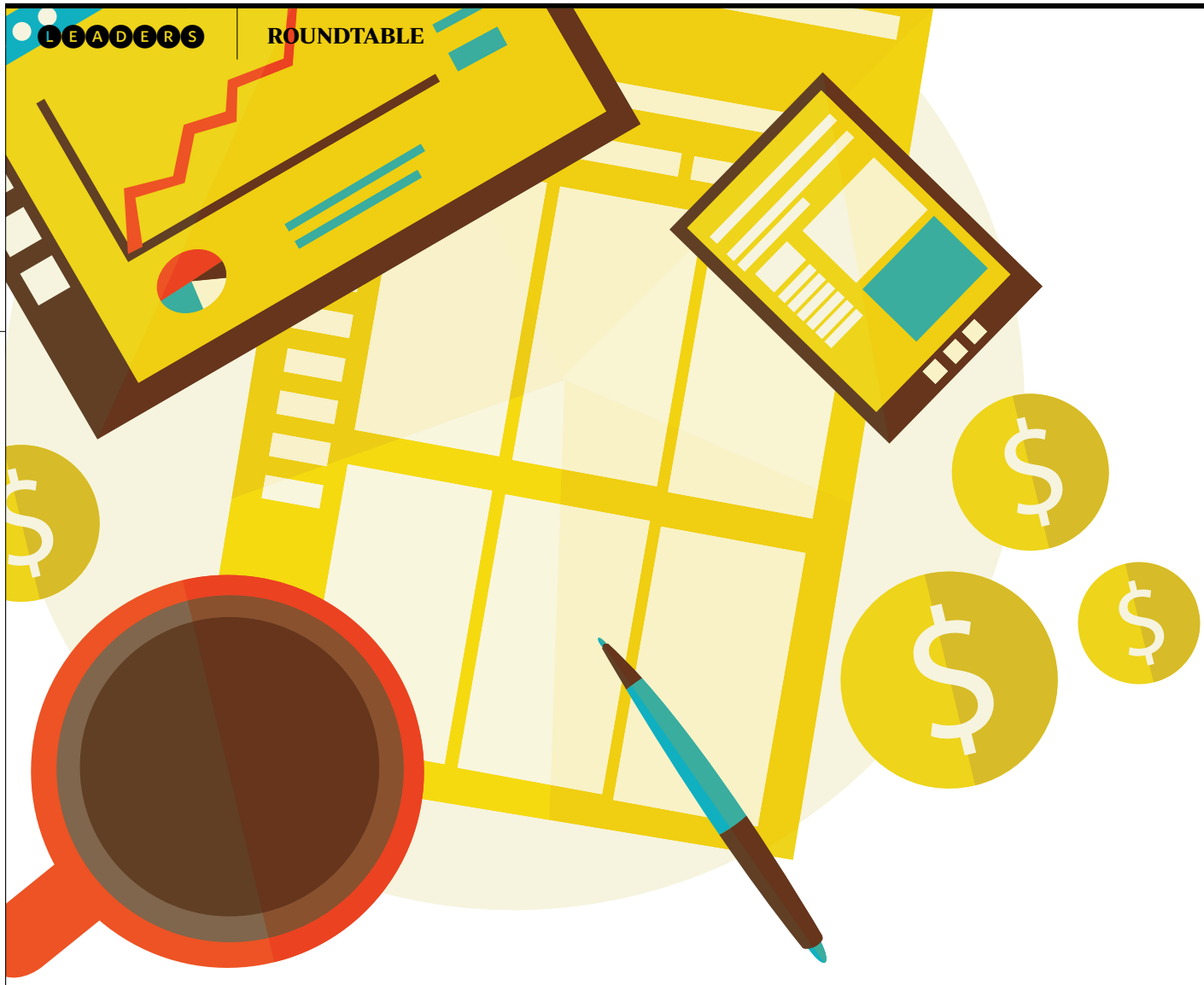

The Art of Optimizing Small Biotech Market Caps

— From Scientific Dreams to Strategic Reality

Moderated and edited by
WAYNE KOBERSTEIN Executive Editor

A Life Science Leader Editorial Roundtable

PART 1

As the sun cast a rosy glow over the city's horizon, bathing us in dawn light through the wide windows of our meeting room, a small group of company executives and investment experts shared breakfast and chatted before taking up the business at hand. Their purpose here: Trade insights across the table into how small biotech companies can achieve the best possible market capitalization at every stage of their development.

As the panelists subsequently confirmed, factors that determine the valuation of such companies vary from straightforward and objective to unpredictable and highly subjective — making for a fascinating discussion whether you are an expert or a lay person in life science investment. We held our roundtable in San Francisco during the confluence of industry events surrounding the JP Morgan Healthcare Conference in January 2014. Our intended audience was not in the room with us, but consists of our readers, essentially all of whom are affected by the issues we discussed.

The panel's actual makeup of people resulted partly by plan — invitations went out to a select list a month in advance — and partly by accident: who among the invited wished to and were able to answer our call. We had targeted a range of people reflecting the leadership of small and large Biopharma companies and investment firms. As it happened, the panel was evenly divided between the company and investment sides: Around the table were five leading investors, four small-company chief officers, and one head of business development for a large biotech known for its long line-up of successful partnerships and acquisitions.

The following is an edited transcript of *Life Science Leader*'s Optimizing Small Biotech Market Caps roundtable.

LEADING OFF

Chief Editor Rob Wright welcomes the panelists, and they begin to define the objective and subjective factors that determine a small biotech's valuation from its earliest stages.

ROB WRIGHT: Good morning. Thank you for coming. One of the most valuable things we have in our lives is time, so I'd like to make sure I thank you for taking the time to be with us today. We wanted to do something more interactive than bringing a bunch of people together and having a separate group talking up on the stage. We also want to develop this discussion into future editorial that our readers find valuable. Now I'm going to turn it over to Wayne. But first let's go around the table and have everyone introduce yourself.

The panel answers the roll call:

A Dennis Purcell Senior Partner of Aisling Capital
B Rich Vincent CFO of Sorrento Therapeutics
C Jacob Guzman Corporate Client Group Director at Morgan Stanley
D Allan Shaw Managing Director at Life Science Advisory Practice, Alvarez & Marsal LLC
E Ford Worthy Partner & CFO of Pappas Ventures
F Kenneth Moch President and CEO of Chimerix
G Jaisim Shah CEO of Semnur Pharmaceuticals
H William Marth CEO of AMRI
I George Golumbeski Senior Vice President, Business Development at Celgene
J Henry Ji CEO of Sorrento Therapeutics

WAYNE KOBERSTEIN: Great to see you all here this morning. My top priority today is to elicit your thoughts on three central questions:

- What are the most important factors in how the market cap for small biotech companies is calculated?
- How are the companies affected by the value of their market cap at key stages in their development?
- What actions can companies take to achieve/optimize their market cap at those key stages of development?

I had the idea for this meeting mainly because I don't know what the answers are to those questions. I don't know what goes into determining the market cap and valuation of a biotech company, either private or public, at the small-cap level. I can guess and observe like any other layperson, and I imagine that a lot of the answers have to do with subjective factors. But, that's fine, we can discuss what those are. Why is valuation important? What should it be in an optimum world? And then, how can companies actively work to reach that optimum valuation market cap?

So, let's start, clockwise to my left. Dennis, can you begin with a general answer to the first question — what factors determine a small-cap company's valuation, from start-up on?

DENNIS PURCELL: It starts with supply and demand. If you're starting a company, the more options you have, the better the valuation will be. It's really important to get the right people around the table at the beginning because the valuation going forward is largely set based on insider participation — whether the insiders have enough money and whether they will support you and your strategy. You can't start by doing present value calculations or following set formulas. It's really more of an art than a science right at the beginning.

KOBERSTEIN: More art than a science — I suspected that. Can you follow from that, Rich?

RICHARD VINCENT: From the very early stages, before you can even attract VC money, you've got to step back and figure out how you get a company off the ground. In San Diego, we see a lot of start-up companies, and it's very difficult for many good companies to secure seed money. We often have to go to friends and family and some of the angels in town or in other major cities in the bay area or on the East Coast. We actually try to avoid the question of valuation with some of the seed money we raise, by offering convertible notes. The notes will typically carry a standard 6 to 8 percent interest rate and some sort of discount factor toward the next financing (typically a VC-led round whereby the VCs lead the due diligence effort). So we take the valuation question off the table at that stage and defer until the VCs or other larger investors invest. A lot of the seed people like that, because then they don't have to do all the hard work the venture folks do to determine the quality of an asset.

KOBERSTEIN: What about thereafter, once you get past that very early stage?

VINCENT: Then you follow the lines that Dennis mentioned: it's all about supply and demand. We do that by being tactical across the spectrum of the business, whether it's bringing in the right management team, board, and opinion leaders, or IR (investor relations) firms to

make sure the company is doing all of the qualitative things, meeting its milestones, executing well in all phases of the program.

KOBERSTEIN: So the seed money comes in when the new company might have a scientific premise but before proof-of-concept?

VINCENT: It could be pre-proof-of-concept because oftentimes the VCs won't come in until there's some sort of proof-of-concept, whether it be in the right species or in man. It certainly challenges the niche area strategy among start-ups in today's environment. You often hear that start-ups are the backbone of the country, but it's very difficult for them to raise money — much more difficult than people realize.

PURCELL: Private companies are much more efficient than public companies. Is Intercept worth $6 billion more today than it was on Friday? I don't know. If you were a big shareholder in Intercept and it was a private company, you probably would have held it at cost or marked it up a little bit, but as a public company, it is now worth $7 billion.

JACOB GUZMAN: I see a lot of companies, and I'm a finance man, not a scientist, so I look at a lot of fundamental issues of value outside of science. In some ways, the science part is irrelevant to me. Building a company, developing a management team are important fundamentals — Dennis made a very good point. I always look at interesting facts about a company, something that others may overlook, for example, why a certain person is on the board of a small, little company in West Philadelphia. What does this successful former large pharma CEO see in this specific company? There must be something there; this intrigues me. We also seek out the best CEOs, in whom we look for a mix of businessman and scientist — the businessman to go out and raise the money; the scientist to explain what they are trying to sell. We meet a lot of people who are too much of one, and we can't understand what they are trying to sell. And we also meet a lot of people who are too much the other, and we can't understand what they're trying to sell. In the end, the most successful companies we've dealt with have had an interesting team, successful science, and have been able to effectively explain things to us. This makes me interested in learning more and developing a strong relationship.

SCIENCE, BUSINESS, & ART

The conversation takes a turn toward the qualitative assets needed in a young company to maximize its value during the formative fundraising stages.

KOBERSTEIN: You raised an interesting point about the scientist-business executive and the various personalities you encounter. So it's not just a matter of the prestige of the scientist or the purported value of that person's work, but one factor is the ability of that person to interact with and understand the business side, right?

GUZMAN: Absolutely. Even though someone believes in the science, they might not be willing to invest in a particular person because they don't know how many other people will understand what the CEO is talking about. Investors don't want to be the only ones in the pool. The CEO won't get very far without being able to get their message across in a clear and concise manner.

KOBERSTEIN: Allan, we have been talking mainly about starting up a company and the role that valuation and market cap plays at that stage. What are some other factors that can influence it at that point?

ALLAN SHAW: I'd like to build off the comment Dennis made, "It's more of an art than a science." There are many qualitative considerations that you need to take into account. We touched on the management team. There is also the therapeutic focus. Like platform shoes, therapeutic areas or targets go in and out of fashion; cancer is the flavor of the day right now. Also, time-to-market or development timelines are not inconsequential. There is increased emphasis on orphan drug development and focused drug therapies right now, and developers are trying to bypass Phase 3 studies and use Phase 2 trials as the pivotal stage studies to achieve registration. To underscore these dynamics, the spirit of the times is very important. Right now, everyone's taking capital market happy pills, and the word risk seems like a distant dream. That has a real psychological impact on access to capital and the underlying valuations at the end of the day. When everyone is feeling good about themselves, the relative valuations will inevitably expand — a high tide raises all boats, and a low tide lowers them.

KOBERSTEIN: So one factor is very general, just the environment at the time.

SHAW: Absolutely, and it also strikes me that there's a disconnect between valuations of established companies that have been operating in this space for a period of time versus some nouveau companies that have recently come to market. It speaks to some of the qualitative differences, because the new companies haven't had time to disappoint yet. By and large, they haven't had any notable clinical failures. Some of these qualitative factors transform themselves into the market valuation.

KOBERSTEIN: Yes, I encountered a relevant situation yesterday. I interviewed the head

of a company that had basically reinvented itself after a Phase 3 failure. It's been in business for 12 years, but now it's like a new company, with new management and all new products in new areas. I asked him, "How does that affect your valuation?" He said, "We are really undervalued because of what happened in our past, even though it has nothing to do with what we're doing now." He said when the company goes public, its current state may be a factor, but at this point it's not boosting the value.

PURCELL: No company proceeds like you think they're going to proceed. We were an investor in Intercept in a different indication than the one it announced. (Lots of laughter.)

GUZMAN: That underscores the importance of management.

FORD WORTHY: From the venture perspective, valuation is very much an art, as Dennis says. There is no net present value, discounted cash flow analysis typically done. But it's all about looking at other companies in the market — both companies that you've financed yourself at similar stages as well as other companies for which you have good data — and comparing, through a myriad of adjustments for the various risks involved, how a particular company compares with a pool of similar companies. Your initial question has the word "calculated," as in how market cap is calculated, but ultimately, it's really negotiated. You start with the best information that you can collect at that stage, looking at comparable companies, and then it's a negotiation.

KOBERSTEIN: I used "calculated" somewhat as a red herring, knowing I'd probably get a reaction. But when you say valuation or market capitalization, it does sound like something a financial person sat down and calculated, with formulas and so forth.

SHAW: We could even have an interesting conversation about "what is market cap?" What do you mean by market cap? Is it simply the price of the share, the last price paid times all fully diluted shares outstanding, or is it ultimately the value of the company — what someone would buy for the whole enterprise?

KOBERSTEIN: Right. So there are the tangible assets, and then there is the actual price it might be purchased for, which could include intangibles.

EXPECTATIONS MANAGEMENT

Do some companies get ahead of the game in boosting their market caps based on unrealistic hopes about later stages of development? Or is "judgment" an inevitable and necessary part of early investing?

KOBERSTEIN: There has been much public discussion recently about a few companies that have achieved enormous market caps based on early, conditional approval in one narrow indication along with a strategy of subsequently expanding approved indications for the same product into much larger markets. It seems market cap can sometimes

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grow very large for a company based on such expectations, but when problems arise, say, with safety in the follow-up trials, the valuation can fall quickly.

PURCELL: Well, that's why some of those companies have a very high price to yearnings! (All laugh.)

KENNETH MOCH: If you look at the theory of the capital asset pricing model, stock prices are the present value of future earnings, discounted for risk. If you project what you believe are relevant future earnings, you have to include the exogenous discount rate of the markets, right? At least to some extent, you can watch the water rise and fall based on those internal and external factors, and it kind of makes sense. But nobody can really predict the future earnings of a product that's not yet marketed, so the whole thing is a series of judgment calls. That's the way valuations have evolved — with judgment a key aspect of it all. Somebody said to me recently, "There's no such thing as behavioral economics; all economics are behavioral." So the pricing model fits into the capital asset model, as well.

KOBERSTEIN: How different is valuation for life sciences companies versus companies in other sectors, then? Is it more subjective or less subjective than in other sectors?

JAISIM SHAH: I can speak to fundraising in innovation, including the judgment aspect, because we raised $30 million Series A less than six months ago. We had no angel funding. We actually had no product. (Everyone laughs.) We had an idea, to address a hot topic raging through the country: the compounding mess, which had led to about 700 fungal disease infections and 100+ deaths from a New England pharmacy and other compounding pharmacies. We decided to focus on chronic back pain, and to come up with a formulation that will address all the issues causing pharmacies to compound.

We talked to only a few venture funds, and they gave us a term sheet. There were only three things that anyone wanted to know: One, can you price this product and get reimbursement? Two, was there a clinical rationale? That was a challenge, because there are no drugs approved to treat these patients; all drugs currently treating the condition are used off-label. And three, would there be a company that would have interest in partnering with us? We did no press release on the fund-raise; we really wanted to stay under the radar screen. We just filed a Form D [Notice of Exempt Offering of Securities, U.S. Securities and Exchange Commission], and someone in the press did a write-up

about this, saying this "stealth biotech" came out of nowhere, raised $30 million, and got really marquee firms to invest in it. We still haven't disclosed publicly what we are working on. (Everyone laughs.) But we've had companies contact us, ask for diligence decks [company slideshows], and nonconfidential presentations. We plan to be in Phase 2 this year. It gave me hope that anything is possible these days. (Laughter.) This is the right opportunity, and we have, of course, a really good team. I have worked and closed on other start-ups like Elevation Pharmaceuticals, partnerships, and acquisitions, and my cofounder and chair, Mahendra Shah, has founded and sold four other companies.

KOBERSTEIN: That was an interesting case.

WILLIAM MARTH: I'm rather new to this forum, so if you think I can top not having a drug or a rationale and raise money then . . . (Everyone laughs.)

SHAH: I think it's more about your 12+ years at Teva and growing the American companies from $2 billion to $12 billion.

MARTH: I've had some experiences, and I've found the science is important but the strategy is critical. If there isn't a strategy, if you cannot articulate what it is you're trying to do and how you're trying to do it, and what the endpoint is, it is very difficult to get investors. I started in the early days at Teva, back when we were $350 million here in the U.S., and we grew it to $10.5 billion here and $22 billion globally by the time I retired last year. We started out talking to a lot of people who really didn't want to listen to us in the beginning, but we had a strategy, and people understood the strategy. We could articulate it, they could understand it, and so those who invested in us did very well. And those who didn't, wished they'd invested. But it's really critical; science needs to be linked with the strategy, above all other factors.

KOBERSTEIN: Is there a process of critiquing the strategy? When you have a strategy, do you typically encounter people who are skeptical and try to take it apart?

MOCH: The investors can talk to that better than the company side. Our job is to create the vision, and their job is to tell us why it's wrong. (Laughter.)

KOBERSTEIN: Good point.

MOCH: That's the ying and the yang of the business, of investing and creating, right? It's about trying to define the inflection point between the overt optimism of the CEOs and the "I've been through this before and lost money" pessimism, which is not illogical, for the investors. Some people say, "Okay, I see your vision at this price, because that's where I think I can make money." Dennis can certainly speak to the process. Everybody comes in with a billion-dollar idea, and your job is to say, "I've seen this before."

"I always look at interesting facts about a company, something that others may overlook."

JACOB GUZMAN
Corporate Client Group Director
at Morgan Stanley

PURCELL: We look at 700, and we do 10, and a few work. It's a hell of a business. (Everyone laughs.) George sees them, too, at Celgene. As the CEO, you're just trying to build your company, and one of the elements of strategy is to understand the world around you, not just to operate in your little niche. Too many times people come in, and they just don't see the big picture.

KOBERSTEIN: So you can't fault any company for going out and saying, "We're going to do this." It's really up to the investors to judge.

GEORGE GOLUMBESKI: Recent history tells us that whatever the market climate, how high is the tide or how low the tide is, not all companies go up or down exactly the same. I'm trained as a scientist, I'm a long-term BD guy, and though I don't have the sophistication in market theory, my view follows from everything I've seen working with many small companies. In some ways, my business is really not dissimilar from the investors'. We have all these companies come to us. We invest in some of them, we buy some of them, and we are very motivated to work with them because we want the drugs, not the equity appreciation. Some are going to fail, and some are not going to fail, so you have to have a portfolio because that's the business we're in. But all these market reactions and contortions!

People understand — investors, the market — that developing a real, innovative, safe, and efficacious drug is very difficult, and any hint that there's a real drug in the works, the prices spike. But suggest there may not be a viable drug, they crater. Just look at recent events: We do a deal with OncoMed. That's a good company. We're very happy to have gotten a deal. The stock price goes up 100 percent in one day, but the data haven't changed. Or we pay a milestone to Epizyme, and the stock goes up 40 to 50 percent in one day. It's because people believe a drug will come out of the deal. Of course, I would also say, historically, a deal with a large, respected company validates to the market that the smaller company has a real drug in development.

MOCH: And it attenuates the perception of risk. Again, if you go back to the simple capital-asset pricing model, such a deal actually changes the perception of risk, and so the value should change.

GOLUMBESKI: But companies going it alone, like Ariad or Sarepta, experience the most volatility, even though many people are eager to believe in their products. Over the long term, I believe the real value will become clear, but at any one moment there's a hell of a lot of emotion out there.

VALUATION VALIDATION

Partnerships and other deals with major pharma and biotech companies may reinforce trust and perception of value in a company's clinical development potential. But the pool of candidates for such deals is shrinking, raising the stakes of success or failure and amplifying stock-price volatility.

PURCELL: George, you're probably the most active guy in the industry right now. What's your total view of the opportunities presented, deep dives, number of deals, and so forth?

GOLUMBESKI: Oh, that's a really good question. We have a process that's probably not disparate from other large companies. An amazing amount of information comes in from partner seekers, from writing us letters to calling a board member. We get hundreds of company disclosures, but out of every 100 that come in, we may decide to ask for more information from 10 to 15 of them, maybe sign CDAs (confidential disclosure agreements) on eight or 10 of those, and probably end up doing due diligence on only three or four. My group tries not to burden the rest of the organization with too many projects because, although our job is to do deals, we're going to look deeply at something before involving the clinical people, finance people, or the top people. So we usually have a fairly high rate of attrition before that stage.

PURCELL: Have you ever eliminated one, in retrospect, that you wish you hadn't?

GOLUMBESKI: I'm sure it's happened, but I honestly can't think of one off the top of my head. We try to set the filter wide enough, if you will, so that we don't have that happen. So far, I believe our selection process has mostly gone well. But going into the next two to three years, I'm not concerned at all that Celgene will run out of financial resources, corporate resolve, or CEO and board support, which I must say is exemplary. I'm just worried that the assets are getting harder and harder to find.

PURCELL: Versus five years ago?

GOLUMBESKI: In my mind, no doubt.

PURCELL: No doubt.

GOLUMBESKI: I've seen a lot of data, bad and good. If I put my time at Novartis and Celgene together, I've had the privilege of seeing everything in oncology for 13 years now — everything from early stage to on-market — and there were always some interesting things going into the clinic. Now, there are a few drugs out there, but the predictions for future assets are not robust.

MOCH: Is that because of the number of new technologies and products or because of the prices of new technologies and products?

GOLUMBESKI: More of the former — the sheer number. Up to now, we've been smart, fortunate, blessed, however you want to look at it, but we've recruited some really great partners: OncoMed, Epizyme, Agios, Quanticel, and so on. We could do five more deals a year if we could find the companies.

KOBERSTEIN: You mean companies with a bona fide drug in development, from what you've said. Is there a standout criterion or factor that helps you select them out of the crowd of contenders?

GOLUMBESKI: We probably all have our own biases as with our training and background, but there's no doubt in my mind that in the end, it is all about the team, the data, and the molecule. Even the best team cannot turn a bad molecule into anything, and a bad team can really destroy a good molecule — you really need both, and some luck. What drives us to invest? It's data and a belief that the data will translate to a meaningful drug. And I think over time, you get a meaningful drug, and then one realizes value. In the short term, investors can make tons of money on premature excitement about a drug. I've seen data about companies that never produced anything but made money anyway. But it's not just about money. In the end, we feel we only really succeed when we get new drugs to patients, and the patients benefit.

Thus ends Part One of The Art of Optimizing Small Biotech Market Caps editorial roundtable. Part Two of the discussion will appear in our next issue, covering the effects of valuation and market cap on companies as they grow and ways they can optimize their value at every stage in their development. More case studies and experience-based lessons arose in the remaining half of this thought-leader discussion, along with worries about drug-candidate shortages and unsustainable investment cycles. Part Two shows the panel detailing the importance of managing company and scientific communications, establishing relationships, winning patient-advocate support, spending cash carefully, and other actions companies can and should take to optimize their value and growth. L

> *"Right now, everyone's taking capital market happy pills, and the word risk seems like a distant dream."*

ALLAN SHAW
Managing Director, Life Science Advisory Practice at Alvarez & Marsal LLC

VAT And The Clinical Trial Enterprise

APRIL MULRONEY

As clinical trials become more global, sponsors and CROs face a myriad of financial, contracting, and compliance challenges. One of the most pressing: understanding and managing the impact of Value Added Tax (VAT).

For trials based solely in the United States, VAT is a non-issue. But when a trial extends into any of the 150 countries that assess VAT, sponsors and CROs must be prepared to navigate the complexities — and manage the costs. This article captures key insights shared by a recent panel of experts from CFS Clinical, EY, and a leading specialty pharmaceutical company.

VAT: THE BASICS

VAT is a transactional tax (also known as consumption tax or indirect tax) that applies to all transactions — products and services alike. In the clinical trial realm, VAT could therefore apply when a local investigator provides trial-related services.

VAT should be considered when planning for a clinical trial, as these taxes are not inconsequential. Ranging from 5 to 27 percent, VAT can instantly add to the grant spend budget if the appropriate planning is not done. Adding to the complexity is the fact that rates and rules can vary from country to country. For instance, Japan has the lowest rate at 5 percent (rising to 8 percent in April 2014), while Hungary has the highest individual rate at 27 percent. The European Union indirect tax rates range from 15 to 27 percent; Latin America, 15 to 35 percent (combined; there are several indirect taxes in Brazil); and Asia, 5 to 17 percent.

The good news is, depending on the tax laws of the countries in question, sponsors and CROs may have opportunities to minimize or recoup some of the VAT exposure. The bad news is that if VAT must be paid, the ability to obtain such refunds in a number of countries can be complicated and comes without guarantee.

SOME BASIC PLANNING

The primary consideration for VAT planning is the clinical trial agreement (CTA) structure with the investigator, as this will form the basis of determining whether VAT will be applicable. By having an understanding of available VAT exemptions and reduced VAT rates in each country, it is quite possible to develop a go-to model of CTA contracting that will decrease the risk of irrecoverable VAT on a study altogether. It is always better to not pay VAT in the first place, than to pay VAT and then try to get it back.

RECOVERING VAT

To the extent that VAT is to be paid on a clinical trial, there are a number of best practices for increasing the likelihood of its recovery:

1. Be diligent about documentation. If a trial is audited, the likelihood of recovering VAT is slim if the documentation is not thorough, organized, and up to date. This applies to all the parties of the CTA — from sponsor to CRO to investigator. The CTA should be evaluated on a country-by-country basis to determine the applicability of VAT in accordance with the local VAT legislation of each country. This will form the baseline to monitor the process so that VAT is not being charged when it doesn't apply. Agreements should cover these key questions:

- To whom are the services actually being provided?
- What is the VAT treatment of those services?
- How are the invoices being raised, and do they meet certain requirements?
- Who is making the actual payments?

2. Maintain visibility. Determine up front whether or not VAT is factored into the grant spend estimate and whether the CTA budget is inclusive of VAT. In addition, if VAT is to be paid, ensure there is a robust reporting function to track VAT paid by country by protocol and where the VAT credits are in the reclaim cycle. This will provide the basis to follow up on available VAT credits with local authorities and ensure that the credit is ultimately applied to the correct grant account.

3. Invoice properly. Each country has its own VAT rules and invoicing requirements. As legal documents, invoices must meet local legal requirements. Failing to submit a legally binding invoice based on the template of the country in which the investigator is operating exposes a trial to tax assessments. Further, it decreases the chance for a refund—even when one is merited.

4. Mind the cash flow. Even if the sponsor does qualify for a refund, the VAT must be paid first, and then the sponsor can file to receive the payment. Depending on the invoice payment terms and the country the VAT is paid to, it could be months or even years before the refund is issued. Thus, it's critical to factor the temporary payout into the budget to avoid a cash-flow crisis for the trial.

NETTING IT OUT

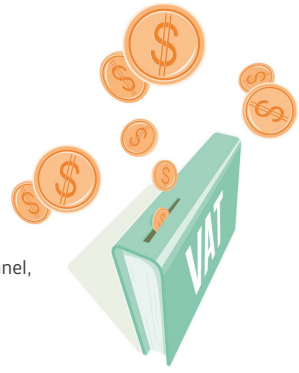
As the geographic reach of clinical trials widens to include investigators in other countries, VAT stands to have a huge impact on the budget, cash flow, and bottom-line performance of any global study. It is essential for sponsors and CROs to recognize the potential impact, to plan for that impact sooner rather than later, and to be realistic about whether and when they may receive refunds.

While VAT rates and rules are complex and ever-changing — comprehensive, consistent, and current trial documentation

is an enduring best practice. If managing documentation presents significant challenges, consider partnering with a service provider offering the people, processes, and technologies essential to navigating multi-country VAT rules and regulations and keeping a watchful eye on a global trial's bottom line.

April Mulroney, CPA, CA, is VP of strategic account management and tax services at CFS Clinical (CFS). She is responsible for the Strategic Account Management Group at CFS Clinical where she ensures accounts which are engaged in the multiple service lines from the DrugDev portfolio are well-executed.

Case in Point: Managing VAT in Brazil



Sponsors and CROs have an opportunity to mitigate VAT impact — but only through careful planning. Often, the VAT cost comes down to the contracting arrangement. In the panel, the experts used Brazil, which has five different VAT taxes, as an example.

VAT with a local model

In this scenario, the CRO is based in the same country as the investigator. The investigator will be raising invoices for the clinical trial services to the CRO, which means there are two types of taxes:

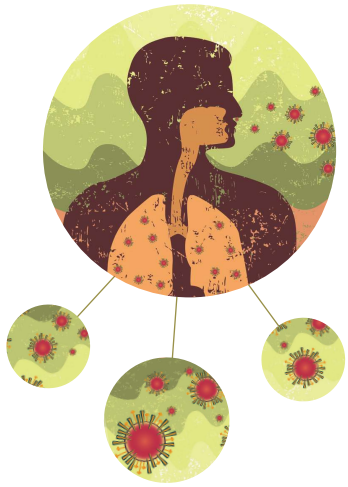
- ISS tax (a Brazilian tax applied to the services provided to a third party by a company or professional and is paid by the service provider) of up to 5 percent, which is not recoverable
- PIS/COFINS turnover tax of up to 9.25 percent, which is complex to recover and in many cases is unrecoverable. Thus, by working with a CRO and investigator both based in Brazil, the sponsor may have a total of up to 14.25 percent additional costs.

VAT with a regional model

In this scenario, the CRO is based in Mexico, but the investigator is based in Brazil. Like many countries, Brazil has special rules for cross-border services. The rules are very specific to each country, but in Brazil those services may be free from the relevant indirect taxes for services (ISS and PIS/COFINS), because they are supplied to or consumed by someone outside of that country. Therefore, with careful up-front consideration and review, no ISS or PIS/COFINS taxes may be applied (this, of course, depends on the specific facts for the clinical trial services).

This comparison illustrates how a simple change in the structure of the arrangement can affect the VAT impact dramatically — by up to 14.25 percent in this example. If the investigative grant spend is $1 million, using the regional model could save $142,500.

Antibiotic R&D Gains Traction: A Mid-Cap Company, Not Big Pharma, Leads The Way



CATHY YARBROUGH Contributing Editor

The industry leader in developing antibiotics against "superbugs" and other multidrug-resistant bacteria is not a Big Pharma corporation, but Cubist Pharmaceuticals, headquartered in Lexington, MA.

Because antibiotic therapy is short-term, a company's potential return on investment can be much higher for a chronic disease drug. However, as major pharmaceutical companies began eliminating antibiotics from their core therapeutic areas, bacteria were becoming tougher to treat with existing agents. "The world now faces a perfect storm of a declining antibiotic pipeline and a rising threat of antibiotic resistance," said Steven Gilman, Ph.D., executive VP of R&D and CSO of Cubist.

Among the most threatening microbes are Clostridium difficile (C. difficile) and methicillin-resistant Staphylococcus aureus (MRSA), both of which are targeted by FDA-approved Cubist drugs. In addition to marketing the antibiotic Dificid for the treatment of C. difficile infection, Cubist has developed a new compound, surotomycin, against this superbug, which the CDC has labeled as the most threatening of the multidrug-resistant microbes. Surotomycin is under evaluation in Phase 3 clinical trials.

Worldwide about 2 million patients infected with the MRSA superbug have been treated with Cubist's flagship product, Cubicin, since its FDA approval over 10 years ago. Cubicin generated $1 billion in worldwide sales in 2013. "Thanks primarily to Cubicin, Cubist's market cap has grown from approximately $1.5 billion in 2008 to approximately $5.5 billion today," said Gilman.

In Cubist's pipeline are five compounds, two of which are late-stage antibiotic candidates. They are tedizolid, which tackles serious Gram-positive infections including those caused by MRSA, and ceftolozane/tazobactam, which is designed to treat certain Gram-negative infections, such as those involved in complicated intra-abdominal and complicated urinary tract infections.

Tedizolid was developed by Trius Therapeutics, which was acquired by Cubist in 2013. Later that year, Cubist submitted an NDA (new drug application) for tedizolid to the FDA and expects a response from the agency in late June 2014.

Also in 2013, the company acquired Optimer Pharmaceuticals and its FDA-approved drug Dificid. When it was approved by FDA in 2011, Dificid was the first new drug in 25 years to treat diarrhea caused by C. difficile.

SINGULAR FOCUS PROMOTES ACQUISITIONS

"Unlike many companies that overdiversify, we have a singular focus, and it's a big factor in why we're considered the acquirer of choice for biotechs in the antibiotic space," said Gilman. "Antibiotic development is so different from drug development in, for example, chronic disease areas such as oncology," he added. "In antibiotics, deep knowledge is required to be able to judge what will be successful. As a result, we understand not only the risk, but, importantly, the equity, the financial value of the company or asset to investors."

In addition to the company's in-depth knowledge of antibiotic development, Cubist's track record of success in navigating complex regulatory landscapes and in commercializing drugs has contributed to its reputation as acquirer of choice. "With Cubicin, we have developed a commercial strategy that supports clinical benefits as well as economic benefits for the healthcare system," Gilman said.

Like other drug developers, Cubist must demonstrate to global payers and providers that a particular new therapy provides clear clinical and economic differentiation. "Because of rising healthcare costs, pricing pressures, health technology assessments, and healthcare reform, regulatory approval no longer is the 'end game' for a new antibacterial therapy," said Gilman. "Our clinical programs now include multiple health economics and outcomes parameters, such as length of stay in hospitals or readmission rates, to be able to assess overall value, not just clinical efficacy," he said.

A NEED FOR MORE R&D SPENDING

This year, Cubist will spend about $400 million on antibiotic R&D, "which is believed to be more than any other company in the world," said Gilman. However, Cubist's investment in antibiotic research is not sufficient. Industrywide investment in innovation as well as appropriate use of antibiotics in certain patient populations is required to stay ahead of the inevitable development of bacterial resistance to antibiotics. "Bacteria simply have too many mechanisms they can use to create new ways of becoming resistant," he said.

Gilman also pointed out, "Policy makers and members of the infectious diseases community need to face the reality of rebuilding the global antibiotics pipeline head-on and ask: 'How do we attract the kind of long-term capital that will draw small and medium-sized companies into the space?' We think additional incentives

that target pricing and reimbursement would likely work."

PUBLIC POLICY EFFORTS CREATE INCENTIVES

Cubist engages policy leaders at all levels in the U.S. and Europe about the global antibiotic pipeline. Along with the Infectious Diseases Society of America (IDSA) and other groups, the company has called for regulatory reform to create the incentives that will persuade companies to continue their development of antibiotics against multidrug-resistant bacterial infections and, if they are not invested in antibiotics, to add it to their list of target therapeutic areas.

The public policy efforts of Cubist, IDSA, and other groups have resulted in bipartisan legislation to make antibiotic development more attractive. The legislation, the Generating Antibiotic Incentives Now (GAIN) Act, which was signed into law by President Obama in 2012, may be one reason that two pharmaceutical giants, Roche Holding AG and GlaxoSmithKline, recently initiated R&D programs focused on antibiotics.

The GAIN Act provides incentives such as priority review of NDAs, and for certain new antibiotics that are approved by the FDA, the act extends the period of market exclusivity by five years. Under the GAIN Act, specific proposed indications for tedizolid qualify for the incentives.

Additional legislation to encourage investment in antibiotic R&D also may be enacted. In December 2013, a bipartisan group of representatives introduced a bill that would build on GAIN by creating an accelerated approval pathway for antibiotics designed to treat specific patient populations. If approved by Congress and signed into law by President Obama, the Antibiotic Development to Advance Patient Treatment (ADAPT) Act would require the FDA to approve antibiotics and drugs against fungal infections for these populations based on, for example, clinical trials with fewer patients than required in conventional clinical studies.

STEVEN GILMAN Ph.D.
Executive VP of R&D
and CSO of Cubist

Will Cubist's success combined with legislative initiatives such as GAIN inspire more companies to add antibiotics against multidrug-resistant infections to their core therapeutic disease areas? As Gilman pointed out, industrywide investment in antibiotic R&D is required to stay ahead of emerging superbugs and prevent what many public health authorities fear could be a return to an era when infectious diseases will overwhelm cardiovascular diseases as our number-one killer. L

Are You Prepared For The New European Pharmacovigilance Guidelines?

MIRANDA POTHIAWALA

EVMPD (EudraVigilance Medicinal Product Dictionary) requirements have moved back up the agenda for pharma companies marketing products in Europe, now that new requirements on data maintenance have finally been published.

For the 30 to 40 percent of organizations still struggling with initial electronic submissions, the new demands will be a bitter pill to swallow. To sweeten the transition, companies should look for the additional efficiency benefits that are possible once they have their data management ailments under control.

Following much anticipation, in late January 2014 the European Medicines Agency (EMA) finally issued expected guidelines on how to update/maintain data submitted to the extended EudraVigilance Medicinal Product Dictionary (XEVMPD). This aims to catalog all human drug products marketed in EU countries. The requirements come under Article 57(2), the official EU legislation that brought about the requirement for the XEVMPD database.

Any life sciences company distributing products in Europe had a mandate to submit complete product information and documentation to this central electronic database by July 2012. But to give the agency a chance to absorb and organize all of this content, companies were asked not to submit updates to this initial information until new guidelines had been issued on the process and timescales for ongoing data maintenance. That guidance has now been published, putting pharma organizations under new pressure to respond and get their submitted information up to date.

THE NEW DIAGNOSIS

It had been expected that ALL changes to marketing authorizations would have to be made within as short a time frame as 15 days; however, according to the issued guidelines, the 15-day period will only apply to new marketing authorizations. Updates to existing submissions will have a 30-day window, but even that is hardly any time, given the sheer volume of product files that will be affected.

Those firms that had been diligent in submitting their original product information well ahead of time will be dismayed to learn that updates will be required across almost all content — because new data fields have now been introduced. For instance, the agency now requires that companies indicate the size of their operations, i.e., whether they are small, medium, or large organizations. They must also provide information about the legal basis of the marketing authorization for each submission — i.e., which act they are applying under. Then they must apply the right product code, from a consolidated and cleaned-up list, to ensure it is correctly categorized as herbal, pharmaceutical, etc. Finally, an authorized pharmaceutical form covering the dosage of products must be included.

MAKING UP FOR LOST TIME

The agency is proposing a transition phase, between June and December of this year, during which marketing authorization holders are expected to bring their product data up to date and improve the quality of the data they have already submitted. But, however prepared companies feel, this won't be easy. As organizations prepare to respond to the new requirements, they will need to take stock of where they are today and how far they still have to go before they are able to meet the latest XEVMPD requirements reliably and as painlessly as possible.

A conservative estimate based on our regular contact with pharma companies suggests that 30 to 40 percent of affected organizations have yet to finish their original submissions, so they do not yet even have a complete data set registered with the XEVMPD. Worse still, many firms had shelved XEVMPD initiatives while the new guidelines were being con-

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> *"Over time, the EMA's requirements will only become more stringent."*

firmed, so they have made little progress during the last 18 months. Now that there is no longer an excuse for inertia, companies have a lot of catching up to do.

COORDINATION CHALLENGES

Although much of the required content already exists in companies, it is widely dispersed and is often captured manually in spreadsheets. The EMA provided a free online data entry tool, EVWEB, to make the process easier, but its parameters are basic, and use of the tool has resulted in variable quality in the information that has been submitted. In other cases, any initial sense of urgency soon became diluted once the deadline came and went and organizations realized that there were no real consequences for noncompliance — in that no firm has so far been penalized for noncompliance.

But the EVMPD/XEVMPD initiative is a work in progress, and now that standards have been issued concerning the way data must be updated, the EMA is likely to come down more heavily on companies that do not get their data in order. At the very least, this could lead to reputation damage if high-profile brands are exposed as being tardy in their submission activity, especially given that the whole point of pharmacovigilance is to improve consumer safety.

FINDING THE RIGHT CURE

The only safe way to achieve compliance is to have reliable, fit-for-purpose processes and systems in place, which are geared toward clean, easy, and stable data capture, management, and reporting. By doing so, companies not only improve their ability to meet their EVMPD obligations, they also stand to benefit from all sorts of additional internal efficiencies. For example, capturing information in a central location means there is a "single place of truth": information only has to be entered once yet can be accessed readily by anyone who needs it (assuming they have the relevant authorizations) and repurposed in all sorts of different ways. Other operational improvements could include accelerated workflow, improvements to data quality and reporting, easier auditing, and broader information compliance. By smoothing administrative processes, the right software also could help companies get new products to market in better quality and more quickly.

DATA QUALITY CONCERNS

One of the issues the EMA has been grappling with has been the poor data quality that companies have submitted to its central database to date. For a limited period, the agency encouraged pharma companies to input their own categories into the controlled vocabularies used in the medicinal product dictionary. This has led to overlapping fields and duplication of content.

As it has sought to clean up this data, the agency has had to consolidate some of these codes, which is one of the reasons companies now need to resubmit a lot of content.

Going forward, companies will need to ensure that the data they submit is cleaner and more accurate. This means removing duplication and manual entry in internal data capture and management processes.

With eCTD (electronic common technical document)-based electronic regulatory submissions, validation criteria and tools exist to provide assurance around data quality. It is likely that similar aids and tools will be made available in due course to help ensure clean, compliant data for EVMPD.

RESTORING DATA HEALTH

Quality control is vital if the goal of increased patient safety is to be met, and any life sciences company that takes pride in its brand will want to pay close attention to what goes into these central records. Whether penalties are applied or not for inadequate attention to EVMPD submissions, the last thing companies want is to fail to deliver against public health and safety improvement targets. However, it is likely that the XEVMPD data will be used for establishing marketing authorization holders' pharmacovigilance fees, a subject that is being hotly debated at present.

There is some good news, too. The update process is being simplified so that it is no longer necessary to track each variation that is made to a product license. But overall there isn't a great deal to smile about as pharma companies' administration workloads multiply.

The only way to lighten the load is to get help to streamline processes, alleviate repetitive practices, and drive up data quality. Whether submitting for the first time or resubmitting and updating information, companies need to be able to extract and send the right content readily — and be able to vouch for its quality.

Getting this right sooner rather than later will pay dividends though. Over time, the EMA's requirements will only become more stringent. The next iteration of XEVMPD — ISO IDMP, likely to become mandatory in 2016 — will take pharmacovigilance reporting to the next level, introducing significantly more data requirements and additional controls over data quality, among other measures. It is expected to have broader geographical application, too, i.e., beyond Europe. So making the effort to achieve compliance now will provide an important building block for the future. L

Miranda Pothiawala is director and head of software at Samarind RMS. Steeped in knowledge of regulatory submissions and data management in the pharmaceutical and medical device industries, she is also an expert on EudraVigilance and compliance with the EMA's (European Medicines Agency's) EudraVigilance medicinal product dictionary.

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6 Steps For A Sustainable Approach To R&D Through Big Data

TODD SKRINAR AND THADDEUS WOLFRAM

Near the end of 2013, many in the life sciences industry were looking for clear evidence that the FDA was willing to work with industry to get more needed drugs to patients. Eyes were focused on the "scorecard" of new drugs approved, which for the first eight months of 2013 reached 18.

While this number was down from 22 during the same period in 2012, it still outpaced what was a very sluggish approval pace through much of the 2000s. The FDA's most recent trend seems encouraging.

The bigger challenge is the sustainability of the R&D process itself. Clinical trial costs, in particular, are driving intolerably high R&D expenditures. In the midst of slow sales growth, it is no surprise these costs remain a focus of the industry's continued belt-tightening.

The industry is demonstrating an interesting range of strategies to make R&D more efficient, including dispersing risk through open innovation, collaboration, and partnerships, as well as diversifying by targeting personalized medicine and orphan and niche disease markets. But a key question remains: How does one reduce clinical trial costs while still meeting the rising demands of regulators and payers for more data that demonstrates that the drug is a significant improvement over current standards of care?

Effective use of Big Data is increasingly seen as the path forward. It offers opportunities for cutting clinical trial costs while providing the type of robust data required for both approval and reimbursement.

THE VALUE OF BIG DATA

Big Data for R&D is less about velocity and more about variety, viability, and sometimes volume. The key analytics capability for this data is the ability to visualize relationships and patterns. By combining real-world outcomes data with clinical data and through the mining of genetic data and a broader understanding of regional and population data, analytically savvy organizations can begin to recognize research failures faster, design more efficient clinical trials, and speed the discovery and approval of new medicines while lowering costs along the way.

Whether it is "-omics" data, patient-relevant social media, payer claims, or patient electronic health records, a limitless amount of patient data is now available and is enabling companies to achieve impactful R&D goals including:

- streamlining patient recruitment and informing patient selection and enrollment to recruit the right patients for trials, as well as excluding patients who are likely not to benefit from treatment or likely to suffer adverse events
- tying trial outcomes to real-world outcomes data and health economic data
- minimizing the number of patients and trials needed to deliver the necessary regulatory information, as well as limiting the timeline of trials needed to produce required endpoints
- allowing for the monitoring and incorporation of data collected outside of the clinic, including data gathered through smartphones and other device trackers
- analyzing data to reveal where a drug can positively impact a new population/indication, allowing for a new, streamlined trial.

Given the rapid changes in technology and the ambiguous regulatory environment surrounding the use of such data, many companies are struggling to meet compliance, privacy, data quality, and other challenges. However, there are several steps companies can take today to keep pace with, or even leapfrog over, their competitors in harnessing the power of Big Data to improve their R&D efforts.

STEP 1: Establish a clear analytics strategy. The first step in incorporating Big Data into your R&D operations and decision making is to define an analytics strategy and operating model that includes a center of excellence. The center of excellence provides a sustainable core to drive the ongoing execution of the analytics strategy within the day-to-

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"Companies that master these steps will build a more sustainable approach to R&D and develop competitive advantages in the life sciences space."

day running of the business, and fosters a collaborative environment that generates the necessary tools for both creators and consumers of analytics to extract the greatest value from Big Data. The R&D analytics strategy will be driven by the needs of the business, not technology. A strategy motivated by available or interesting tech will too often cloud decision making, not clarify it.

STEP 2: Identify the most relevant sources of Big Data. Given the large and disparate amount of data now available to life sciences companies, it is easy for an organization to quickly become overwhelmed. The defined R&D analytics strategy (mentioned in Step 1) will, by nature, provide initial guidance for why any data source is valuable or not. The data that offers value can be filtered further based on the potential impact it holds for the business. The process then advances from targeting the right Big Data opportunities to an assessment of key factors, including accessibility of the data, security requirements surrounding the data, and the effort it will take to make the data usable.

STEP 3: Master large-scale data management. The capability to appropriately access, pool, and maintain large volumes of data from varied sources will, of course, be critical to success. While there is a wide range of tools, technologies, and platforms available for delivering this capability, the appropriate choices depend on the sources of Big Data and the analytics targets identified in Step 2. Assessing the current foundational IT and analytical state will present a clear picture of the steps needed to reach the appropriate level of large-scale data management.

STEP 4: Pursue meaningful collaborations. The structure and demands of today's healthcare ecosystem mean no one organization can go it alone. Data access is one of the many activities that at times requires cooperation between two or more parties. For example, collecting patient information is certainly not something that a biopharma company can just go out and do. However, what that company can do is gain access to the right information from electronic health record data by partnering with the institutions that are able to collect and maintain it. Establishing data partnerships with other life sciences companies as well as academic institutions, providers, and payers is key to gaining access to the widest range of Big Data possible. Companies pursuing these partnerships also need to think "win/win" when determining their positions on intellectual property, risk, and resource commitments. Success will depend on selecting like-minded business partners and using trusted third parties to support the data-management challenges.

STEP 5: Optimize your analytics organization for performance, value, and continuous learning. Improving the performance of R&D requires a constant search for new insights by combining and analyzing nontraditional data sources. Complacency around Big Data will eventually lead to missed insights, overlooked efficiencies, and an inadequate analytics function. To guard against this, establish a continuous feedback loop to understand the results of analytics and apply them to future analytics efforts. This process requires skills, structure, and management behavior that all drive a culture of continuous learning and improvement.

STEP 6: Derive and define your value. Successfully utilizing Big Data is ultimately about deriving value from the data in a manner that drives effective decision making and that enables a company to demonstrate the value of its product to patients and to the healthcare system overall. After providing the right information to drive better decision making, the biggest challenge remains: articulating both the quantitative and qualitative benefits of R&D analytics efforts and the downstream R&D efforts to the appropriate stakeholders, including internal clinical development and operations teams, as well as payers and patients.

In communicating the analytics benefits, it is important to have predefined short-term and long-term metrics for assessing the impacts. By doing so, the results are aligned to specific targets and can easily be used to inform the selected audience of the value that R&D has created for them.

Companies that master these steps will build a more sustainable approach to R&D and develop competitive advantages in the life sciences space. They will be better poised to deliver products and solutions that meet the specific needs of patients — individually, stratified, and at a population level. And they will be able to do this with lower R&D costs, with a streamlined route to market, and with a clear knowledge along the way of exactly which patients can benefit from the therapies they deliver. L

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VALEANT PHARMACEUTICALS

PRE-CONFERENCE WORKSHOP: **REGULATORY & STRATEGY SUPPLY CHAIN MASTERCLASS: MAKING THE RIGHT BUSINESS DECISIONS IN LIGHT OF THE DRUG QUALITY AND SECURITY ACT**

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The FDA's Focus
On Metrics, Performance, And Quality

ELLEN LEINFUSS

Ellen Leinfuss serves as the SVP and Life Science practice leader for UL EduNeering.

At the PDA Quality Metrics Conference in December 2013, FDA CDER (Center for Drug Evaluation and Research) Director Janet Woodcock set out her goals for the conference: "to shift [the FDA's] focus to performance and away from compliance." Under the FDA's lead, the life sciences community will have no choice but to follow suit in its own operations and approaches to quality.

Product quality is the inherent goal of life sciences companies. It is their mission in developing and producing products, delivering those products to patients, and ensuring the futures of their organizations. Historically, the standard of quality was compliance, but highly publicized recalls, product bans, and drug shortages have forced companies to rethink quality. At the CDER, QbD (quality by design) has nudged the industry to build in quality controls at the beginning of a drug's life cycle. At the Center for Devices and Radiologic Health (CDRH), the rallying cry has been around the case for quality. And the FDA is seeking industry input about the metrics essential to quality control in order to make risk-based decisions, ranging from inspection scheduling to assessing the potential for drug shortages because of product quality issues. The FDA wants objective measures of product quality, site operations, and site systems performance.

THE VALUE OF METRICS

The FDA challenged life sciences companies to identify the key objective metrics that indicate product and site health. The agency wants to see product and site metrics for trend comparison across the industry.

The use of metrics would seem to be self-evident to quality and compliance managers, yet product recalls, plant shutdowns, enforcement actions, and product shortages continue. At the PDA conference, attendees agreed about the main goals and benefits of using metrics: to eliminate subjectivity, provide a benchmark and visibility for continuous improvement, and ensure side-by-side training across multiple operational functions, including quality assurance, operations, and production. With such agreement, the questions have to be asked, "Why are so few organizations successfully integrating metrics into their operational systems?" and "Why are we still seeing too-common product recalls, plant closures, enforcement actions, and drug shortages?"

METRICS VS. DATA

Life sciences organizations have data — hundreds of thousands of pieces of data, often unorganized, inaccessible, and inconsequential as a quality tool. At the conference, participants voted on preferred site metrics, ranking the top five as confirmed out-of-speculation (OOS) rates, CAPA (corrective and preventive actions) effectiveness, batch-failure rates, critical investigation rates, and environmental monitoring grades. The same question was provided for product metrics, with the top five listed as complaint rates, OOS rates, process capability, critical investigation rates, and batch-rejection rates.

Interestingly, these identified metrics can spark initial red lights, or they can form the resulting action plan. Consider, for example, OOS rates compared month over month for one facility. A deviation — often very small — is noted, setting a benchmark and warranting attention. If the trend increases, questions must be asked. Is the deviation local or enterprisewide? Did the deviation begin with the installation of new equipment or systems? Has a new workforce been hired or the existing workforce been downsized? Is a new manager in place? Do training metrics show any drop in completion rates or levels? Have budgets been cut for maintenance of production equipment?

The same questions should occur in reverse with the right metrics. Consider training metrics that show a drop in successful completion rates for a specific topic. Is the decrease limited to one facility, production line, or product? Is it common across production lines at multiple plants? Does it correlate with quality issues such as OOS rates or batch-rejection rates? Based on those answers, what is the action plan? Remedial training for a defined group of learners? Manager training? A renewed commitment to an enterprisewide culture of quality? New training materials? Additional new-hire onboarding?

The answers and subsequent actions based on useful, accurate metrics will determine a company's quality, compliance, and financial profile. With the FDA's evolving approach to quality, how a company collects and uses metrics will also identify a company's risk for quality failures — and whether or not those risks warrant added scrutiny and inspections by the FDA.

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Leadership Rules for the New Normal

JAMES KOUZES
AND BARRY POSNER

It wasn't long ago that normal meant slow and steady. Today, normal means expect the unexpected, requiring a new set of leadership rules. To help leaders fully engage people and strengthen their resilience in uncertain times, we took a fresh look at what leaders do when they are at their personal best. We identified six common strategies you should incorporate into your leadership practices to be successful in turning adversity into opportunity.

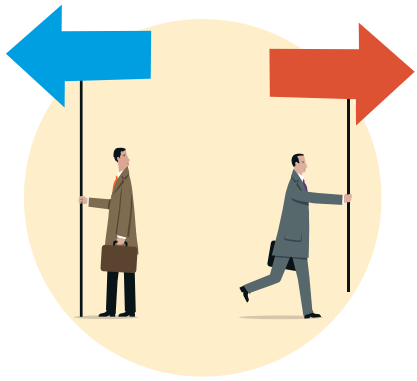
1 **Broaden the context:** View what's happening from a historical perspective. Doing so provides an understanding of how others have dealt with challenging times. Research has shown that people who first reflect on their past during stressful circumstances and tell positive stories about handling hardships are more effective in dealing with adversity and rebound more quickly.

2 **Defy the verdict:** People want to know the truth, even if it's bad news. If you want your team to respond with fierce determination during periods of business adversity, you need to increase your level of communication about what is really going on. Exemplary leaders acknowledge reality, but do not dwell on the threat. See change as a challenge and move quickly to mobilize resources in order to defy the verdict.

3 **Fully commit to what's important:** During tough times, exemplary leaders make certain everyone understands the purpose that guides decisions so as to gain alignment between people and values.

4 **Take charge:** Michele Goins, a veteran CIO in high-tech firms, said, "Leadership opportunities are in the moment. What makes the difference between being a leader or not is how you respond in the moment." You have to respond assertively to moments of trial and adversity.

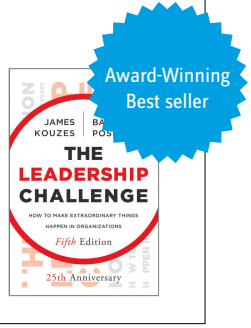
James Kouzes (top) and Barry Posner have been working together for more than 30 years, studying leaders, researching leadership, conducting leadership development seminars, and serving as leaders themselves in various capacities. They are coauthors of the award-winning, best-selling book *The Leadership Challenge*. They have also coauthored more than a dozen other award-winning leadership books.



5 **Engage others:** Collaboration and trust among your team are essential to building capacity to get through difficulties. Neuroscientists are discovering that our brains are wired to connect. People engaged with one another are motivated to strengthen their relationships with one another, resolve interpersonal conflicts, and find win-win solutions.

6 **Show you care:** Ajay Godbole, IT principal consultant with Oracle, notes that "Leaders who have the courage to show how they care for the team and the organization build strong interpersonal connections among their team. This bond is the difference between a team that can overcome challenges and a team that disintegrates at the first challenge." Showing you care is personal. But if you want people to hang in there when times are tough and continue to give it their all, let them know — regularly — they are valued.

Adapting these six leadership rules will enable you and your organization to take the initiative and move forward in the new normal environment.



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