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THE SEEKERS

Stimulating Disruptive Innovation at GSK

"We want to become really good at doing something that might not be doable now but is going to be important in five years." p. 18

(L-R) Magalie Rocheville, John Baldoni, and Lee Shorter of GSK

The Blockbuster Revival p. 44

Changing The Culture At Endo p. 24

The FDA Innovation Agenda p. 30

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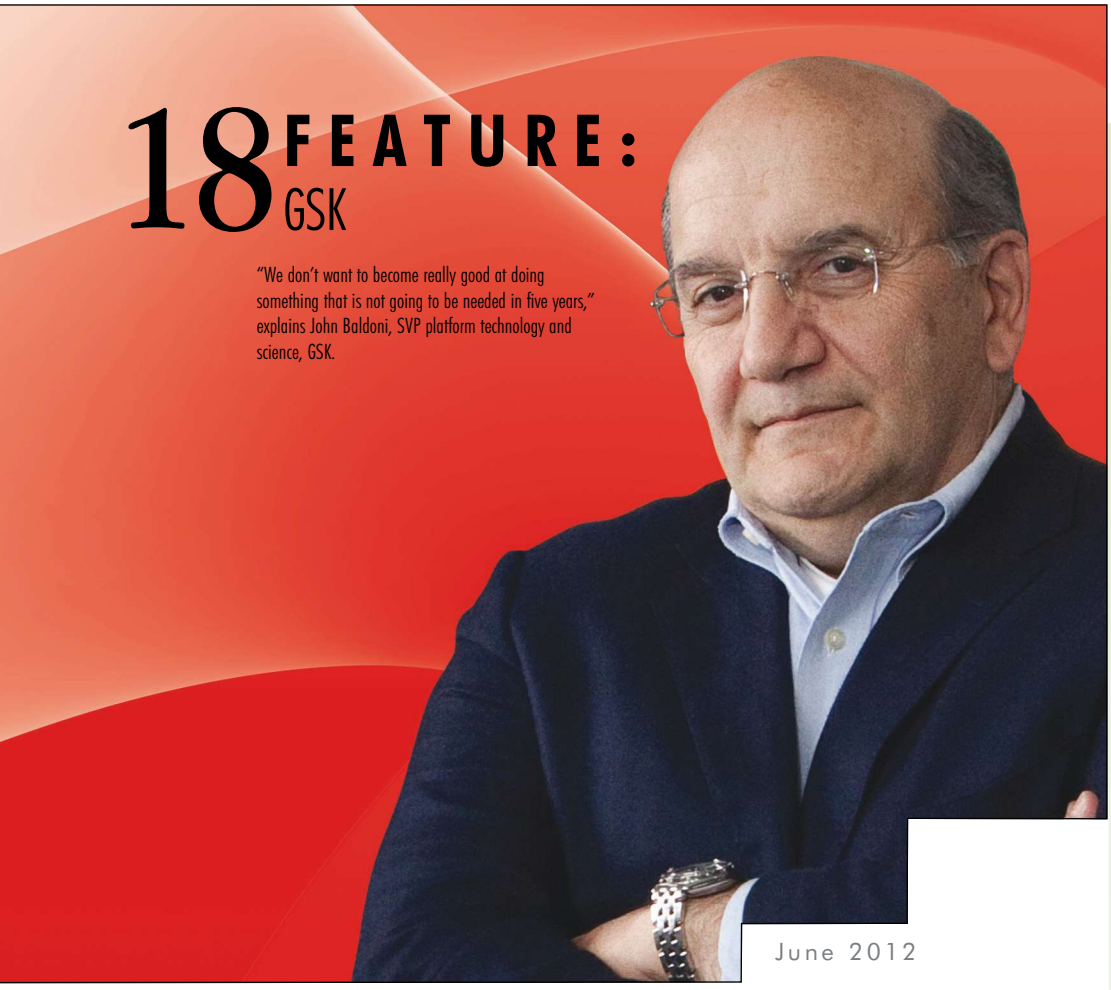

18 FEATURE: GSK

"We don't want to become really good at doing something that is not going to be needed in five years," explains John Baldoni, SVP platform technology and science, GSK.

June 2012

Welcome to *Life Science Leader*

CONTENTS

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EDITOR'S NOTE

Looking For Innovation Inspiration?

According to Steven Johnson, author of *Where Good Ideas Come From: The Natural History of Innovation*, cities have historically been great drivers of innovation, because when people gather in close proximity, collaboration and ideas flow more easily. Given the advancements in communication technology, being in close proximity is not as important to spur innovation as perhaps it once was. In addition to communication, key drivers to innovation are teamwork and entrepreneurial leadership.

Researchers at the University of Nebraska-Lincoln investigated innovation and the impact on which teams and leadership have. You might be surprised to learn that organizational environment, team member characteristics, and team design were not among the variables listed as having a significant impact on team success. Those which did impact team success include demand of task, goal clarity, group process, understanding by team members of the different ways people work, and the project leader. This doesn't seem like new information, since I was introduced to *The Wisdom of Teams*, written by Jon Katzenbach and Douglas Smith, more than 10 years ago. In my own experience with high performance teams, in many instances, the team leader was not appointed but emerged naturally through the dynamics of team interaction. According to Connie Reimers-Hild, Ph.D., and Susan Williams, Ph.D., faculty members of the University of Nebraska-Lincoln, the keys to innovation in the 21st century are teamwork and entrepreneurial leadership. Reimers-Hild and Williams see the fundamental goal of an entrepreneurial leader as creating an atmosphere of innovation while helping followers to become more entrepreneurial.

This month's *Life Science Leader* magazine is filled with entrepreneurial leaders. For example, Deirdre BeVard, VP development operations for Endo Pharmaceuticals (NASDAQ: ENDP), reveals some of the strategies her company is using to create and sustain an innovative culture — see page 24. Another entrepreneurial leader, John Baldoni, works for GlaxoSmithKline (NYSE: GSK). Learn how this SVP of platform technology and science R&D created The Seekers — an idea-generation team developed to stimulate disruptive innovation and serve as a catalyst for not only creating tipping points, but creating them sooner — see page 18. Want more innovation inspiration? Check out this month's Leadership Lessons article by Vijay Govindarajan, coauthor of the recently released *Reverse Innovation: Create Far From Home, Win Everywhere*. Govindarajan was kind enough to send me three signed copies of his book to be given away in our monthly Ask The Board feature. Perhaps you will get a book to take while on holiday, along with the most recent issue of *Life Science Leader*, so you can generate some ideas in addition to working on your tan.

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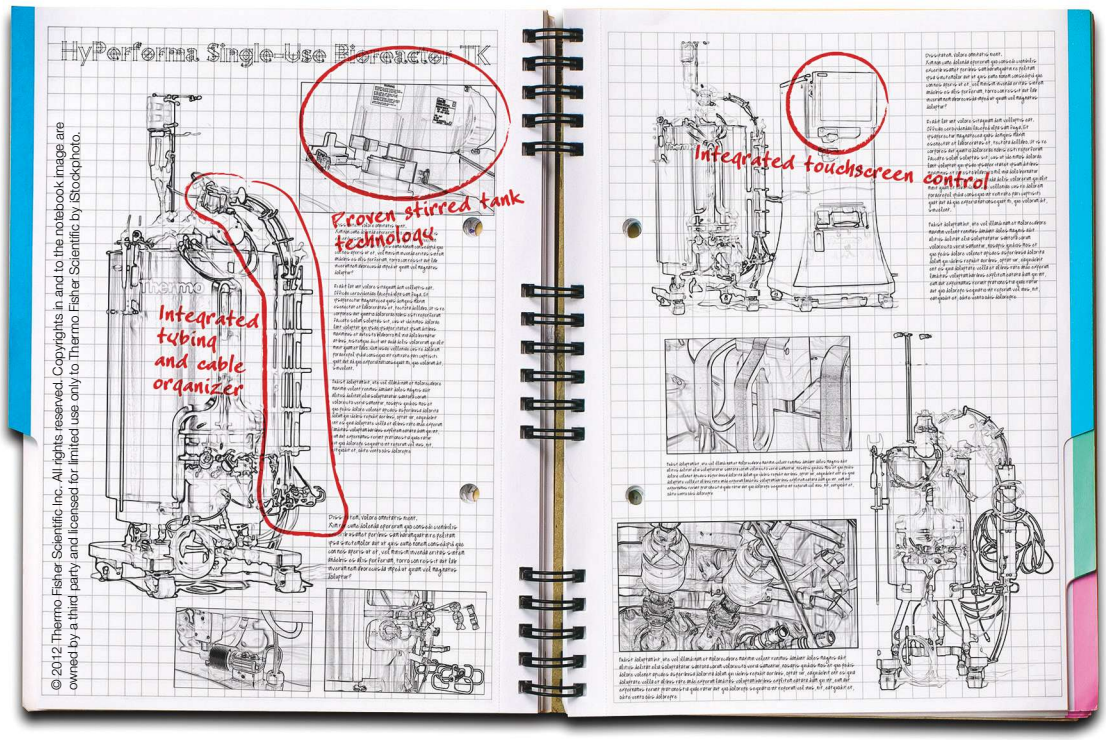

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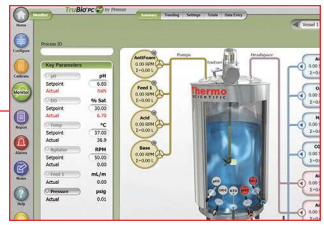

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ASK THE BOARD

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

Q: What was the most important thing you discovered when building your company?

That's easy. Raise all the money you can, when you can. When we started Sequella, we raised our first investor round before we had acquired any technology. The round was to enable us to license in several technologies we'd found in universities. Because we had no IP at the time of the round, we decided to raise only $1 million, which we calculated would let us acquire at least one of our desired technologies and fund us for a year of operations. Our intention was to raise additional capital when we actually owned the IP. Then the tech bubble burst and investment stopped dead. We managed to bootstrap our way through the financial crisis, but we missed several late-stage opportunities, and our cash shortage lengthened our product development timelines, thereby prolonging time to revenue.

Dr. Carol Nacy
Dr. Carol Nacy is CEO of Sequella, a private company that develops new anti-infective drugs. She was formerly CSO at Anergen and EVP/CSO at EntreMed. She previously directed research in tropical infectious diseases at Walter Reed Army Institute of Research.

Q: What recent management trend do you believe brought little or no value and yet companies eagerly adopted and implemented?

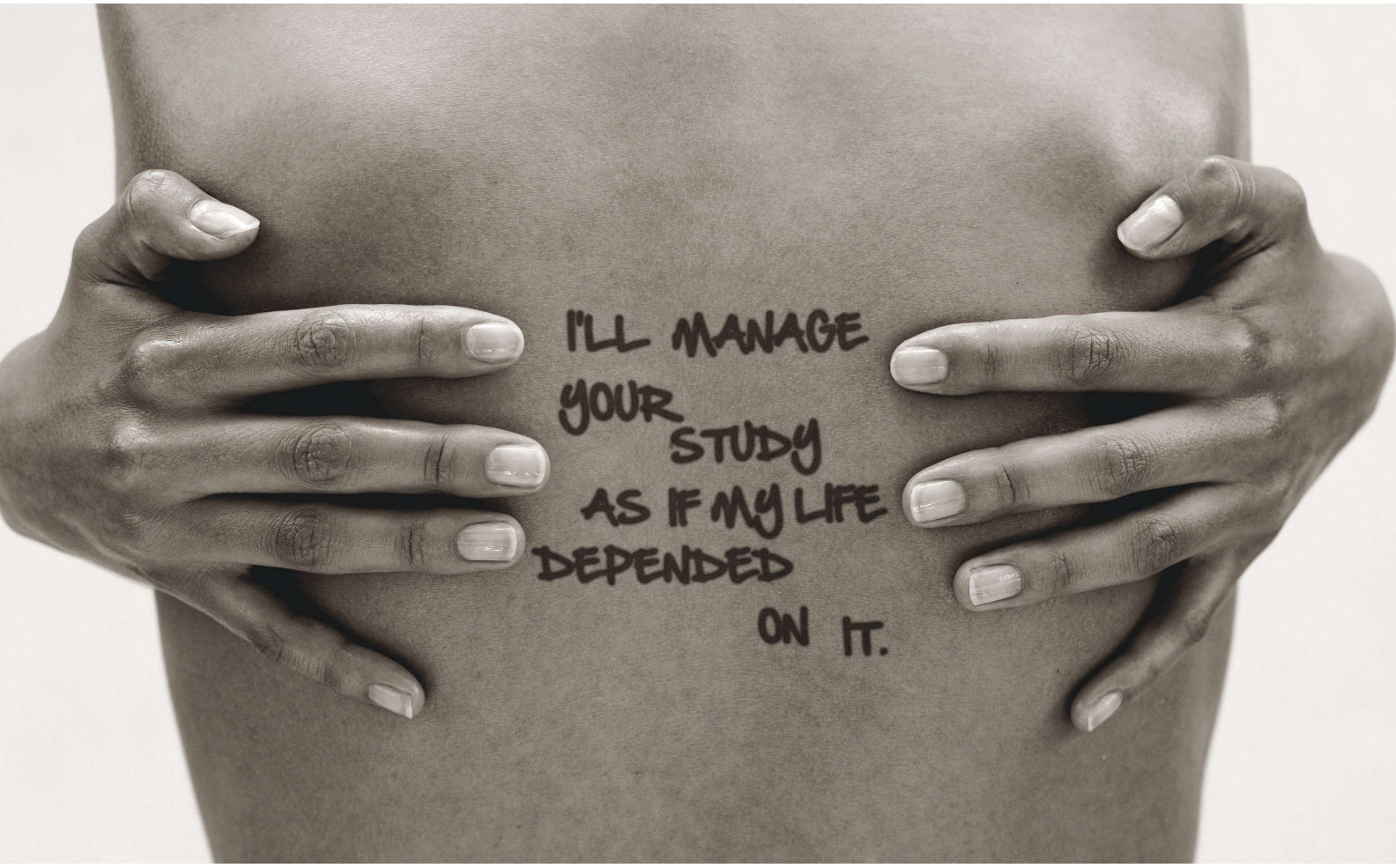
What is coming sooner than later will be the hiring of more employees because employees who are working are stretched thin. That is a good sign. A bad sign is that some hiring managers are making it known that they will not hire anyone who has been out of work for more than six months. That makes no sense given the fact that 14 million employees have been laid off in recent years. Many of those workers are fine contributors. They need to find employment, and they have talents and skills employees can use.

John Baldoni
Baldoni is an internationally recognized leadership development consultant, executive coach, author, and speaker. John teaches men and women to achieve positive results by focusing on communication, influence, motivation, and supervision.

Q: What performance measures have you found useful when implementing strategic collaboration toward portfolio optimization?

Typical performance measures are certainly the sales volume of the collaborator's portfolio by the existing sales and distribution channels, but also any synergistic sales coming from the collaboration. Most commonly the intent of the collaboration is to fill one's own portfolio gap, and with it, to access a new customer base. But the goal is also to introduce one's own portfolio into new accounts, due to the fact that the collaborator's equipment may need such products to complete a unit operation or process. The fulfillment of the customer's request to gain access to a product or service bundle is another measurement, probably the most important. To summarize: Measurements commonly used are incremental sales revenues, new customer relations, profitability measurements, distribution channel expansion into potentially new regions, and competitive advantage measurements.

Maik Jornitz
Jornitz is founder of BioProcess Resources and senior VP at Sartorius Stedim North America. He has nearly 25 years of experience, focusing on biopharmaceutical validation, optimization, and training in sterilizing filtration.



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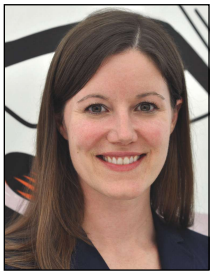

OUTSOURCING INSIGHTS

Strategic Partnering For Innovation

By Kate Hammeke, research manager, Nice Insight

The drug development industry has benefited greatly from the practice of outsourcing. And as the desires and demands on vendors by pharmaceutical sponsors have evolved — from reducing costs to augmenting expertise, to offering competitive advantage — contract services providers have evolved to meet the challenges. But is the maximum benefit being reaped from outsourcing? Innovation experts would say, no. Rather, the global economy/relaxing of trade borders, combined with the strengthening of patent laws in developing nations, have just started to provide the right environment for strategic partnering to drive innovation.

The definition of innovation — the creation of better or more effective products, processes, technologies or ideas — ties closely with the common goal among the various players in the drug development industry: creating better, more effective, and affordable medicines. Consequently, it makes sense that a CRO's or CMO's innovativeness is an important factor when evaluating potential vendors for strategic partnerships. When responding to Nice Insight's Q1 2012 pharmaceutical and biotechnology outsourcing survey, 10% of respondents stated that innovativeness was the most important attribute when selecting a CRO or CMO.

A MECHANISM FOR INNOVATION

Historically, the drug development process hasn't been a completely transparent, collaborative undertaking. Instead, managed risk, intellectual property, and profit were focal points for contract negotiations between the sponsor and supplier, often suppressing any true opportunities that might be leveraged from a strategic partnership. When these concerns take a backseat to driving sustainable growth, strategic partnerships become a mechanism for innovation.

Innovation through strategic partnering is a fluid and flexible means to sustainable growth, and complementary to the more traditional forms of growth. Organic growth of a business is often slow and requires patience, while expansion through the acquisition of complementary or competing businesses requires substantial capital. However, growth through strategic partnering has low financial barriers, and as discussed in the March and April editions of Outsourcing Insights, some of the operational barriers have been resolved through harmonized regulatory guidelines, improved education systems, and free trade. Of course, these partnerships still require significant due diligence, as the business will become an extension of the sponsor's brand.

Innovation through strategic partnering is a fluid and flexible means to sustainable growth.

HOW INNOVATION RANKS

Survey respondents who ranked innovation as their number one criteria for partner selection were most likely to come from the biotech sponsor segment (32%), followed by Big Pharma (24%) and emerging/niche/start-up pharmaceutical companies at 19%. Interestingly, it was outsourcing executives from large companies — 44% worked for a business with 500+ employees — who ranked innovation over quality, reliability, productivity, regulatory, and affordability (listed in their respective order).

Among these innovation advocates, outsourcing partners were most frequently engaged during the discovery (51%) and preclinical (49%) phases. This practice makes a lot of sense, considering it is during these phases that new technologies or breakthrough science, such as high throughput screening and proteomics, have the greatest potential for impacting pipeline vitality. It is also a reflection of how the evolution of outsourcing R&D during the past decade — which has grown from approximately $9.3 billion in 2001 to $25.4 billion in 2010 — will continue to mature. A natural byproduct of this maturity is the strengthening of the outsourcing relationship from one based on cutting costs to one based on adding resources that create value, which will, in turn, improve the competitiveness of both parties.

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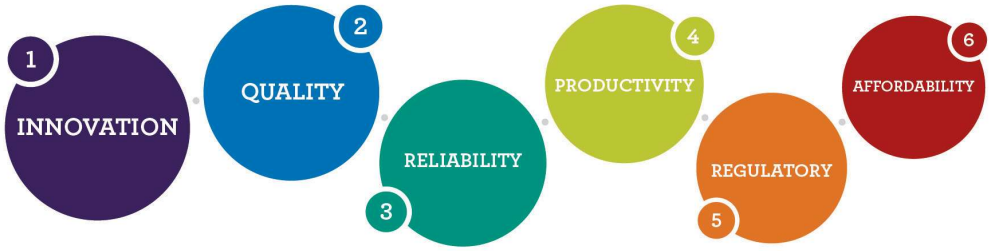
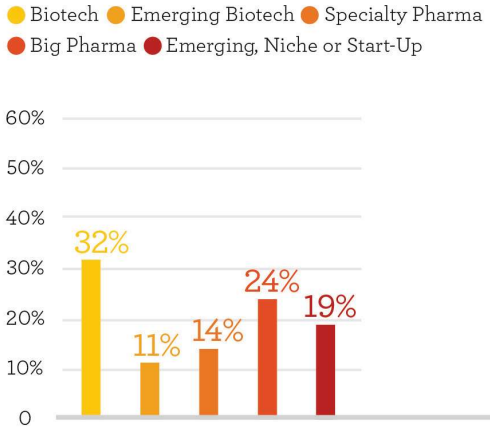
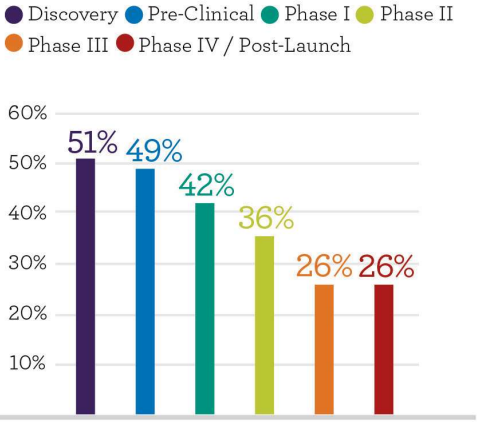
Ranked Order of Drivers Among Innovation Advocates



Innovation Advocates Work for the Following Types of Companies



Innovation Advocates Engage Outsourcing Partners During the Following Phases



Survey Methodology: The Nice Insight Pharmaceutical and Biotechnology Survey is deployed to outsourcing-facing pharmaceutical and biotechnology executives on a quarterly basis/four times per year [Q1 2012 sample size 3,523]. The survey is composed of 750+ questions and randomly presents ~30 questions to each respondent in order to collect baseline information with respect to customer awareness and customer perceptions on 300 companies that service the drug development cycle. Over 1,200 marketing communications, including branding, websites, print advertisements, corporate literature and trade show booths are reviewed by our panel of respondents. Five levels of awareness from "I've never heard of them" to "I've worked with them" factor into the overall customer awareness score. The customer perception score is based on six drivers in outsourcing: Quality, Innovation, Regulatory Track Record, Affordability, Productivity, and Reliability; which are ranked by our respondents to determine the weighting applied to the overall score.

If you want to learn more about the report or how to participate, please contact Victor Coker, director of business intelligence at Nice Insight, by sending an email to niceinsight.survey@thatsnice.com.

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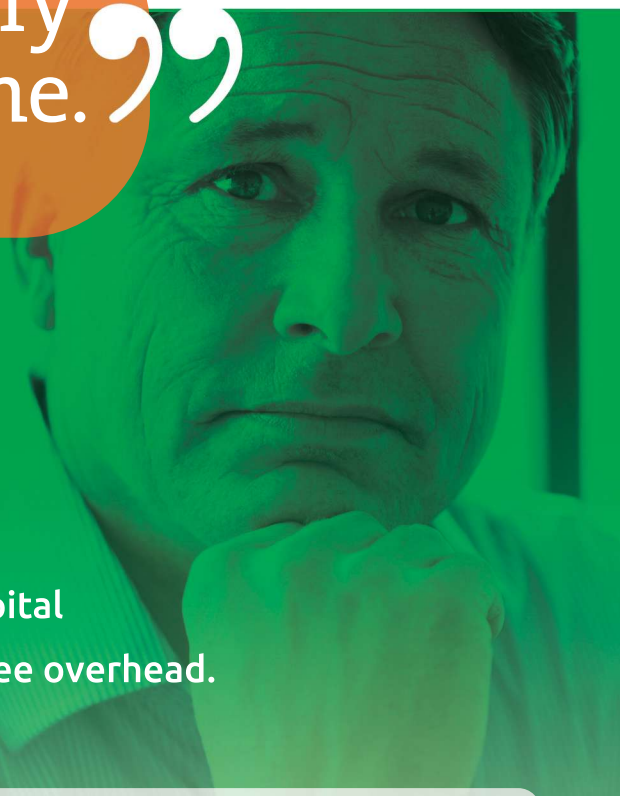

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BIO DATA POINTS

Biopharma Hiring Trends In The Right Direction

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

Over a quarter of global biomanufacturers are having problems hiring and retaining their production staffs. Data from our newly released 9th Annual Report and Survey of Biopharmaceutical Manufacturers indicates that the industry is experiencing hiring difficulties, but is now willing to invest in staffing and training to fix the problems. For example, the 302 global biotherapeutic developers and CMOs we surveyed said that, on average, they would spend 2.6% more on hiring new operations staff and 2% more on hiring new scientific staff this year. Although these are both decreases from last year, they represent a sea change from 2009 and 2010, when hiring budgets were mostly expected to decrease (by more than 3% in one instance). Indeed, although these are lower budget forecasts when compared to last year, current budgets may be simply seeing some natural corrections or leveling-off after the generally larger increases last year. Clearly, though, with hiring budgets looking up for the second year running, the industry has rebounded from a more difficult economic time.

Behind this predicted budget growth is a recognition that the right employees are critical on the operational end. Indeed, this year, when we asked survey respondents their top operational changes for 2012, 1/3 (including an impressive 51.9% of CMOs) said they would increase their number of production operation employees, up from 26% just two years ago. By comparison, just 1/4 said they would cut hiring at their facility.

If the right employees can boost production operations and efficiency, then the lack of key staff can have the opposite effect. When respondents were asked which factors are likely to create biopharmaceutical production capacity constraints at their facility in five years, the top reason, cited by 27.7% of respondents, was "inability to hire new, experienced technical and production staff." The inability to retain this staff was noted by 22.6% of respondents. Recent contamination events in the industry have highlighted the need for hiring and retaining experienced scientific staff who have experience in cell culture and purification as well as operating technologies like pasteurization and disposables.

The continued growth and importance of manufacturing sites for biopharmaceutical production means that more process development is being done, relative to basic research. As in prior years, R&D staff are continuing to experience cuts, and some are moving more toward applied research, manufacturing operations, or process development. This can be a difficult transition for some scientists. To meet industry needs, more importance will need to be placed on transitioning research-oriented staff to the needs of companies producing biologics.

This pattern is evident when we look at the data on where respondents expect new staff to be hired this year: According to our survey results, one-third of new staff will be hired in production operations, while 21.8% will be hired for process development and R&D. By contrast, basic R&D will account for just 13.9% of new hires, down from 18.5% a year ago. Production and process will continue to be the areas of focus for years to come, too; when asked where the new staff will be hired in production facilities in five years, 33.9% said in production operations and 22.8% said in process development and R&D, compared to just 16.2% for basic R&D. Regulatory hiring, which jumped to 20.9% of predicted hires this year, will fall back to 15.7% by 2017, according to our respondents.

PROCESS DEVELOPMENT PROFESSIONALS MOST IN DEMAND

We also surveyed where hiring will take place in 2017. Although production and process professionals are slated to account for almost three in five hires over the next five years, that doesn't mean they are easy to find. Indeed, while there has been a steadily increasing demand for scientists with operations and process engineering backgrounds, there has not been an increase in the number of scientists moving into these fields. Separately in the study, when we asked respondents which job positions at their facility they are currently finding it difficult to fill, hiring of process development professionals was the most commonly cited area. This was especially true in the case of upstream process development.

THE DATA PAINTS A MIXED PICTURE

In many ways, the results of this year's survey show a bright hiring future. Budgets for hiring are clearly up, and biomanufacturers and CMOs alike are recognizing the productivity and efficiency benefits of hiring employees with the right skills. And yet, while it is not surprising to see that the top three most-difficult-to-fill positions involve process improvement and engineering specialists, it is discouraging that no major changes appear to be occurring to fill these vacancies. The way these skilled employees are being produced is often through internal training, which leads to "poaching" from one company to another. In order to break this cycle, stronger relationships between employers and leading universities will have to be forged.

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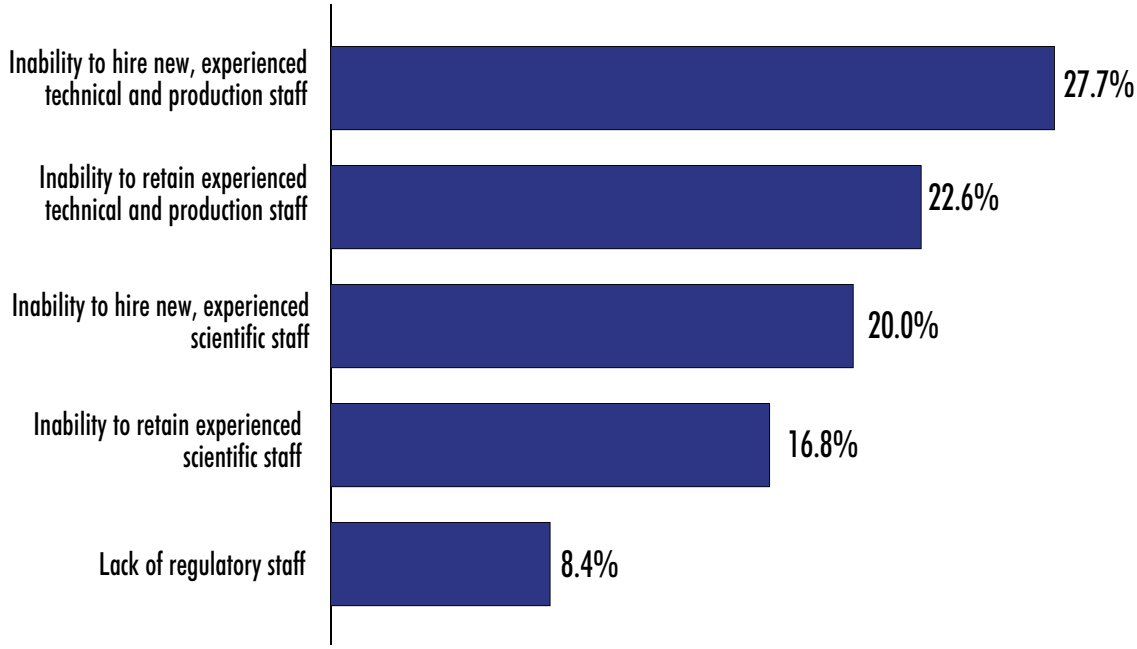
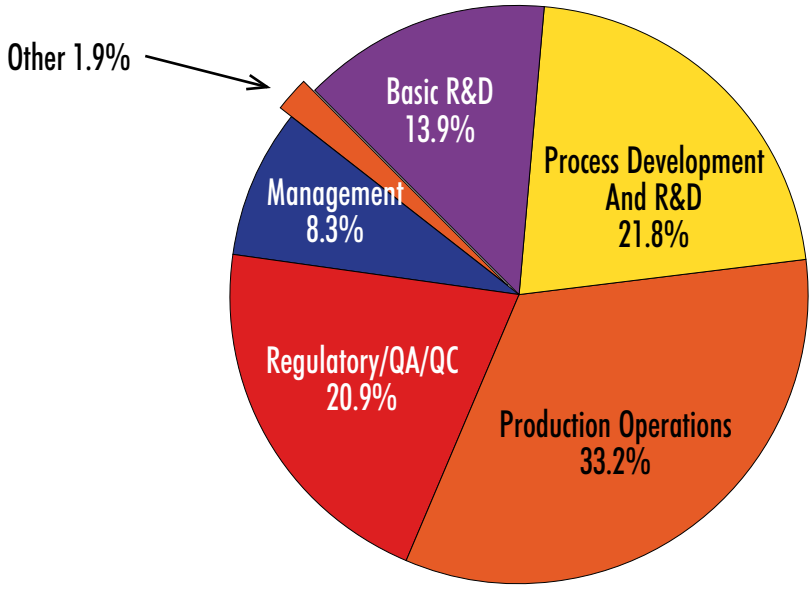
Factors Likely To Create Bioproduction Capacity Constraints In Five Years (by 2017)



Where Will The New Staff Be Hired In Biopharmaceutical Production Facilities? % Hires In 2012



Survey Methodology: This ninth in the series of annual evaluations by BioPlan Associates, Inc. yields a composite view and trend analysis from 352 individuals at biopharmaceutical manufacturers and CMOs from 31 countries. The methodology also encompassed an additional 186 direct suppliers (vendors) of materials, services, and equipment to this industry. This year's survey covers such issues as current capacity, future capacity constraints, expansions, use of disposables, trends and budgets in disposables, trends in downstream purification, quality management and control, hiring, employment, and training. The quantitative trend analysis provides details and comparisons by both biotherapeutic developers and CMOs. It also evaluates trends over time and assesses differences in the world's major markets.

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

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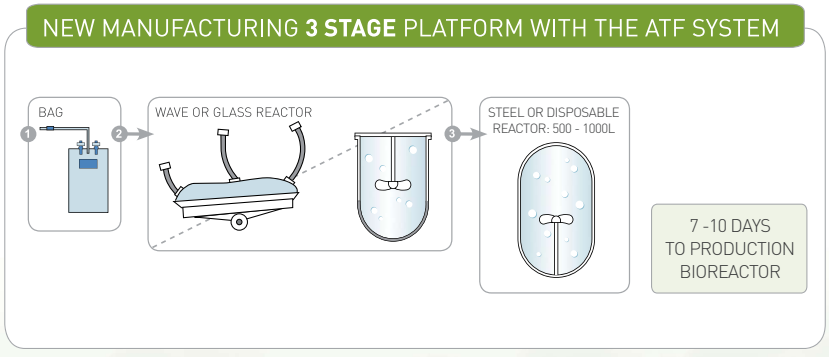

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(L-R) Magalie Rocheville, John Baldoni, and Lee Shorter of GSK

GSK's Seekers Of Disruptive Innovation

By Rob Wright

What is GlaxoSmithKline (NYSE: GSK) — the seventh largest pharmaceutical company in the world — doing to become even more innovative? Just ask John Baldoni, SVP platform technology and science (PTS) within GSK R&D. Baldoni is the creator of The Seekers — an idea generation team developed to stimulate disruptive innovation and serve as a catalyst for not only creating tipping points, but creating them sooner.

A tipping point is a term coined by Malcolm Gladwell in his bestselling book of the same name. It signals a key moment of crystallization that unifies isolated events into a significant trend. It can be used to explain a range of phenomena, e.g. the rise in popularity of seemingly innocuous products to the origins and spread of most major epidemics. Tipping points just don't happen by accident. They usually have a basis in being able to be traced back to a small group of individuals who can be classified as "Connectors." Baldoni and the Seekers explained to me the impetus for the Seeker program, how they structured it, and what they learned — including some interesting pitfalls — in their search for innovation.

EPIPHANY LEADS TO PROGRAM CREATION

Inspiration often comes at times and from areas we least expect. This was certainly the case for Baldoni when he came up with the idea for the Seekers. Baldoni, trained in enzyme chemistry, was visiting his son who lived near a university. He decided to stroll through the school's science building early one morning. As he walked the hallways, looking at the posters and papers being published, he noticed some very fascinating work. He also observed that there seemed to be a disconnect in that much of the work was from individual labs. He began to wonder why the researcher of one poster hadn't connected with the researcher

of another, located just a few offices down the hall, as they seemed to have potential synergy. As he reached the end, Baldoni thought to himself about how this group of brilliant chemistry professors, located in the same building, were apparently failing to see the potential transformational type of step-change possible on those walls. "That trip was the epiphany for me," he states. "Here is a group of very smart, successful academics who don't seem to connect. This must be happening in many places, including my organization."

Back at his open-plan office, a space he shares with about 20 other people, Baldoni pondered the process of innovation, the means by which it naturally evolves and how it could be stimulated. He began to reflect by classifying innovation into three buckets: continuous, evolutionary, and disruptive — all important and necessary. For example, continuous innovation is something that should be taking place all the time, i.e. as people gain more knowledge and experience in their jobs, they naturally develop means of improving efficiency. Evolutionary innovation is a process whereby people realize that there are other better ways of doing things, and through experimentation and asking questions, they make a conscientious effort to change. Disruptive innovation is revolutionary. It can completely change the way something is done, eliminate a need, answer a heretofore unanswerable question, eliminate required infrastructure, and produce dramatic result with a variety of business benefits. If you have ever reflected on the process by which a project evolved from conception, implementation, and course correction all the way through its completion, you have probably thought of things you would do or approach differently. Perhaps, there exists an evolutionary point of divergence, a tipping point that could accelerate the project, possibly taking it in a totally different direction. "Knowing what I know today, what would I do differently?" Baldoni asks. For him, the answer was the realization of the important role people and culture play in the innovative process and how they could be intentionally changed to find or create a tipping point sooner. Baldoni believes many good companies, given a positive trajectory, will usually continue to evolve in a positive direction with little or no intervention taken from the latest scientific breakthroughs. "I decided I was not going to let innovation evolve in only that way," he affirms. "I decided to create my own tipping point, a different way of thinking about disruptive innovation." He envisioned a process where instead of innovation naturally occurring in 10 to 15 years, it would do so in less than 5. The challenge was to create a culture of disruptive innovation without altering his department's necessary, and equally important, emphasis on continuous and evolutionary innovation. The solution — The Seekers — a team of individuals selected to go out into the world, seek ideas, and bring them back to GSK for evaluation.

SEEKERS — GETTING STARTED AND BRINGING PASSION BACK TO GSK

Seekers typically start investigating topics by browsing the Internet or attending external conferences. Once they have a group or company in mind, they make contact. "In many organizations, it is hard to find the right people to talk to, so introductory phone calls to pitch our interests is critical," says Magalie Rocheville, one of the Seekers. When meeting with companies, often outside the pharmaceutical industry, the Seekers ask "What if" questions, such as, "Do you ever foresee a day when people won't use paper books?" or "If you wanted to put a person on the moon without a rocket, how would you do it?" Being a successful Seeker isn't about thinking up questions alone. "It's about how you interact with people," says Rocheville. "It's about being able to get people to be willing to meet with you, communicate, and share their ideas in a fluid and passionate way. That makes all the difference." Seekers are not only interested in the company's current research, but curious to hear about the company's predictions on where particular fields are likely to go next and why. This helps them understand where areas are likely to mature and what "may" be possible one day beyond what is apparent today.

According to Lee Shorter, another Seeker, the Seekers are interested in many aspects of nonpharma company business models. For instance, what can GSK's Platform Technology and Science group gain from working with industries that do not compete in the same market, i.e. a market-leading electronics company. "Can advanced electronics or material science or nanotechnologies apply to biological or chemical questions faced in the pharma world?" ponders Shorter. Seekers are also curious to find out what underlies a company's success at innovation. In particular, they are interested in better understanding the costs of success and necessary failures for a given product launch. "There may be parallels to be drawn with the issues of late-stage drug attrition for instance," explains Rocheville.

With nearly a year of seeking under their belts, Shorter and Rocheville realize they may not continue to remain in this role, which is okay. "A little bit of what we are trying to bring back to GSK is the passion in people who are out in the world developing ideas," says Shorter. "Our role as directors is to create an environment within GSK R&D so scientists can be passionate about their jobs, whether they are a Seeker, working in the line, making tablets, or doing assays." So, in addition to bringing back ideas and catalyzing tipping points, the Seekers are adding their unique passion to that of many others across GSK and creating a reinvigorated 297-year-old organization. Not a bad way to spend a day.

INNOVATIVE APPROACH TO INNOVATION TEAM

As Baldoni began to formulate the Seeker program, he was given a variety of suggestions on how to operationalize it — Lean Six Sigma, develop an organization structure, put an idea engine on the Web, etc. "As I was being given suggestions, I was struck by how many people desired to do things better, and yet, these same people were unwilling to let go and stop doing something else that in time may no longer be necessary." During a leadership meeting, Baldoni stated it this way, "We don't want to become really good at doing something that is not going to be needed in five years. We want to become really good at doing something that might not be doable now, but our judgment is that it is going to be important in five years." Considering all of the suggestions on how to structure the Seekers, he did the opposite, electing to set up the program in

a very unstructured way. With the counsel of a colleague from the HR department, Cynthia Orme, he decided to use an emergence process for the Seeker program — meaning, the job description they developed and the organization structure was not overly defined for the Seeker position. "We defined it enough to pique interest and posted it to fill the position," he attests. This lack of definition was deliberate because Baldoni was seeking to find people who were naturally curious and willing to take risks. About eight people were intrigued enough to show up for an interview, and each person had different expectations. During the interview, Baldoni asked, *If you had a blank sheet of paper and were in charge of creating a tipping point or a catalytic event in a department such as ours, what would you do?* "Three really hit the nail on the head, and those are the three we picked — Magalie Rocheville, Graham Simpson, and Lee Shorter."

Once selected, Baldoni provided them with the following direction — don't go where everybody else goes. Talk to people who aren't necessarily in the pharmaceutical industry. Talk to people who are early in their careers, so they don't have built-in biases as to how things get done. Go to people who are late in their careers who have a track record of reinventing themselves in different areas. Baldoni advised the Seekers to start by visiting the chemistry department he first walked through to see if they made the same connections he did. In addition, he asked them to research a class of materials that have not yet been used in the drug discovery or development process. One question the Seekers would ask was how they would know if they had found something of value. Baldoni's answer, "You will know it when you see it. If you say 'Wow', that is when we start getting interested."

Baldoni gave a lot of freedom to the Seekers to set up their own team in a self-directed and empowering way, helping to favor creativity and ingenuity. "A process for something like this automatically constrains what you want to get out of it," he attests. With that in mind, he asked the Seekers to create an advisory board consisting of one external person and four internal employees of GSK who review what the Seekers are doing and give them advice. "It's an advisory board, not a decision board," he clarifies. During the first board meeting, he explained to the group, "If you don't see the Seekers doing what you would do, that is okay. Your role is only to provide advice." Along with the advisory board, he implemented a vetting

process for ideas, which involved the Seekers pitching ideas to him and then discussing if additional research was necessary. If the idea was interesting and worthy of pursuit, depending upon the cost of testing, Baldoni could elect to pursue and manage it out of his budget. If an idea would involve a significant investment beyond Baldoni's budget and still seemed worthy of additional consideration, they would then present it to the GSK Technology Investment Board. If approved, a team would be assembled to work out the plan as to whether to manage the process externally or internally and create milestones and associated payments. As the Seeker program evolved through the process of emergence, Baldoni discovered early some pitfalls to avoid.

WHO ARE THE SEEKERS?

Magalie Rocheville and Lee Shorter, Disruptive Innovation Seekers, are two people selected by John Baldoni to develop GSK's Platform Technology and Science (PTS) Seeker program. Rocheville, based in the United Kingdom, has been with GSK for over 10 years with experience in leading several innovation opportunities as well as drug discovery programs for PTS. She has a Ph.D. in pharmacology and belonged to the department of Assay Development within PTS. Shorter, a 26-year GSK veteran based in the United States, has a Ph.D. in chemistry and experience in pharma and consumer healthcare product development, as well as open innovation. The diversity of their backgrounds is part of the beauty of the Seeker program. Rocheville comes from the early drug discovery phase and a biology perspective, while Shorter comes from late phase product development, bringing a chemistry perspective. Combined, they span the continuum of line functions that make up PTS, which allows them to ask each other the naïve questions and thus brainstorm an idea from an open-minded point-of-view. Both admit that taking the position of Seeker has been exciting, fun, and thus far "a dream job."

According to Shorter, becoming a Seeker seemed a natural career progression. For Rocheville, the attraction was not only the freedom of being able to investigate problems beyond her distinctive function within GSK, but an extension of her appointment to the PTS technical innovation work stream from the previous year.

According to the Seekers, the process of getting the position was tough. "They were looking for people with an open mindset, who were extremely curious, driven, and having the ability to see and make links beyond what others might be able to do," explains Rocheville. These attributes were assessed during a number of interviews and brainstorming sessions with members of HR and Baldoni. Meanwhile, in the back of their minds, the Seekers were cognizant of the risks involved in taking the position. "The risk for us," explains Shorter, "was that we were going into an unknown, moving outside existing silos, and not necessarily knowing the future of the position within the organization." The initial Seekers were selected based on their ability to think and act differently. For example, according to Rocheville, the objective of a Seeker is not to go out and look for technology. "We look at problems and try to find the 'right' questions to ask ourselves," she explains. "During the process, we aren't just challenging ourselves, but challenging others to have the willingness to change." The Seekers find that the conversations start easily when they visit people. It starts with the business card and their job title, Disruptive Seeker, which they say usually elicits questions, enthusiasm, and curiosity.

LEARNINGS, PITFALLS, AND MISTAKES TO AVOID

One of the Seekers' favorite things to do is Friday afternoon "What If" sessions, where the team contemplates different ways of approaching a project. For example, what if you couldn't use water to do quantitative sample analysis? Or, could you select a lead series of drug candidates without knowing the structures in the lead series? Or, can you imagine other formulations to therapeutics other than tablets? This was one of Baldoni's early learnings when developing the Seeker program. "During brainstorms, make sure you bring in people who don't have a preconceived notion of how it should end up," he advises. Other advice to creating your own Seeker program: Make sure people are comfortable with an emergent style of learning and implementation. Spend time up front defining the kind of individuals you want. Build the team with a diversity in background, personality, and preferences. "Go with your gut in this instance," he contends. "Put your handheld mirror away so you aren't finding people like yourself. Look for people who are different, but can work together in harmony. Trust them." Finally, Baldoni ensured that the Seekers had the support of senior management, including Moncef Slaoui, then chairman of GSK Pharma R&D, and Patrick Valance, now president of GSK Pharma R&D. "The entire R&D senior leadership team supports innovative and transformative ways of working," he affirms. Slaoui met with the Seekers and expressed his enthusiasm for the program, encouraging them to seek things that would transform how GSK translates its work to patient benefit.

Baldoni suggests finding Seekers who are enthusiastic about future possibilities and lateral thinkers who are extremely curious, nearly to a fault. Finally, keep in mind that Seekers seek, while implementers implement. The role of the Seeker is to gather ideas and, with the help of the advisory board and Baldoni, assess their viability. Once that has been determined, the company then places the idea in the hands of implementers — people who are excellent at project management. Baldoni sees these as two distinct tasks not to be mixed.

Baldoni cautions that you shouldn't think that a process is transformational and disruptive just because it made something go faster or cheaper. It may still be beneficial, but if it doesn't redefine the paradigm of an operation, it is not a disruptive innovation. Another potential pitfall is the possibility of a Seeker getting caught up in strategizing how to implement the idea. Some of the ideas brought back by the Seekers will naturally have a very low likelihood of being implemented but are meant to spark other ideas. Baldoni says to be certain to ensure that everyone involved in the process is aligned with regard

to the risks associated with the implementation or commercialization of the idea, another potential pitfall. "People can talk themselves out of even trying to implement something simply because it is not in the time frame in which they think a return on investment is needed," he states. Another pitfall is focusing on the financials before actually understanding the scope of the opportunity or tying a technology to a specific compound, which could then die if the compound does not succeed.

The initial Seeker program began as a pilot in June of 2011 at an estimated cost of around $1.5 million, with the majority of costs being Seeker travel, salary, and any type of Phase 0 testing to see if an idea was feasible. Baldoni is already seeing some benefit from the approach. One of the original Seekers, Graham Simpson, found a technology that he felt could redefine the characterization of protein-protein interactions. He was so convinced of the merit of the approach that he authored a proposal to investigate it further, which was accepted by GSK's Discovery Investment Board. Simpson is now leading a small team to test his hypothesis. If successful, the Seeker, now turned investigator, may end up as an implementer, applying the technology in PTS. Baldoni is optimistic about a number of other Seeker tipping points, including infinitely adjustable chemical scaffolds to explore metastable protein conformations, integration of a number of unconnected technologies, and the application of emerging science in the petrochemical industry to pharmaceutical process chemistry. Based on its initial success, the program is going through the process of being adopted as an ongoing venture with the creation of the implementer component. In addition, a group has been carved out of Baldoni's organization to be an incubator of ideas, not just from the Seekers but from across his department.

Baldoni admits he made some mistakes, though, during the creation of the program. He regrets not having spent time informing the leadership team about the Seekers during start-up. Also, he confides, "I think the Seekers would agree that I did not spend enough good quality time with them early on. Luckily though, I didn't make the mistake of imparting my prejudice onto them as to what I thought they should do." The Seekers have identified over 30 fresh ideas spanning the continuum of drug discovery and development, performed more detailed investigations and due diligence on eight areas, and advanced four opportunities that have the potential of being transformational to business development colleagues, as well as internal or external funding bodies. Perhaps one or more of these ideas will lead to the next big medical breakthrough at GSK.

How To Create An Innovative Culture

Deirdre BeVard, VP development operations at Endo Pharmaceuticals, explains what it takes to boost innovation in a pharma company.

By Rob Wright

Endo Pharmaceuticals' (NASDAQ: ENDP) history dates back to the early 1920s. But having a lengthy history is no guarantee to a company's future success. In the pharmaceutical world of today, companies are seeking innovation — in spades. For some, the answer is outsourcing, while for others, the process involves creating centers of innovation and placing people in positions whose titles actually include the words disruptive and innovation. For Endo, the answer was to take a deep look into its corporate culture. Could a company that had a very traditional business model of developing 505(b)(2) or specialty generic drugs shift its culture to one of innovation, and if so, how?

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In 2010, Endo achieved total revenue of $1.7 billion, a 17.5% increase over 2009, earning shareholders $3.48 adjusted diluted earnings per share (EPS) — a 22.5% increase over the previous year. How does that compare in the industry? Well, the company is achieving EPS above the likes of Pfizer (NYSE: PFE) and Merck (NYSE: MRK), and its P/E ratio of 18.67 falls in between the likes of such powerhouses as GlaxoSmithKline (NYSE: GSK) and Novartis (NYSE: NVS). One of Endo's 4,900 employees, Deirdre BeVard, VP development operations, has some useful advice — don't focus on innovation or the innovative process. Rather, focus on eliminating the roadblocks that impede innovation, and then create an environment with the necessary infrastructure where innovation can thrive. And it all starts with leadership.

LEADERS OF LEADERS

One of the tenets of successful leadership is to give credit to others for success, which BeVard readily does. She credits the Endo culture change initiative and its early success to CEO David Holveck, who joined the company in 2008 — just one year prior to BeVard. When Holveck arrived, his goal was to redefine how Endo approached healthcare by making the company more diversified. Since 2008, the company's diversification strategy has been achieved through a series of acquisitions, including Indevus Pharmaceuticals, HealthTronics, Penwest Pharmaceuticals, Qualitest, and American Medical Systems (AMS). The company once focused on pain management now has two additional therapeutic categories, urology/oncology and endocrinology. But this acqusition strategy also brought with it a hodgepodge of cultures, presenting the challenge of how best to integrate them all into a cohesive enterprise. So, the first step in Endo's innovation culture change initiative was to determine the leadership attributes it values and wants to see in each and every employee. "Everyone in their role has some leadership responsibility, whether it is as a senior leader, a people leader, or an individual leader," BeVard says. With the help of HR, executive management landed on four key attributes — accountability, breakthrough thinking, collaboration, and customer focus — and developed descriptions for what those attributes look like at the various leadership levels.

The next step was the creation of a strategic alignment team, of which BeVard was a member. "Our role," she explains, "was to take these attributes and decide what behaviors we would want people to model." From there, the creation of criteria for screening new candidates began, as well as for evaluating the performance of current employees. By building leadership attributes into the performance management program, employees understand the importance of demonstrating expected behaviors.

To create culture change and gain employee buy in, Endo utilizes three R's — recognize, reinforce, and reward. Tying the leadership attributes to employee performance

BEVARD ON ENDO'S CULTURE CHANGE INITIATIVE

What have you discovered from being involved in this process? You have to prepare an organization for culture change, not just jump into it. The culture of an organization lives within its people, so the desire to change and the belief in that change has to come from the people doing the work every day. I constantly had reaffirmed that people just need the support, encouragement, and opportunity to meet their full potential. Most times, they surprise themselves with what they are capable of. There is creativity in everyone; we just need to create the environment where they can safely explore and then express that creativity.

What advice do you have for other executives attempting to implement a culture change? Find your zealots, get senior-level support, and then just get on with it. Culture change is hard and not really tangible. Most people want simple, straightforward solutions — things they can measure — but it's not that easy, and it can be uncomfortable. That's why you need zealots, i.e. people who are passionate about it and are not easily discouraged. They also need to be people who suspend judgment and give ideas a chance to grow before judging them as right/wrong, good/bad, or relevant/not. Since the change has to be adopted from all levels and supported at the top, you also need at least one (if not more) executive-level sponsor. This change will call for an investment of time, money, and resources, so you need to get the support of someone who can access those things or remove obstacles. You also need to be able to articulate and show how this change benefits the company and supports the company's business strategy. Many of the efforts have to be ingrained into the fabric of the organization, and that has to be modeled by the top levels of management. Then, just go. Just start to do things, and let go of previous expectations, so you can pull value from the things that work and the things that don't. Live what you talk about — reach outside your normal circle and comfort zone to other parts of the company in order to get new perspectives and others who want to help achieve the change. Be fearless, passionate, and persistent!

How did you go about preparing for your role in the process? I read, researched, and talked to many people inside and out of our industry. I viewed talks on TED (a nonprofit website devoted to the spreading of ideas and a repository for a wide variety of free video presentations) and from the World Innovation Conference, as well as subscribed to listservs from a number of different sites on innovation. One significant influence for me was Daniel Pink, author of *A Whole New Mind*. I use a lot of his concepts, tools, and techniques. It all resonated with me, and I love the idea of still relying on the left-brain side of what I do, but bringing in a right-brained approach. In his book he describes a notion of six senses, and there are two that really hit home with me: symphony and play. Symphony speaks to bringing things together. This is what we are doing at Endo — integrating pieces into an even more valuable whole. It also means crossing boundaries, connecting things that, on the surface, appear not to be related. It opens up so many possibilities. Play, well, who doesn't love to play? We work in a serious industry and under some pretty tight regulations and other constraints. We are in the business of improving people's health and improving their lives. That's serious stuff, so we must go about it seriously. However, we don't have to be so serious about ourselves. We can have fun while doing it. We can lighten up and still be taken seriously. I have noticed that when you add levity and playfulness it changes the mood and the environment. It allows more openness and freedom, and relaxed people interact more freely and offer up their ideas more readily.

evaluations is one example of this concept. The second part is a quarterly recognition program whereby employees can be nominated for consistently demonstrating any of the four attributes. Nominations are reviewed by a committee, and each one is assessed according to how the person met a specific business need — consistently — not just someone having a really good day. Winners are recognized at a special event. "Winners become, quite literally, the poster child for that attribute," states BeVard. Following the event, posters with the employee's picture are put up throughout the organization, noting the attribute the employee exhibits. All of this has combined to create what BeVard refers to as a "shared language" in the organization. "When we first started, if you walked down the hall and randomly asked people to describe Endo's culture, you would have gotten wildly variable responses," she affirms. "Today, if you do the same thing, you will hear the four attributes coming out of everyone's mouth. The leadership concept has gotten infused into the fabric of the organization."

ACCELERATING CULTURE CHANGE THROUGH LEADERSHIP

One of the leadership attributes identified, breakthrough thinking, is at the core of innovation. BeVard explains, "Regarding innovation, we are advancing on a business strategy that is unique. We cannot read somebody's memoirs on how they led their organization in this manner. We have to create the future."

Therefore, Endo initiated an accelerated leadership development program, which included 23 participants selected by the executive committee as high-potential leaders. BeVard was one of the participants. They were broken up into three project teams, all tasked to scope out, develop, and implement projects under short time constraints for specific company needs. "Every project was focused on advancing and unifying the culture of the organization," says BeVard. For example, one group was tasked with connecting people across the enterprise — internal communication. "That group came up with an internal video that profiles employees from all different parts of the company," she explains. The theme is "I am Endo." Another group was tasked with the cultural element of customer focus — external communication. "Their goal was to look at our customer service process and make sure we were sending a unified message," she states.

BeVard's group had to determine how to create an innovative culture. "For benchmarking, we started by looking outside the company," she states. The group began researching other

companies known for being innovative, such as Southwest Airlines, Netflix, Virgin, and Google. They read the book *Nuts,* which is about Southwest. They reviewed innovation articles in *Harvard Business Review*. They sought inspiration from Innovations Daily and a number of different websites, including the99percent.com. They watched presentations by Tony Hsieh, CEO of Zappos, and Clay Christensen, one of the world's foremost authorities on disruptive innovation. They met with the innovation consulting team. They even had a member of Google's creative lab in New York City, David Bryant, come to Endo (he was not paid, and he did this at his own expense) and explain the Google model. According to BeVard, Bryant provided her team firsthand insight about the fundamental elements of innovation that can be applied to nearly any organization. The team then "pressure tested" these elements by surveying Endo employees, asking questions such as: Where do you think innovation lives? How does it show up? Do you have any obstacles to it? "We discovered that people who are going to innovate, do so naturally," says BeVard. "You don't really have to do much for them other than get out of their way. You don't even have to set up special programs and special rewards, as the innovative process is an intrinsic reward for these folks." BeVard's team uncovered that most of the people who innovate are often willing to do it on their own time. But they also uncovered the things that pose potential roadblocks to creating an innovative culture — fear, environment, communication, and time.

LESSON LEARNED THE HARD WAY

Deidre BeVard, VP development operations at Endo Pharmaceuticals, is part of an advanced leadership development team involved in creating a culture of innovation. During the process, her team learned a valuable lesson the hard way. "My project team was focused on innovation and approaching things in a new way," she says. The team had embraced the concept of innovation with such vigor that they decided to take a vastly different approach when conducting a midpoint presentation to the executive management. Rather than doing a traditional PowerPoint presentation, the team used flip charts. Instead of standing at the front of the room, members of the team were dispersed throughout the room. The idea was to engage executive management by making them have to turn and focus on what the team was talking about. "It didn't work out so well for us," she states. The audience anticipated a more traditional presentation approach, which provided BeVard's team with two lessons — one, change is often resisted, and two, if you are going to do something different from the norm, let the audience know what to expect, to improve buy in.

Prep Your Audience

BeVard's advice from the above experience: If you intend to take a different approach to something, be sure to prepare the audience so they are not surprised. "You have to lay some groundwork and introduce the concept gradually," she says. "We didn't do that with our executive team. We just came out with this whole new creative approach, rather than telling them what we were going to do. We got a brutal critique, in front of the entire group. It was tough. It was uncomfortable." BeVard's team had to learn the very thing they were trying to teach — how to take critical feedback without personalizing it. "This was hard for a group of high-potential people used to succeeding," she admits.

Executive management also learned a lesson. "They had to learn to wait and not judge immediately," she elaborates. In the group's final presentation, they did revert to using a PowerPoint presentation, although it consisted solely of black slides with white words.

WANT INNOVATION? ELIMINATE ROADBLOCKS

Fear can take many forms and needs to be removed to stimulate idea generation. "Sometimes people are not comfortable putting themselves out there and sharing ideas," says BeVard. "For others, it is fear that their manager will reject an idea, or if their idea fails, it will reflect poorly on them."

With regard to environment, she says people often underestimate its importance in the innovation process. "We are not talking about building an office playground-like atmosphere," says BeVard. Instead, they created innovation stations — physical locations in a couple of the buildings that are equipped differently from your typical office. There is more vibrancy to the décor, and these stations include whiteboards, sticky notes, crayons, Think Pads, markers, and other tools to foster and facilitate the creative process. "People can just walk into one of these rooms, and there are things to help stimulate them," she explains. "It takes them out of their normal structured environment." These collaborative spaces are not to be reserved, so anyone can use them at any time to bounce ideas off each other.

Another roadblock to innovation is communication or, more precisely, the ability to capture and share ideas. How do you get the idea out there, past a gatekeeper, so it can be heard and expanded upon? Answer: Create an online collaboration tool designed to capture ideas. "This platform allows anyone in our company, just through access to our intranet, to submit an idea for a business solution," explains BeVard. "If they have an idea for a cost-saving solution or something else, they put their idea into this collaborative tool, even if it is not fully formulated." The idea submission triggers a process, assigning the idea to an advisor whose job is to guide them all the way through the process. This tool also facilitates online collaboration. For example, everyone within Endo has an online profile identifying their particular skillset. This allows people to search for folks across the organization who may have skills they think would be helpful in pursuing an idea, solicit them for feedback, or ask them to join the project. "It provides an opportunity — cross-enterprise collaboration — we didn't have before," says BeVard. "And they don't all have to be sitting in the same building." It also prevents an idea from being shot down by just one person (e.g. someone's direct supervisor).

Another roadblock to innovation is time. According to BeVard, people need to be given the time to innovate. "There have been a lot of things written about Google providing its employees 20% of their working time to be used for innovation on noncore

businesses," she says. For example, Gmail is one of the Google products that evolved from the 20% time concept. "Not that we are sitting in a pharmaceutical company and somebody is going to try to create the next Bose stereo," states BeVard. "It involves using 20% of one's time on things related to their core responsibilities." Endo is creating an environment where folks can actually carve out time for innovation and is removing the fear of management looking over their shoulder. "With that said," she clarifies, "if there is a critical business deliverable, obviously that takes priority. You have to use good judgment, but you also have to allow people time to get outside of their heads."

One of the last roadblocks to innovation is the word itself. When speaking with employees, BeVard found the word innovation to be quite intimidating to some. "We found that people thought that if an idea is not game-changing, then it is not innovative," she says. Her project team believed the process of innovation to rest on a continuum, from creative thinking on one end, breakthrough thinking near the middle, and innovation on the other end. "The reason we did this is because we wanted to make sure everyone in the organization could relate," explains BeVard. "An administrative coordinator in a department might hear that we are trying to be more innovative and think, this is not me, that is the scientific group, or that is the commercial team." The team defined these various forms to improve employee understanding. For example, creative thinking is a way of approaching a problem in a new way. Breakthrough thinking is more of a radical new approach that overcomes constraints or disregards perceived constraints. Innovation takes it to the level of coming up with a process or an invention that results in a good service offering of some sort that has value to the customer. "That perception of value by the customer is what really defines it more as innovation," she affirms. "It has to be actionable and very much change their value proposition."

BeVard says that Endo is not trying to turn every employee into the world's most creative inventor. The company is trying to cultivate an environment that allows those with ideas to have their voices heard. It is tough to put a dollar figure on the cost of this initiative, which is viewed as ongoing and taking place in concert with other projects. The real question is: What is the cost of failing to try such an initiative? "There is so much potential and talent throughout the organization," she concludes. "The only way we can leverage it is to give it space and shine a light on it. This is best achieved in an environment supportive of experimentation."

Speeding Up The Evolution Of Personalized Medicine

By Wayne Koberstein, contributing editor

"Please, come to the FDA, and help boost innovation!" It is a call that would leave the agency's detractors rolling in the aisles. But, it is a call that Commissioner Margaret Hamburg has issued, nevertheless — as she seeks to bring new talent and perspective in to help rebuild the FDA into a clear champion rather than a suspect gatekeeper for innovation in new drugs, biologicals, and devices. And, it is a call answered notably by Dr. Vicki Seyfert-Margolis, who left her post as chief scientist at the Immune Tolerance Network and professorship at UCSF (University of California, San Francisco) to become Hamburg's senior advisor for regulatory science and innovation.

Seyfert-Margolis completed her first main assignments late last year: a strategic plan on regulatory science that outlines the agency's reform priorities and its "innovation agenda." She then turned to some broad scientific issues related to implementing those plans and achieving the goals. A central tenet of the innovation agenda and related reforms is the need to prepare and equip the agency for supporting the development of personalized medicine (PM) — an ever-changing and uncertain paradigm.

PRODUCTIVITY GAP

Seyfert-Margolis recognizes the ongoing decline in Big Pharma R&D output and then catalogs typical FDA failings such as famously difficult procedures, inconsistent communications, and lags in scientific expertise. (See the sidebar, "How The FDA Can Unblock Innovation.") But, she doesn't believe the industry or the agency can reverse the decline alone.

"This is a complex ecosystem of many different stakeholders that must evolve to enhance innovation in the medical product sector — physicians, patients, academia, government, payers, small businesses and large pharmaceutical companies, as well as the FDA as a key component," she says. "Together, we all need to put some serious thought into a national strategy for moving medical product innovation out of its current model into the next model."

She stresses that, for the agency, a primary concern is to adopt better regulatory practices informed by advanced regulatory science. But, in the context of the innovation ecosystem she describes, the stakeholders must examine broader policy issues.

In academia, for example, Seyfert-Margolis observes that research is "still fairly focused on the individual investigator as opposed to the team." She says it will also take broad stakeholder cooperation to make significant reforms in clinical research, such as a national network for efficient patient recruitment.

ENTREPRENEUR OUTREACH

The agency's innovation agenda focuses on small life sciences companies — doing more to help the companies navigate the regulatory process, and rebuilding the FDA's small-business outreach services. Seyfert-Margolis makes a connection between the outreach project and the overarching goal of collaboration with key stakeholders.

One example of small-business outreach is a new FDA Small Business Liaison (SBL) program that will bring experienced life science entrepreneurs into temporary advisory positions in the agency. In tandem, a Young Entrepreneurs (YE) program will train nonbusiness students on the basics of regulatory review.

"We want to bring people in from small businesses for short-term stints within the agency, people who've successfully brought a product to market, and help them meet with the people in the FDA." Currently, she says, the agency is working toward bringing in more outside experts to work on specific projects related to the agency's Innovation Pathway. The Innovation Pathway aims to shorten the overall time it takes for the development, assessment, and review of breakthrough medical devices.

"Some key areas of focus include the development of new decision tools to help the

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FDA assess and characterize benefits and risks to patients and new collaborative ways for the FDA and innovators to share ideas about new device concepts. Where applicable, these new approaches, practices, and tools will be used in other pre-market programs."

She says the goal is to give the agency staff a better understanding of the unique challenges for small businesses in product development. "We want people in the agency to have an understanding of a milestone plan, of capital, and how hard it is when you're undercapitalized to move through product development, and of the cost of lost time."

Seyfert-Margolis sees the SBL program as especially useful to academics who are contemplating or instigating a start-up company. The most common need among such people, based on their own frequently stated comments, is to understand what it really takes to bring a product to market, she says.

"We can enhance information and education about that process, so that when you go in, you go eyes wide open, knowing what you have to do."

The liaison program is still at a preliminary stage of organization and communication. Ideal candidates will be former company executives who are retired or on an extended break between jobs, but ready to share their experience, lessons, and acquired wisdom in company and product development. Likewise, the YE initiative is still gearing up but has a useful prototype in the Commissioner's two-year fellowship program for health professionals and scientists.

THE FDA AND NIH: NATURAL ALLIES

Small life sciences businesses have a special relationship to one of the stakeholders in the innovation ecosystem that Seyfert-Margolis describes — the NIH. She says the FDA will be working more closely with the NIH to "bring increased attention and focus to regulatory science, which really is the science between discovery and product, or the whole part of the life cycle called product development."

The agency has identified numerous challenges in product development that it believes must be addressed scientifically — not just clinical trials, but the technology that underlies all development, such as *in vitro* toxicology platforms. Seyfert-Margolis cites a joint commitment by DARPA (Defense Advanced Research Projects Agency), the NIH, and the FDA to the Organ on a Chip program, tasked with developing new *in vitro* toxicology assays leading to better predictive platforms. "Such platform technologies not only offer new businesses opportunities for entrepreneurs, but they may also help solve a large common problem."

Similarly, the Center for Drug Evaluation and Research (CDER) has started a partnership program for qualification of new drug-development tools (DDTs). A company may apply to qualify a tool or a marker for clinical use, and if qualified, the tool will be put into the public domain. It can still be patented but must be shared.

What does the company gain? The same as the industry in general: the ability to use the tool — say, a specific biomarker or other patient-rating instrument — in developing its products. An FDA guidance, "Qualification Process for Drug Development Tools," furnishes the details of application, evaluation, and terms of the program.

"All the new tools and strategies for applied science offer opportunities for the NIH and the FDA to work together in a different way," Seyfert-Margolis says. "The NIH SBIR [Small Business Innovation Research] program, for example, might be one way you can spur a generation of new technologies to help fill in gaps that still hold major challenges in the regulatory science arena."

THE GAMBLE OF PERSONALIZED MEDICINE

In product development, much depends on wise, informed company management and careful FDA guidance. But, products — therapies, diagnostics, and platforms — ultimately rise or fall on their demonstrated risks and benefits, on their safety, efficacy, and cost for performance in clinical practice.

"We want people in the agency to have an understanding of a milestone plan, of capital, and how hard it is when you're undercapitalized to move through product development."

Dr. Vicki Seyfert-Margolis, FDA

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HOW THE FDA CAN UNBLOCK INNOVATION

Starting in mid-2011, FDA Special Advisor Vicki Seyfert-Margolis and Commissioner Margaret Hamburg conducted meetings around the United States with leaders of small life sciences companies, who voiced near consensus on what the agency should do to encourage their innovative efforts.

- Do more to inform, engage, and help small life sciences businesses navigate the FDA regulatory process.
- Adapt current FDA policies and procedures to address the scientific realities and opportunities presented by personalized medicine.
- Take advantage of cutting-edge information technology and scientific computing to enhance benefits to patients and the American public.
- Address regulatory uncertainty within the FDA.
- Streamline FDA policies and procedures whenever possible.
- Develop more efficient regulatory pathways to support devices and diagnostics, including highly innovative devices.
- Build regulatory science capacity both within the FDA and the broader medical development community.

Perhaps the largest gamble in innovation is one that industry and regulators are making together: personalized medicine (PM), which has yet to prove itself as a scientific, medical, or business model. Only isolated and highly limited cases offer clear proof of the concept. What are the consequences for the agency and for industry if PM stalls short of its promise?

The badly needed turnaround in biopharma R&D productivity could be delayed for many more years. And, the innovation ecosystem will have sustained great damage and wasted many resources.

"The basic issue of personalized medicine usually comes down to what level of understanding we have of the underlying biology of disease and how to treat it, reverse it, or prevent it, and that's always been the first order of challenge," Seyfert-Margolis says.

She points to the recent FDA approval of the cystic fibrosis (CS) drug, Kalydeco (ivacaftor), approved January 2012, as an example of "how science can really work, and how, when you have an understanding of the genetics underlying a disease, you can go about developing a targeted therapy and bring that to market. It can be highly innovative and highly effective."

An admirable breakthrough, Kalydeco nevertheless treats only about 4% of CS patients in the United States, those with the G551D mutation. And, by some estimates, it is among the world's top ten costliest drugs at a reported $294,000 per year.

But, Seyfert-Margolis signals some balance to the PM approach in FDA thinking. "Clearly, not every personalized drug is going to fall into the breakthrough category, so our new Deputy Commissioner for Medical Products, Steven Spielberg, will be looking more deeply into the considerations and challenges associated with the personalized medicine paradigm."

She observes that a common definition of PM can be self-limiting. "It's not truly personalized in many cases; it's really subpopulation by definition. The size of the subpopulations may vary greatly from disease to disease. Gaining an understanding of what influences the different subpopulations is a huge challenge."

In type 1 diabetes and multiple sclerosis, where knowledge has long existed about the genetics and the increased risk for certain HLAs (human leukocyte antigens), identical twin studies suggest a larger story, she says. "We have to go well beyond genes and gene variance, even though I believe that's an incredibly important contribution to our understanding of disease."

Seyfert-Margolis believes PM may actually lead to greater understanding of common mechanisms among different diseases. "The immune system is central to many chronic diseases, not only in their initiation, but in their maintenance. We still don't truly understand the inflammatory component of many diseases, but we know it can be influenced by environmental impacts. We have such a long way to go toward a clearer understanding of the elements that affect immunity and immune responses, which is a very dynamic system, but it will be critical for moving so many areas forward."

She also envisions the possibility that such greater understanding of disease mechanisms may one day lead to a great leap forward in safety and efficacy for most drugs, even ones treating large patient populations.

"To the detriment of trying to get better products to patients, we have not been investing enough in some of the broader, practical research programs, like the Serious Adverse Events Consortium, that really help us use science to overcome development obstacles, achieve a higher level of innovation, and improve overall product quality. We need to use some of the intellectual capital of academia and industry — large companies to small companies — to work together in partnership to address some of the most common problems and solve them. The primary need is not just for basic research that tells us the next interesting pathway or gene, but also applying what we know in biology to practical innovations in product development."

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A 14-Year Quest For An Approved Drug

By Cliff Mintz, Ph.D., contributing editor

Stuart Peltz, Ph.D., was very satisfied with his life as a tenured professor at the University of Medicine and Dentistry of New Jersey (UMDNJ). He had spent most of his professional career studying the effects of post-transcriptional RNA (ribonucleic acid) control (all the regulatory events that take place after an RNA molecule is made) on the regulation of gene expression and protein synthesis. However, by the late 1990s, after studying RNA biology for 20 years, Peltz was convinced he could effectively use post-transcriptional regulatory control targets to identify new treatments that might provide therapeutic benefits to a wide variety of patients — especially those with rare genetically inherited diseases like cystic fibrosis (CF) and Duchenne Muscular Dystrophy (DMD). This prompted him to leave his life as a tenured UMDNJ professor and start Post-Transcriptional Control Therapeutics (PTC) in 1998.

PTC was founded to identify and commercialize small molecule drugs that work at the post-transcriptional level to modify protein production in a variety of therapeutics areas including oncology, infectious diseases, and orphan diseases. And after 13 years of R&D, the company is very close to realizing its goal. Currently, the South Plainfield, NJ-based company employs 175 people. Approximately 100 employees are involved with drug discovery, and the remainder are tasked with drug development, commercialization, and company management. Unlike most biopharmaceutical companies started in the late 1990s, PTC is privately held and still led by Peltz, its co-founder and CEO.

RAISING $550 MILLION IN FINANCING

While Peltz did not have any formal business training or experience in the private sector before starting PTC, he learned very early in his academic career to seek out smart and talented people who possessed the knowledge and skills to achieve his goal and aspiration of building a fully integrated biopharmaceutical company. "Also, I am a good listener and a quick learner," he adds.

It appears that Peltz's listening and learning skills and his penchant for smart people has paid off. During the past 13 years, he and his carefully assembled management team have raised over $550 million in financing for the company. Peltz is quick to point out that only $183 million was from venture capital and private equity sources, and the lion's share was from research collaborations and licensing deals ($259 million) and grants from nonprofit foundations and from patient advocate groups ($118 million). Some of these include the National Institutes of Health, the FDA Office of Orphan Drugs, the Wellcome Trust, the Cystic Fibrosis Foundation, the Muscular Dystrophy Association, and the Spinal Muscular Atrophy Foundation.

AN UNUSUAL APPROACH TO IDENTIFYING THERAPEUTIC TARGETS

On the surface, PTC resembles many other biopharm companies that started out as platform technology developers. However, early on Peltz used a somewhat unconventional approach to identify therapeutic areas where PTC technology platforms could possibly make a difference. "In the early days, Claudia Hirawat, senior VP of corporate development, and I visited a large number of patient organizations to understand the best opportunities to apply PTC's technology to a particular disease, explains Peltz. This led to our current emphasis on developing small molecule drugs for orphan and ultra-orphan indications, including DMD, CF, and SMA (spinal muscular atrophy). I thought from the outset that our technology platforms could be universally applied to discover novel molecules for these indications, all of which currently have limited or palliative treatment options."

Peltz's initial plan for PTC was to build a variety of discovery platforms and use an empirical approach to determine the best way forward for the company. In other words, "Anything that worked well as a discovery tool, we advanced, and things that did not perform well were quickly abandoned," offers Peltz. While his initial thinking was to exclusively rely on PTC's internal R&D activities to bring new drugs to market, Peltz quickly learned the changing economic conditions in the early 2000s would not permit him to execute this strategy. "Things were tough back then; there was not as much VC available, and an IPO was no longer a viable option to capitalize a company. This forced us to reconsider how we were going to advance our drug candidates and ultimately ensure the financial future of the company," says Peltz.

Continued On Page 40

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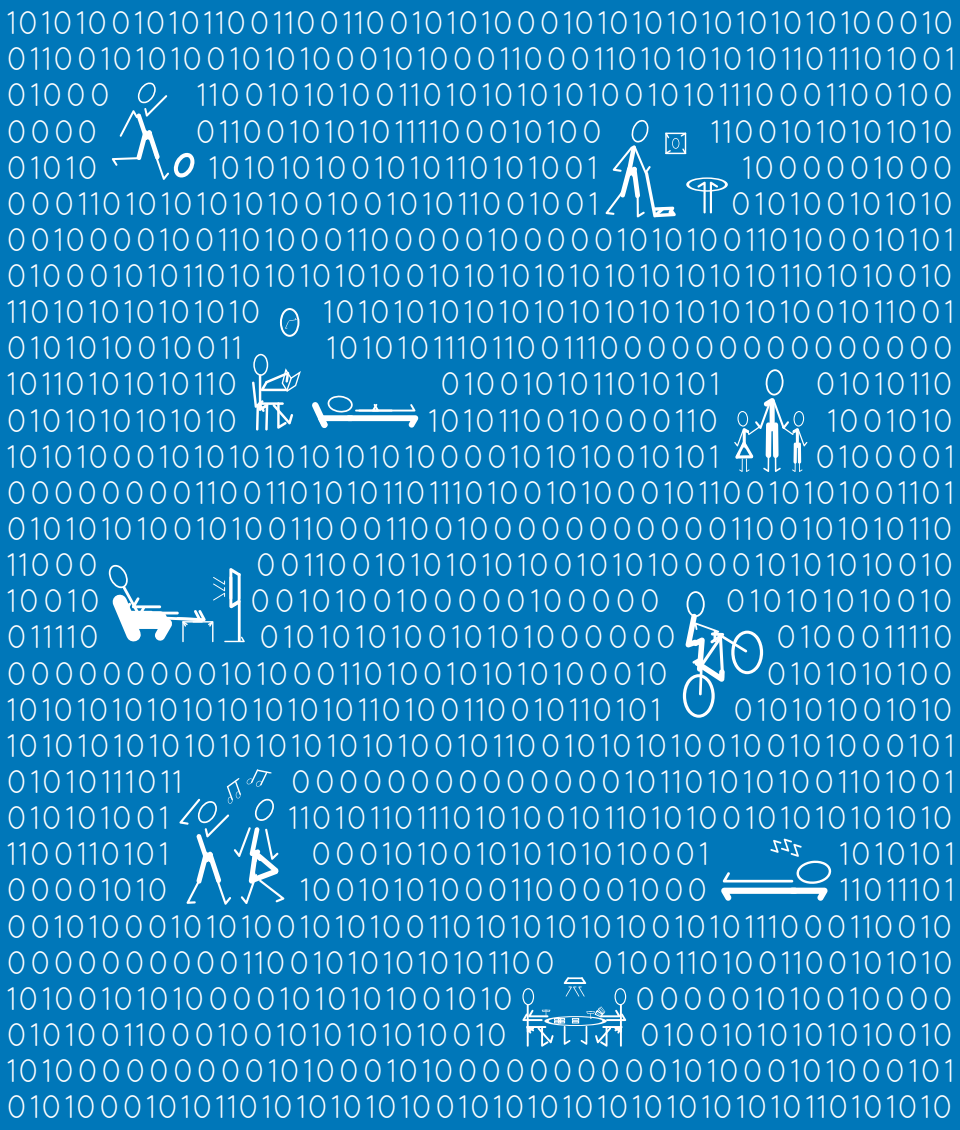

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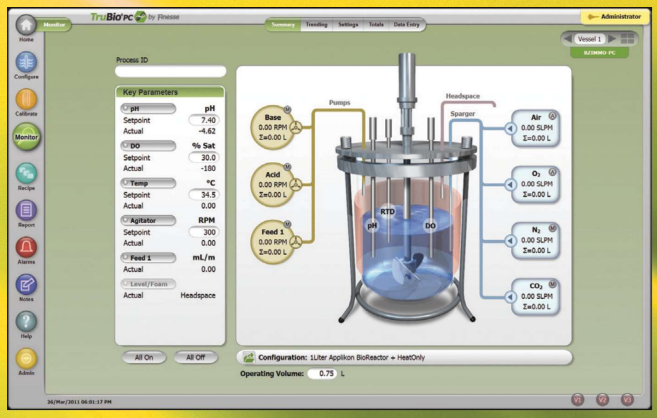

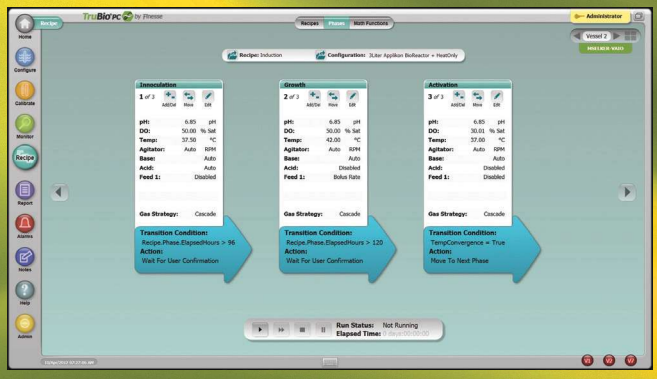

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BIG-NAME LICENSING DEALS AND 3 INDs

Luckily, the promise and novelty of PTC's drug discovery platforms were sufficient for Peltz and his management team to convince some of the world's leading pharmaceutical and biotechnology companies like Pfizer, Merck, AstraZeneca, Genzyme (now Sanofi-Aventis), Gilead, Roche, and Celgene to enter into licensing deals with the company. These revenues plus copious funding from government agencies and nonprofit sources ultimately provided sufficient capital for PTC to develop three novel and proprietary drug discovery platforms that include: 1) Gene Expression Modulation by Small Molecules (GEMS); 2) nonsense mutation suppression; and 3) an RNA alternative splicing discovery platform.

To date, the GEMS and nonsense mutation discovery platforms have yielded three investigational new drugs (INDs), two in mid- to late-stage clinical development. These drugs include the company's lead product, ataluren (formerly PTC124) to treat CF (Phase 3) and DMD (Phase 2b), and PTC299, a vascular endothelial growth factor (VEGF) inhibitor (Phase 1/2) being tested in multiple oncology indications. The third candidate — an orally bioavailable treatment for Hepatitis C virus infections — is in preclinical development. Most recently, PTC entered into a potential $460 million licensing deal with Roche to use its RNA alternative splicing discovery platform to identify a small molecule drug to treat SMA, a genetic neuromuscular disorder (for which there is no current treatment) that causes muscle weakness in one out of 9,000 children born in the United States.

"Anything that worked well as a discovery tool, we advanced, and things that did not perform well were quickly abandoned."

Stuart Peltz, Ph.D., CEO, PTC Therapeutics

"While working on orphan diseases is very rewarding, it is also very challenging," offers Peltz. "In the beginning we didn't really understand how much pioneering work would be involved with developing new drugs to treat these diseases." To that point, PTC had to pioneer a new clinical outcome measure for patients with DMD — the 6 minute walk test — to assess whether its leading drug candidate ataluren provided any therapeutic benefits to patients suffering from the disease.

As anticipated, results from Phase 2b clinical trials showed that ataluren improved the performance of patients with DMD in the 6 minute walk test by 30 meters. Because of PTC's pioneering efforts, many companies now targeting DMD have adopted the 6-minute walk test as the standard to evaluate their new treatments. "Looking back, I think that the real keys to our success were working closely with nonprofit foundations and patient advocacy groups and identifying populations of physicians committed to finding new treatments for their patients," says Peltz.

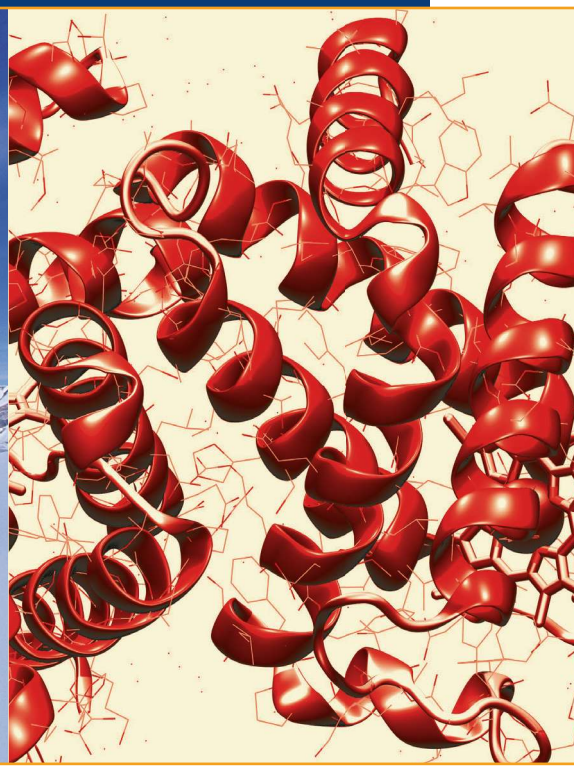
BEYOND ORPHAN DRUGS MEANS A SEARCH FOR PARTNERS

Although PTC's current emphasis is on orphan disease drug discovery, Peltz understands the need to expand the use of the company's discovery platforms into other therapeutic areas. To that end, the company has active internal discovery programs (mainly grant and business development driven) in antibacterial drug discovery, stem cell research, oncology, and several undisclosed indications. However, Peltz is quick to point out that PTC does not intend to bring these new products to market by itself. "The plan at this point is to advance these programs into safety/toxicology studies or early-stage clinical development and then look for partners interested in helping us commercialize them," he says.

Despite his lack of formal business training, Peltz's transition from academia to the private sector was not a very difficult one. "I was always very goal oriented and entrepreneurial, so I tended to run my laboratory at UMDNJ like a small business. This mindset greatly aided my transition from academia to industry," he says. Further, Peltz opines that his successful transition was likely a result of his ability to freely admit to others that he does not know everything, an attitude which is very uncommon among academics, who tend to avoid that admission at all costs. Also, unlike many academic scientists, he is not afraid to surround himself with talented people with strong personalities who, similar to him, are opinionated and willing to argue, at any cost, for what is in the best interest of the organization. "I think to be a successful CEO you have to be transparent, extremely flexible, and open to any or all business opportunities that are in the best interest of moving the company forward," offers Peltz.

Yet despite his extraordinary fundraising skills and research accomplishments, Peltz understands that his position as PTC's CEO can never be guaranteed. "I am always looking for new investments and business opportunities to keep the company moving in the right direction. It never really ends; no matter how much progress you think that you are making," he says. And while PTC is developing pretty much the way Peltz thought it might when he decided to start the company back in 1998, he is keenly aware that the company will never be considered a success until it has approved products on the market and is able to turn a profit.

Value through Innovation



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Rare Disease Drug Development: A Thriving Business Model

By Chris Garabedian

Of the approximately 7,000 rare diseases that have been identified, fewer than 5% have drug therapies available, and many of these provide limited benefit. With the advancement of diagnostics and corresponding patient stratifications, "rare" diseases should be a high priority therapeutic area for our industry, especially when considered as a single, collective patient population.

The birth of a viable business model for rare disease drug development can be traced back to the Orphan Drug Act of 1983, which established the definition of an orphan drug as treating a disease that affects less than 200,000 patients in the United States. Since then, the FDA has approved 398 orphan-designated drugs, while prior to the Orphan Drug Act, the agency had only approved about a dozen such drugs. Today, momentum for orphan drug development is accelerating to an unprecedented level, fueled by the convergence of several factors, including:

- a high unmet medical need combined with an increased understanding of rare disease biology and the advancement of the technology that can address it;
- an evolving regulatory environment and proactive legislative agenda;
- an increasingly influential patient and disease advocacy community;
- a supportive reimbursement environment enabling a viable business model.

Together, these factors make the rare disease business model more attractive than ever, creating a wellspring for the discovery and development of promising drugs.

ADVANCEMENTS IN SCIENCE AND TECHNOLOGY

Historically, the interest in seeking treatments for rare disease has been limited by knowledge of the etiology of many rare diseases and/or the technological approaches — which were lacking or immature — to effectively treat these diseases. Advances during the last several decades in biotechnology, combined with knowledge gained since the mapping of the human genome, have significantly enhanced our understanding of the origin and genetic makeup of many of these diseases. Furthermore, the technological approaches that may be most effective in treating these diseases have also advanced and matured.

This convergence of factors has increased the interest in conducting discovery research against rare disease targets. Since there are no effective treatments for most rare diseases, there is often a quick pathway to establish proof of concept for a new technological approach and to demonstrate if a given treatment will have a meaningful effect.

One example of the increasing interest in rare disease research is an NIH-sponsored initiative called the Therapeutics for Rare and Neglected Diseases (TRND) program. The TRND program provides funding for new therapeutics to cross the gap from basic discovery research to testing in humans — often termed "the valley of death" of drug development. This program is intended to speed the development of new drugs for rare and neglected diseases by establishing partnerships with academic research institutes, biopharmaceutical companies, and other nongovernmental organizations.

EVOLVING REGULATORY AND LEGISLATIVE AGENDA

While the number of orphan drug designations has risen every year, the number of orphan drug approvals has not. To realize the promise of scientific and technological advances, the regulatory environment has to provide a clear and achievable path of drug development that reflects both the risk-benefit tradeoff that exists with many rare diseases, as well as the practical limitations of clinical studies, given the low prevalence of these diseases. The Orphan Drug Act of 1983 established incentives for orphan drug development, such as seven years of market exclusivity, tax credits on development costs, expanded access to the Investigational New Drug (IND) program, and, through later amendments, waiver of the Prescription Drug User Fee Act (PDUFA) application fee. In the last decade, drug development for small markets has been made even more feasible by the Rare Disease Act of 2002 and the Brownback/Brown Amendment of 2010. Respectively, these legislative acts instituted the Office of Rare Diseases as a federal entity and established a dedicated FDA review group composed of rare disease experts.

Looking ahead, the reauthorization of PDUFA V later this year will likely include legislation that will expand the application of the accelerated approval pathway to orphan diseases. These legislative acts, called the Faster Access to Specialized Treatments (FAST) Act and the Transforming the Regulatory Environment to Accelerate Access

to Treatments (TREAT) Act, would add clarity to the accelerated approval pathway by requiring the FDA to publish dedicated guidance.

Accelerated approval provides faster access to therapies for patients with severe diseases that have no other options by allowing initial evidence of clinical benefit to be confirmed in later post-approval studies. To truly streamline the regulatory path for orphan drugs, the current spirit of collaboration between the FDA, rare disease researchers and clinicians, the biopharmaceutical industry, and advocacy groups must yield greater alignment on meaningful clinical endpoints. Greater clarity in this area will correspond to greater clarity in the regulatory pathway.

Drug development for rare diseases also can come with greater FDA flexibility. Of the 135 orphan drugs that have been FDA-approved since the Orphan Drug Act of 1983 (excluding drugs for rare cancers), only 1/3 were approved on the conventionally viewed standard level of evidence, commonly referred to as "two adequate and well-controlled studies," according to a 2011 white paper written by Frank Sasinowski, chairman of the board for NORD. According to the paper, the remaining approvals were based on some degree of FDA flexibility in applying the statutory standard for evidence of effectiveness.

INFLUENTIAL PATIENT AND DISEASE ADVOCACY COMMUNITY

In the 1990s, the determination and organization of AIDS activists led to the acceleration of drug approvals for the treatment of HIV, and redefined the influence that an organized disease advocacy effort can have on drug development and access to therapy. This set in motion a number of other patient and disease advocacy efforts that recognized the power of a willful patient voice to partner with industry in drug development. Advances in many disease areas can be linked in part to these collaborations, from the Cystic Fibrosis Foundation's support of Vertex' recent drug approval to the Multiple Myeloma Research Foundation's support of Celgene's approved and investigational drugs for that disease. These groups have influenced drug development and the regulatory pathway in an effective and lasting manner through their knowledge of the disease, an organized approach, and, in many cases, their deployment of capital from their fundraising efforts. Thus, they have earned a place alongside industry, the FDA, and the research community and now have a critical voice in shaping the biopharmaceutical industry's efforts towards drug development.

A VIABLE BUSINESS MODEL

Historically, the pharmaceutical industry has used the prevalence of a disease as a key criterion in determining the commercial viability of pursuing research and development of a particular treatment. Today, many of the innovative drug therapies that were developed to target highly prevalent diseases and conditions are now generic, such as cardiovascular treatments for hypertension or hypercholesteremia, antibiotics, and antidepressants. Consequently, the unmet medical need has been reduced while the ability to gain reimbursement at a high price point for incremental improvement has proved challenging. In rare disease drug development, the industry can focus on areas where there is still a high level of unmet medical need, and thus, the opportunity to create therapies that will produce a significant societal benefit.

The success of Genzyme in gaining reimbursement for rare lysosomal storage disorders such as Gaucher disease, Fabry disease, and Pompe disease, is proof of the ability to derive returns from drugs that have a big impact on a small-disease population. High reimbursement levels can be attributed to the ability of these therapeutics to dramatically lower costs to the healthcare system, leading to a new generation of companies that have achieved success in the rare disease space. For example Alexion, with the drug Soliris, currently holds one of the highest market capitalizations among biotechnology companies that have become commercial entities in the last decade. Investors have also supported the rare disease business model through companies like Amicus, Raptor, Aegerion, Enobia, Synageva and AVI BioPharma.

About the Author

Chris Garabedian is the president and CEO of AVI BioPharma, a company focused on the discovery and development of novel RNA-based therapeutics for rare and infectious diseases.

Blockbusters — Time For A Revival?

By Wayne Koberstein, contributing editor

Targeted drugs and personalized medicines are supposed to be the alternative to the billion-dollar-plus blockbusters that long drove Big Pharma R&D, marketing, corporate strategies, and consolidation. Now almost all large companies only mention blockbusters when they appear to stumble upon them. Many declare their commitment to research driven solely by medical need, and to "finding the right drug for the right patient," regardless of market size. But does that strategy really serve patients — or unbridled pricing? With the decline of mass-market drugs has come the rise of "orphan blockbusters" — drugs with small populations and such high price tags that they generate revenues comparable to the preceding mass-market products — and create a new surge in medical costs.

The trend may be an excellent boon to companies large and small, but it is unlikely to be sustainable. Any practice that puts patients and payers in the position of choosing between treatment and financial crisis may come with an expiration date. Perhaps it is time to re-examine the proposition.

"The blockbuster model is alive and well, if compounds can be found that deliver high pharmacoeconomic benefits to large populations of patients," says Eric de La Fortelle, CEO of therapeutic-antibody developer Delenex Therapeutics AG and a former global head of technology partnering at F. Hoffmann-La Roche. (See "Blockbuster Values.")

Like de La Fortelle, most other experts contributing to this article seem to agree on this general point: Big-market blockbusters and "me-too" drugs may return as a worthy industry goal — but only if the ante is raised. Compared to the mega-drugs of the past, future blockbusters will need to reach a much higher bar of safety, efficacy, and affordability, likely trading premium prices for higher volume at lower margins.

Whether the future belongs to blockbusters or niche products is a high-stakes question for all innovator companies, large and small. Companies must gamble now on which direction they will take in research, though it will be many years before they know if the data and the market conditions justify their choice.

Are there any ways to hedge the bet: actions companies could take to avoid over-reliance on the niche model? One logical way is to place greater priority on exploring platforms that could expand, even if from an initial narrow target, to achieve breakthroughs in broad therapeutic areas — in a word, blockbusters.

BUSTING THE OLD MODEL

Of course, the matter is more than theoretical. Some companies, in some situations, have succeeded in developing products with mechanisms of action (MOAs) that apply to wide or multiple therapeutic areas. Other companies have such products still in development, and still others are seeking wider markets for existing drugs through new strategies such as novel delivery technologies. But with the preponderance of conventional wisdom now favoring niche and targeted drugs, those products are perhaps the exception that proves the rule. Shifting the balance significantly would require a more conscious commitment by companies to the search for broader MOA platforms and products. At least one company claims to have made the shift:

"We believe in the paradigm by which you can ultimately build to a blockbuster even if each separate disease, though an important unmet medical need, may not be a very large commercial opportunity," says Rob Bazemore, CEO of Janssen Biotech. "That paradigm of success will carry us into the future."

Does such a shift mean a return to market-driven R&D, where sales potential outranked science in a company's research agenda? The answer is a qualified no — on the condition that patient and payer needs, not revenue goals, guide the critical decision-making in product development.

The last point calls for a short pause while the cynics sneer. Yet there are sound, practical reasons why companies should take such an approach, not the least among them is that patients and payers will demand it. Moreover, there is a growing awareness among company executives that the industry cannot continue with a "selfish" model of product development and pricing for

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BLOCKBUSTER VALUES

A number of "experts" — people with relevant drug-development experience in large and small companies —contributed ideas and quotations to this article. Below are selected quotes, some expanded from brief citations in the article.

Eric de La Fortelle, CEO of therapeutic-antibody developer Delenex Therapeutics AG and a former global head of technology partnering at F. Hoffmann-La Roche

"The blockbuster model is alive and well, if compounds can be found that deliver high pharmaco-economic benefits to large populations of patients. More adventurous groups will eventually fight the frightening unknowns of areas like RNA therapeutics, cell therapy, gene-to-protein translation and splicing pathways, sophisticated delivery methods, and so on, to come up with a generation of completely novel compounds that will easily fit within the regulatory and payers' constraints, and take huge markets by storm."

Abbie Celniker, CEO, Eleven Biotherapeutics, a therapeutic protein optimization company

"The most obvious opportunities for new drugs may appear to be drugs against previous 'undrug-gable' targets, but there are also significant opportunities built around known targets and well-established pharmacology. This evolutionary — not revolutionary — approach to developing novel drugs based on known pharmacology can open up new opportunities for next-generation therapeutics with the dramatic improvements in specificity, stability, duration and potency, that are necessary in today's environment to become market-leading drug products."

G. Steven Burrill, CEO, Burrill & Company

"We're not done with blockbusters. But we are done with one-size-fits-all drugs. Society can afford to pay a whole lot for things that work, so we need better correlation of the things that work with the problems we're trying to solve. Enormous value can be created by the system as it moves into personalized medicine. Fifty-five percent of the drugs used in this country don't work for the patients, we have a lot of room to improve that. I don't know that we're going to see many more $14-billion drugs like Lipitor, but we will see lots of billion-dollar-plus market opportunities."

Paul Coggin, Principal, the consulting firm Wipro

"The blockbuster model still has plenty of runway, and large Pharma hasn't abandoned it. In the metabolic area, there's STILL great unmet need for therapies that truly improve (or maintain) beta cell function to halt the progression of diabetes. Should we also mention the significant needs associated with Alzheimer's and other neurological conditions? What about oncology-related pain management therapies needed to deliver better tolerability and fewer undesired effects? New, better therapies in these areas and others can potentially be used to help millions and millions of people — and are blockbuster profit opportunities."

Mary Lynne Hedley, President, CSO, co-founder, Tesaro

"Addressing the largest remaining underserved markets will require significant scientific advances. Initial advances will likely result in the development of moderately effective, widely used drugs that could be more reminiscent of the mega-blockbusters. Over time, as the science and understanding of these indications progresses, genetic and other biomarkers will become available and will be used to develop drugs with improved efficacy in better defined smaller patient populations within an indication, and the mega-blockbuster may be replaced by multiple modest blockbusters."

either niche or blockbuster drugs, again because of external pressures and demands. Even if it is ultimately self-serving, companies must not only do good, but be seen as doing good, in the healthcare environment.

CHALLENGING THE TARGETED TREND

Oncology offers the clearest contemporary examples of how the performance of many targeted drugs has fallen far short of their promise. Tumors routinely develop resistance to drugs targeting molecular pathways. What seems like a wealth of molecular and genetic targets in tumor cells may actually reflect their unfathomable heterogeneity.

Cutting off one pathway, or silencing a given gene, typically causes the tumor to find and use another one to stay alive and grow. Preselecting patients based on genetics or biomarkers may thus produce only modest or short-term benefits at best, followed by a fall-off in efficacy and, in many cases, a sharp rise in harmful side effects.

Although the imbalance of promise versus payoff is less obvious with targeted medicines for other diseases, the hazards are similar: drug resistance, molecular and genetic complexity, ambiguous biology, and murky pharmacokinetics, to name just a few. When targeted drugs fail to produce the breakthroughs once promised, pricing becomes an even more sensitive issue. Pressures on pricing are pulling companies in two opposite directions: stakeholders push upward; payers pull downward. Neither side is satisfied.

In the niche-product environment, companies also feel pressure on another front — to hype all potential advances, the earlier and more tenuous, the better. Sadly, journalists too often oblige with headlines and glowing copy touting the latest potential cure for cancer or other diseases, which is almost always based on bench science or preclinical studies and almost never bears fruit in the long run. People pushing the hype are rarely around when the trail grows cold.

BALANCING SCALES

Targeting is nothing new in pharmacotherapy. What is new nowadays is the "microtargeting" of ever tinier patient populations based on testing for distinguishing biomarkers. Single diseases are "recognized" as consisting of multiple conditions, each one requiring a unique treatment with its own MOA.

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In the ultimate logical extension of the concept, doctors would diagnose every patient down to the molecular and genetic level and synthesize a compound specifically for that patient — all in the course of a single office visit. The entire biopharmaceuticals business would thus be reduced to one piece of physician-operated equipment.

Before we reached that Star Trek future, however, nearly all drugs would be linked to separate diagnostic tools, and the entire healthcare system would groan under the weight of their ballooning costs. Clearly, the system will look for more cost-effective alternatives, rewarding approaches based on disease mechanisms that affect many different patients. The niche products defined mainly by their limited efficacy would then wither on the vine; only those targeted at true orphan conditions — rare diseases with no other treatment options — would gain acceptance.

> Whether the future belongs to blockbusters or niche products is a high-stakes question for all innovator companies.

Of course, merely wishing for broad-based treatments does not make them appear. But current scientific and business trends may make them likely. Already active areas include antimicrobials, anti-inflammatories, metabolics, and immunotherapies for cancer and other conditions.

"The most obvious opportunities for new blockbusters may appear to be drugs against previous 'undruggable' targets, but there are also significant opportunities built around known targets and well-established pharmacology," says Abbie Celniker, CEO of the therapeutic protein optimization company, Eleven Biotherapeutics.

Recently, I reported on Novadigm's development of a vaccine engineered to generate a single antigen against members of two different kingdoms, bacteria and fungi (staph aureus and Candida) primarily to prevent sepsis but also related infections. Other companies, such as India's Amrita Therapeutics, are designing compounds with multiple MOAs to treat more than one disease simultaneously. Immunology is now seen as the main alternative to targeted therapy in cancer, as evident in most major-company and many small-company pipelines.

Personalized medicine, whatever its ultimate success, shifts the traditional emphasis on patient symptoms to disease and drug mechanisms. Similarly, molecular targeting sometimes works in reverse — elucidating a pathway in a disease subtype leads to recognition of the same pathway in other conditions. One example is Roche/Plexxikon's Zelboraf (vemurafenib), a BRAF inhibitor approved for mutant metastatic melanoma.

"Vemurafenib's unique mode of action gives us the option of extending it potentially into other diseases where we see the same mode of action," says Thorsten Gutjahr, Global Head of Biomarkers at Roche Diagnostics. "Of course, this has to be shown first clinically and validated, but it offers a potentially huge understanding of how to go forward clinically into other indications to develop the medicine."

Other researchers and companies are focusing on ways to turn existing but under-used drugs into future blockbusters. For example, NuPathe and MAP Pharmaceuticals, also reported on recently, are applying new delivery technology to overcome the limitations of older migraine drugs, possibly opening up much larger markets among the vast number of patients now unable to tolerate or benefit from them.

THE HIGHER BAR

Drug targeting, rather than endlessly segmenting diseases and research areas, may actually unify researchers to solve common problems and elevate drug therapy to a higher plane. Late last year, FDA's Janet Woodcock told us that the International Serious Adverse Event Consortium (ISAEC), which she helped found to explore the genetic basis of SAEs, had discovered HLA (human leukocyte antigen) alleles linked to susceptibility to drug-induced liver injury (DILI), Steven-Johnson Syndrome, and toxic epidermal necrolysis. The discovery now guides screening for some widely used antibiotics and a CNS drug; similar techniques could be applied to more widespread SAEs (serious adverse events) and drug classes.

Such research would have to be central to any future development of blockbusters. Future blockbusters would face a much higher bar of safety and efficacy; they could earn wide use by large groups of patients only by offering a superior benefit-to-risk ratio. In many cases, they would do so by the same means now associated with niche medicines — companion diagnostics — whose added cost would be negligible next to the savings achieved in large patient groups.

Science, business, and customer demand all make the case that more companies developing new drugs should plan for the resurgence of blockbusters in a new form. It would thus be unwise for the industry as a whole to put all or most of its eggs in the single basket of niche products. Drugs targeted to small populations will need ever greater justification, even as the opportunities for broad-based breakthroughs in safety, efficacy, and affordability continue to expand. Where the medical need is broad and great, the industry should be equal to the challenge.

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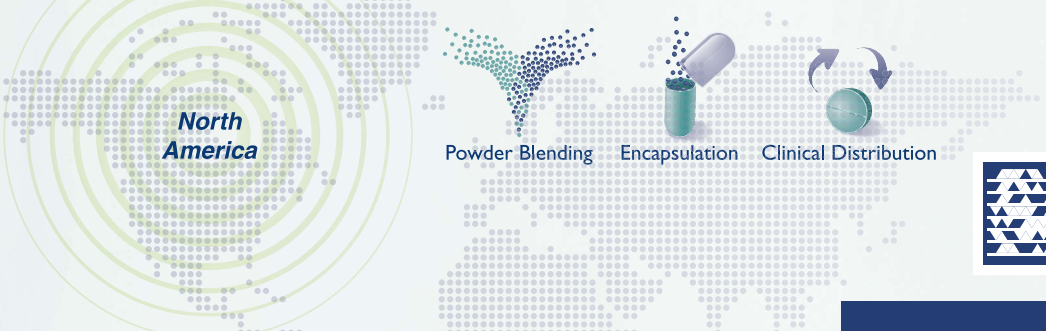

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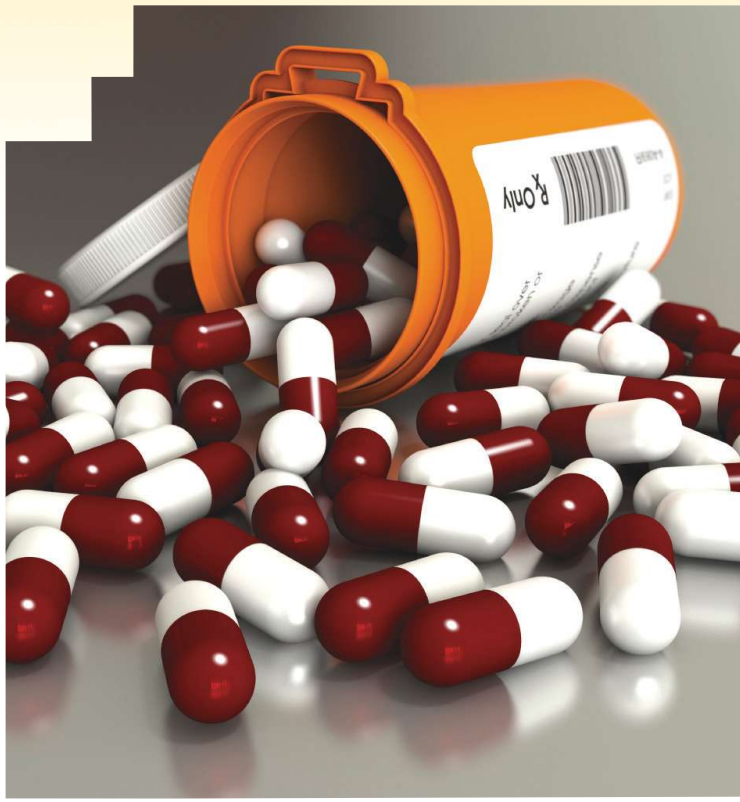
The Business Case For Serialization



By Gail Dutton, contributing editor

The obvious benefit of serialization, aside from regulatory compliance, is as an adjunct to companies' anti-counterfeiting efforts. There are many other potential applications, largely focused around supply chain assurance and integrity, but their return on investment often is less quantifiable. Although those additional benefits may filter through the supply chain, pharmaceutical companies currently are focused on serialization's initial implementation and upon ensuring data system interoperability.

Consequently, developing strategies to mine, store, and analyze data, and then to put that data into context in ways that build broader usability, is a secondary concern. Many executives are just realizing that ePedigree data could be a corporate asset, but even the savviest are still trying to identify ways to leverage that data to support the business units and the supply chain.

Bristol-Myers Squibb (BMS) was among the first to understand the multiple benefits of serialization. It is putting systems in place now to enable serialization data to be used to improve patient safety, enhance its corporate social responsibility efforts, protect the corporate reputation, and provide a competitive advantage. "This is a new capability that puts us in a better place," says Natalie Lotier, VP of strategic supply chain operations and planning.

In implementing serialization, BMS is aligning its supply chain processes more closely to the business processes and to the BMS global integrity council. With the improved supply chain visibility provided through track-and-trace technology, "We'll see the pathway a product follows from our distribution center all the way to the customer. That visibility will enable us to better understand the product flow and thereby improve logistics and transportation efficiency, including reverse logistics, and make quicker and better decisions," Lotier says.

FIGHTING COUNTERFEITING

Aside from regulatory compliance, pharmaceutical companies say the main benefit of serialization will be its support of anticounterfeiting and diversion efforts, which translates to patient safety. Counterfeited or gray-market products enter at the supply chain's weakest points, usually as products flow through multiple countries. In February and April, 2012, for example, counterfeit Avastin was shipped from Turkey through Europe to the United States. In 2008, counterfeit Heparin was reported in a dozen industrialized nations, causing approximately 150 deaths, according to the World Health Organization. Pfizer says its Viagra is the most counterfeited Pfizer drug in the world.

"The counterfeit market is a significant industry threat," stresses Reid Graves, manager, global master data management, Pfizer Global Logistics and Supply. "We feel the need to act now to protect our patients, our products, and our company reputation. Patient safety is our primary focus."

As Mac Hashemian, president and CEO of Xyntek, Inc. elaborates, "Global counterfeiting is a multibillion dollar problem in the life sciences industry. The counterfeiters have technology so advanced that sometimes their labeling is better than the manufacturer's."

The track-and-trace technology that is integral to serialization won't prevent counterfeiting, but it will provide a heightened level of assurance that at least the serial numbers on the product pack-

ages match those issued by the manufacturer and are linked to specific shipments. Any discrepancy makes a shipment suspect. "Serialization is not only a way to protect patients, but also to protect the brand," emphasizes Hashemian.

SMOOTHER REFUNDS, RECALLS

"Serialization will be important when it comes to reimbursing buyers for returned products and for rebates," Hashemian predicts. The current refund system has a significant potential for error, so duplicate payments are made, he points out. "Without serialization, all drugs (of a given type) look the same. There's no unique identifier. But, with serialization, drug wholesalers and manufacturers can ensure that refunds are paid only once for the specific drugs that were returned. Serialization also helps distinguish genuine products from the counterfeit products that sometimes are returned.

Serialization also may reduce the size of recalls. Because drugs can be identified by lots, manufacturing date, plants, production lines, shipping locations, and redistribution points, they can be tracked all the way to the pharmacy or patient. Consequently, recalls can be quite specific, targeting individual pharmacies or regions rather than the large, blind, national recalls that often have occurred. Tightly targeted recalls increase recall efficiency and effectiveness, and also improve patient service by leaving greater quantities of viable product available to patients.

OTHER BENEFITS OF SERIALIZATION

The additional value of serialization lies in the data that will be returned to manufacturers from their supply chain partners. Individual companies remain in the early stages of determining what data they would like to receive from their supply chain serialization efforts.

Improved supply chain visibility is a huge benefit of serialization. As Terry Young, director of enterprise data operations at BMS, says, "With that additional data, analytics become available to us with less manual effort, to enable totally new capabilities we can't imagine today."

As track-and-trace solutions are deployed, however, the synchronization and interoperability of computing platforms and applications throughout the supply chain becomes a challenge. "Currently, Pfizer is focusing on how to capture and exchange data efficiently," says Peggy Staver, director of product integrity for Pfizer. It — along with much of the pharmaceutical industry — is evaluating the relative merits of centralized, distributed, and hybrid data management models. One model, for example, pushes data to supply chain partners. But, because that approach moves high volumes of data, it increases the IT overhead.

Cloud computing, in contrast, uses SaaS and PaaS (platform as a service) technologies to allow trusted users to access a single database. That approach alleviates many of the IT challenges. "We're seeing some IT infrastructure savings in moving to the cloud for data management, storage, and infrastructure solutions," adds Elliot Abreu, senior VP of Xyntek, Inc.

BMS uses a single, globally integrated ERP (enterprise resource planning) application. As Young says, "That gives us a lot of flexibility to select numerous solutions to connect and understand the performance of our serialization efforts across the globe. We also operate a centralized master data management platform, which is a key component of our serialization efforts."

The benefits of serialization are likely to trickle throughout the industry. For example, inventory may be positioned more effectively to reach patients and to control the costs of waste. "At BMS, we had more efficient transportation costs and reduced inventory

(during a pilot serialization program) because it required fewer trucks and buildings. It wasn't a major impact, though," Lotier admits.

Additionally, a thorough track-and-trace program that includes expiration data may improve shelf-life management, demand forecasting, and production planning, and also may enable just-in-time logistics for some hospitals or pharmacies. "Near-term, distributors and pharmacies may realize the greatest value from serialization, through improved inventory and shelf-life management," Staver says.

Having near real-time insight into the supply chain also may help companies target sales and marketing promotions to local conditions and optimize multichannel campaigns. Market intelligence firm IDC estimates the pharmaceutical industry may gain some $11 billion simply by optimizing these areas.

This technology also may be used to drive operational efficiency. As Hashemian explains, the database system used to track serialization data also can be used for other things. For example, he suggests not only applying a unique serial number, but adding additional content to the database. That may include the time it takes the product to go through manufacturing, filling, and packaging, for example. "Collecting data also allows recalls to be linked to specific lines, times of day, operators, and perhaps even the event that caused the need for the recall," he says. Such detailed data can be analyzed to improve processes throughout the organization.

The potential business value that can be derived from serialization initially seems lengthy. When Pfizer first contemplated the business case for serialization, it created a long list of possible benefits. But, as the Pfizer team analyzed those possibilities, it realized that many of those benefits depended upon wide-scale deployment of serialization and track-and-trace across the supply chain, and upon decisions that were not yet made.

DON'T OVERLOOK THE RELATED PROCESS CHANGES

The basic information to be encoded by the manufacturer is obvious. The pharmaceutical industry plans to capture and correlate serial numbers that are kept in the manufacturer's database as they are sent to the packaging lines, applied to the product, and shipped. Additional information will be stored in the manufacturer's database, but not encoded on the 2D bar code. At Pfizer, for example, a unique serial number, product identifier, expiration date, and lot number will be encoded in the bar code, but master data related to the product will remain in the database where it may be cross-referenced.

Clearly, serialization involves more than simply tracking serial numbers. It triggers changes in other business processes. Although serialization doesn't necessarily change distribution strategies, it does change the process. Under serialization, Staver says, "Distribution sites must capture information. That involves scanning information as product arrives and as it leaves, and associating that information with a customer order." Returns undergo a similar process.

Exceptions also must be resolved, with potential ramifications for supplies if resolution is not completed quickly. For example, Staver says, "If 48 products were shipped to a customer but 49 were received, the extra product must be identified and the necessary electronic data exchanged before the additional unit may be sold by the customer. Today, that extra unit is saleable. In a serialized, pedigreed environment, it would be quarantined until the exception is resolved."

Despite the changes and challenges, serialization does offer business value for those innovative enough to find it. Serialization enables a different way of collecting and looking at data — one that can be a nuisance or one that can provide a competitive advantage. But, as Greg Cathcart, CEO, Execellis Health Solutions, predicts, "Before the item-level pharmaceutical serialization can bring much-needed visibility to the supply chain, it will cause significant disruption, escalate costs, and usurp opportunities."

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The Top 10 Partnering Pitfalls And How To Avoid Them

Part Two

By Wayne Koberstein, contributing editor

This two-part series presents the top 10 partnering pitfalls for life science companies — actions, distractions, and missteps that can ruin a company's chances for a successful partnership — plus some expert advice for avoiding them. This month, part two contains the remaining five pitfalls in the top 10. The viewpoint is of small, entrepreneurial life science companies, from the early stages of searching for large-company partners through partnership selection, deal negotiation, and operational implementation. But, the list should be equally valuable as insights for the large companies most often on the other, more dominant side of the deal. Some of the best practices offered may seem obvious but are often overlooked. Experts with a range of small- and large-company experience as well as supporting backgrounds in partnering, contributed suggestions, observations, and advice.

6. HIDDEN ASSETS — MISCALCULATING THE NEED FOR VISIBILITY AND COMMUNICATIONS BEFORE AND AFTER SIGNING THE DEAL.

Public companies have an obligation to announce all material events publicly. But the mostly private, entrepreneurial, scientist-founded companies in the life sciences seem of two opposite minds on external communications — one preferring a "dark" identity and the other, an open face to the outside world. It is difficult to see how the gone-dark companies expect to reach prospective partners, clinical investigators, and opinion leaders to win support for their research.

Small companies can help their partner-seeking efforts through well-targeted media relations, publishing strategies, and opinion-leader management. "It is important to communicate what we do because it is a new science," says Sudhir Agrawal, chairman of Idera Pharmaceuticals, which is developing compounds targeting toll-like receptors (TLRs). "But while we share this story with our investor base and with others in the academic world, our target audience is Big Pharma executives looking for licensing, partnering, and acquisition opportunities — people whom we can influence via multiple-targeted efforts to get interest in the program and interest in the company."

After landing a partner, a company will need to coordinate those efforts closely, so the ground rules should be written into the deal, starting with visibility around the deal announcement. "Big Pharma does not want many of these business partnerships to appear material, while for innovative life-science companies, visibility equals validation of science and deal-value economics," notes Gil Bashe, Health Practice Director at Makovsky + Company. "Not discussing the implications of news flow early at the deal signing creates unnecessary conflict later in the relationship."

But Shaun Grady, head of business development at AstraZeneca (AZ), says his company prefers to leave the financial terms of its deals entirely private. "Obviously partners want to convey to their shareholders the maximum potential from the deal, and we are sensitive to that. It's just about being measured in the information we provide to our shareholders and the shareholders of the company that we're doing the deal with." Whether AZ is leading a new trend by Big Pharma toward nondisclosure of financial terms remains to be seen.

7. ALLIANCE OVERRELIANCE — ASSUMING THE PARTNERSHIP WILL BE PERMANENT, WILL NOT FAIL, AND WILL FULLY SUPPORT YOUR COMPANY.

Many companies assume the deal was the hard part. It's not. Making the deal perform so that the product gets to market successfully is always a monumental challenge, requiring resources that must be planned for, budgeted, acquired, and managed internally.

Partnerships usually fail during the product development process for many reasons, not least among these that drugs usually fail during development. Most deals with Big Pharma or Big Biotech have unilateral cancellation rights for the big player. Make sure there are "outs" in the deal terms to allow recovery of IP, data, materials,

processes, and all the other elements required to go forward and survive when, not if, the partnership fails. Those are hard points for negotiation, but a serious potential partner, and their attorneys, will understand. Also, raise additional money on the "high" of a successful deal, not later when the deal has vaporized and cash is low.

8. INACTIVE EXCHANGE — FAILING TO MAINTAIN CLOSE COMMUNICATION AND TRUST WITH YOUR PARTNER.

"Whether it be the internal decision-making process of the respective organization, timely and complete data sharing, progress updates, or discussion related to program challenges, a lack of openness between the parties can quickly sour a relationship and ultimately result in an absence of trust," says Mary Lynne Hedley, Ph.D., president, chief scientific officer, and cofounder of Tesaro, a biopharma company that is developing licensed-in oncology drugs.

"It takes time to build trust, so begin immediately and keep at it," adds Erin Brubaker, VP, worldwide business development alliance management (AM) and head of the AM Centre of Excellence, GlaxoSmithKline. "Start by communicating frequently and transparently with your alliance partner. Be authentic, consistent, and credible, 'walk-the-talk' — the fastest way to break trust is to not follow through on a commitment."

Being a pest is far superior to losing the partnership due to poor or too-infrequent communication. Particularly when the partners are wildly different in size, the smaller entity has to be extremely careful, diligent, and organized in ensuring that all the stakeholders on both sides are connected, and in keeping the connections live.

Eric de La Fortelle, CEO of therapeutic-antibody developer Delenex Therapeutics AG and a former global head of technology partnering at F. Hoffmann-La Roche, also warns against the David vs. Goliath syndrome between partners. "Biotech may consider the pharma partner as a sluggish cash cow to be milked. Pharma may consider biotech as a corner-cutting group of cowboys that cannot be trusted for solid project management. This is toxic to a partnership. An unemotional review of the facts shows that the pharma department you did the deal with and the biotech are usually evenly matched in scientific skills, scale of operational budgets, and staffing and industry experience, which leads to a convergence in culture. The two sides need each other and can talk on an equal footing."

The most essential communication from innovator to pharma partners is the delivery of bad news, adds de La Fortelle, "The worst-case is that the Big Pharma partner finds out once the alliance is ongoing about unsavory data the biotech would rather not disclose. This lends an unfair advantage to the pharma partner, who is then able to negotiate much better conditions under the threat of exiting the contract for breach, or worse, legal action."

9. DIVERGENT ACTIONS — FAILING TO KEEP ALL STAKEHOLDERS' INTERESTS ALIGNED.

After the deal is signed, make an intense effort to be sure that the interests, objectives, and work plans of all players stay fully aligned and free of conflict. Institute mechanisms to check and maintain that alignment on a regular basis.

"In many cases, a small company is partnering its key asset, and relies on its partner to enhance the value of that asset," notes Hedley. "Once in the hands of the larger company, the asset must compete for resources and may become deprioritized under new leadership or a change in strategy. A different risk tolerance profile may exist between the organizations, and if new data suggests a change in risk, a partner may no longer be willing to move forward or may need to reassess the program and essentially rethink its commitment. The innovative, quick-paced small company can be challenged to understand the length of time it takes for a larger organization to progress an asset or to move through the process of decision making."

When one partner is a Big Pharma and the other is primarily a research organization, there is always a problem in becoming accustomed to doing things that serve each other's needs and requirements. Big Pharma has some almost absolute principles and processes that are quite foreign to a pure research environment. Examples include regulatory requirements prohibiting any discussion of clinical studies by anyone in public, heavy restrictions on publications and presentations prior to full IP review and patent filings, need for creative IP to strengthen and lengthen the commercial runway for the product, need for biomarkers to couple with the product for the new environment of patient selection, therapy monitoring and prognosis; and need for re-justification of the project and partnership on an annual basis by corporate finance and strategy groups. Learn the needs; accommodate them; don't complain about them; and be very diligent in getting them met.

But don't oversimplify the dichotomy. "It's still common to hear 'pharma thinks' or 'biotech thinks.' Both are utter nonsense," de La Fortelle says. "But both sides have interest groups that clash internally. Pharma increasingly faces, for each partnership project, a fixed-sum game that eventually forces out an internal project for each one brought from outside. The decision-making process can be more or less smooth depending on how business development people and management 'sell' the opportunity to operational R&D groups, and how much they involve the experts in the data-gathering and decision-making. Secondary interest groups include accounting, the tax department, portfolio management, and corporate communications, which may need news flow regardless of the value of the opportunity.

"In Biotech, the tension is simpler but potentially more intense, between the board and management for whom non-dilutive capital gives a little more independence from VC money. Transparency is almost always better. The more these various stakeholders can be mapped out in prepartnership discussions, and a joint plan be put

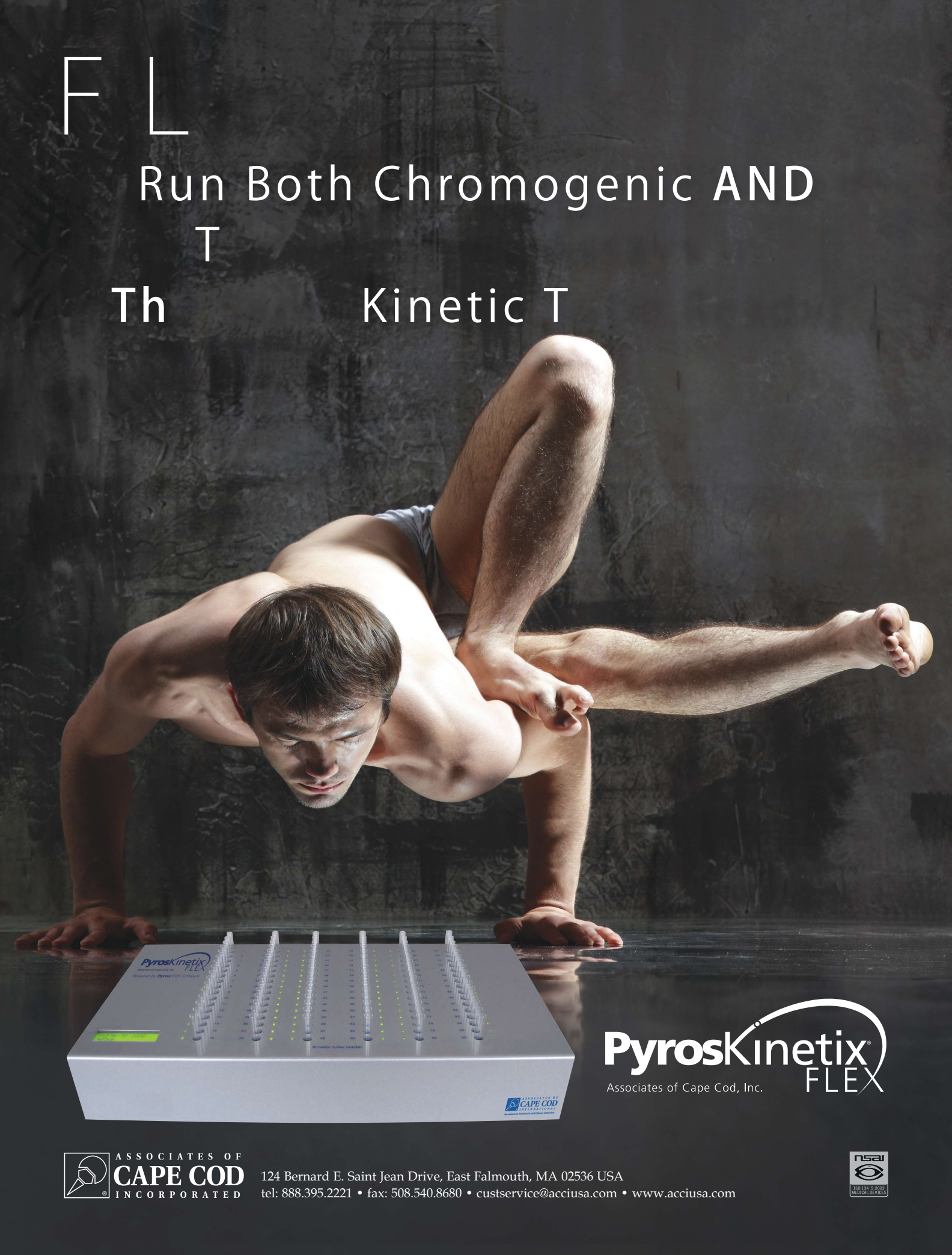
together to smooth the decision process, the less unpleasant surprises will derail the path to signature."

10. BLIND DEVELOPMENT — FAILING TO ENVISION YOUR ASSET'S ULTIMATE USE, POTENTIAL PATIENT NEEDS, AND ENGINEERING ISSUES, INCLUDING MANUFACTURING.

"Many times companies think 'market driven' means marketing driven. And it's not that. It's listening to the customers and finding the unmet needs. And you have to understand the science and technology and combine those two things together," says John McDonough, CEO of T2 Biosystems, originator of a novel "direct detection" diagnostic platform. Generally, he observes, an innovator company starts out by explaining and discussing its technology with clinicians and potential partners. Later, as data accumulates, the discussion turns to an actual product. "Once you have data, you don't have to worry as much about explaining the science."

Jason Rhodes, chief business officer of Epizyme, which is developing a platform of small molecule histone methyltransferase inhibitors and screening technology, describes "market modeling" as a key part of the research and development process. "We make a product profile as soon as we pick a target and begin doing research on it. By then, we have genetically defined our patients, and we work to understand possible indications and how our treatment might fit into the clinical practice currently and a few years down the road. First, you have to design the right clinical trials and enroll the right patients, for regulatory approval but also for opinion leader and clinical adoption."

Inevitably, even before a partnership turns the innovator's asset into a real product, manufacturing — producing the physical compound, device, or even prototype for testing proof-of-concept in patients — will likely become the responsibility of the small company. All the small companies represented by contributors to this article have made production a key concern. Some have already built or hired enough capacity for commercial supply, and made commercial use of their own unique manufacturing platform. In every case, their executives said figuring out the challenging details of making their novel products proved to be an advantage in seeking and keeping their larger partners.



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Change Management: The Sanofi Model

By Suzanne Elvidge, contributing editor

We live in a fast-paced and fast-changing world, and companies have to adapt to be able to keep up. For some people, change is exciting and stimulating; they enjoy the feeling of slight discomfort and uncertainty that goes with transformation. But for others, change is just disturbing and distracting. This is where change management comes in, and Dennis Urbaniak, VP U.S. Diabetes at Sanofi, has learned a lot about managing change and getting the best out of it during his 18 years at the company.

WHAT IS CHANGE MANAGEMENT?

Change management is traditionally thought of as a structured process that moves individuals, teams, or even entire companies from the current work patterns and organizational makeup to new patterns and structures. It should help people to understand, accept, and even see the advantages of the new setup. However, Urbaniak sees it as more all-encompassing — as something that needs to be borne in mind for all changes within a company, however small.

"Change management is about how to handle specific and even major change, but it's also about how to interact with customers, and how to run an organization on a day-to-day basis," he says. "Change is a discipline, not just a single event. Effective change management can alter behavior and have positive and long-term outcomes throughout the company, and throughout people's careers, as well."

CREATING AN ENVIRONMENT FOR CHANGE

In order to make change easy, effective, and positive, it's important to create an environment that fosters and rewards change, supports the ability to learn from change, and even encourages people to be interested and curious about the changes that are being made. But how can companies create this type of environment? According to Urbaniak, it's all about communication.

"The first step is to communicate and share the rationale for change and encourage dialogue across all stakeholder groups, regardless of level," Urbaniak explains. Once an organization or team has established that it needs to change, and this rationale has been disseminated to all its members, the next step in change management is to establish clear, measurable, and sustainable goals and outcomes, and to communicate them clearly.

"Throughout the process, it is really important to remember the goal behind your changes. It sounds simple, but many companies get carried away, and you end up with change simply for change's sake," says Urbaniak. "If change is seen as an ongoing environment, then this can be used as a way to learn, but it is important to stop the activities that don't add benefit and prioritize the things that do."

The measures are just as important as the goals themselves, and deciding the measures for the goals beforehand (and communicating them) can make the whole process of change go faster and be more effective. "A lot of organizations just assess the outcomes after the fact, to see if things have been successful. It's important to have up-front measures and goals, and to be prepared to change the process as you are going along if need be, rather than just defending the course of action afterwards," says Urbaniak. "I have seen pilot projects that have just gone on forever. This always reduces the chance of a positive outcome. The process should be about measuring, learning, and then making an adjustment, rather than getting to a point and saying, 'We are done'." Any change involves risk, and in fact, risk-taking is a key part of change, but it does expose the vulnerability of individuals, management, and even the company, and the leadership needs to declare this risk up front.

GETTING THROUGH CHANGE

Some people don't like change — they just don't know how to deal with it — but others want to be right in the thick of it, and the leadership needs to manage both groups of people. "It's important not to forget or dismiss the people who don't cope well with change, otherwise you run the risk of losing valuable employees. Work with these people to see what their experience is, and see where they can contribute the most, and use their strengths. To help them out, you need to continue the dialogue, show them how things are moving, show them the progress, and share the learning. While it can be

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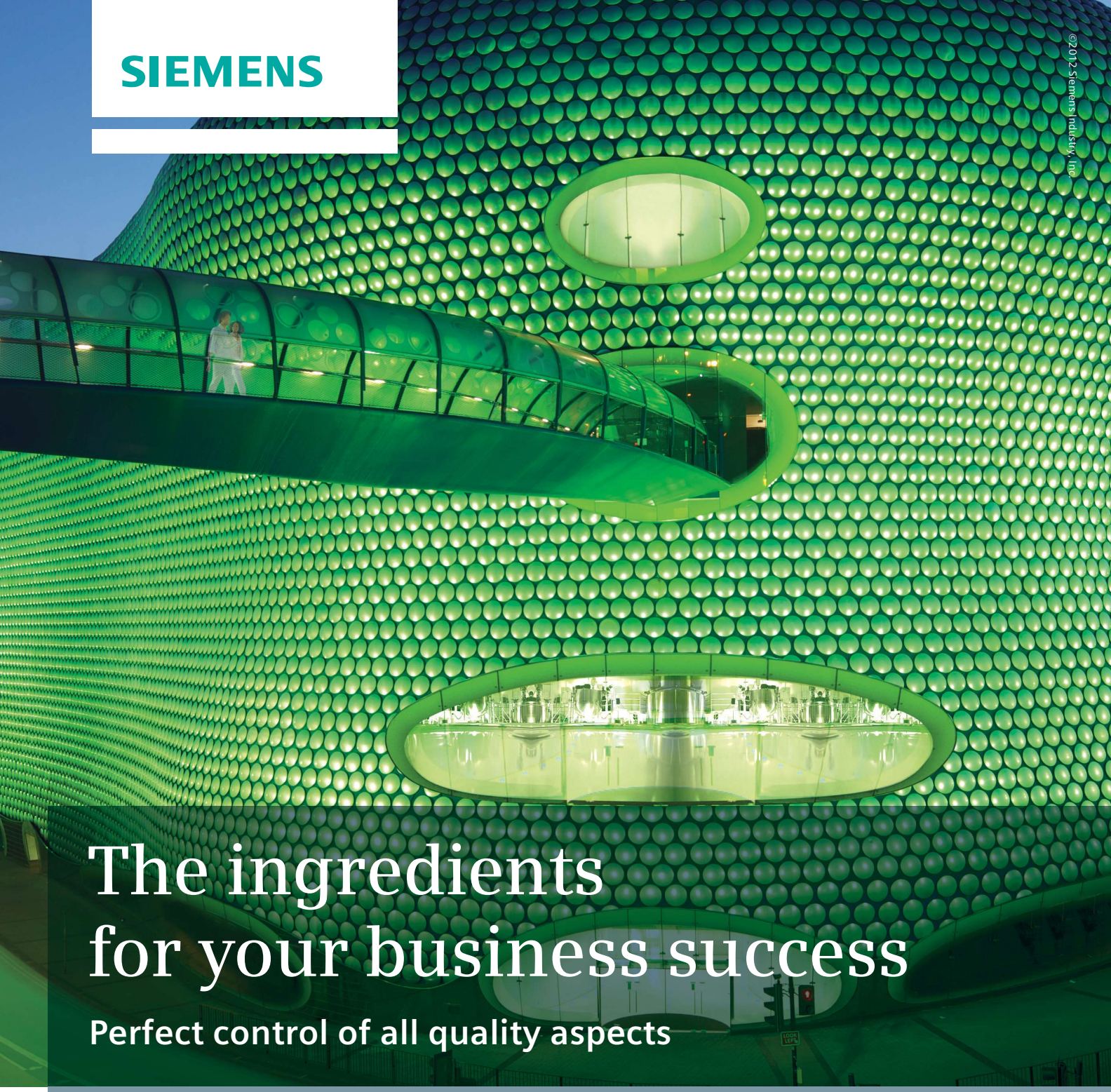

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beneficial to have a team that is open to 'feeling uncomfortable,' it's important not to force the feeling," says Urbaniak.

CHANGE AND INNOVATION AT SANOFI

Urbaniak has worked in core areas that needed to change and adapt, and in completely new initiatives, both of which have required change management. The restructuring of Sanofi's U.S. Diabetes business unit is an example of an area that needed to evolve and was driven by a market need.

Companies have historically carried marketing out brand by brand, and Sanofi's U.S. Diabetes business unit has been no different. Urbaniak is working to change the model toward a franchise offering diabetes solutions rather than marketing individual diabetes products or brands. "This restructuring changes how we communicate and value the offer," says Urbaniak. "The brand-based marketing can look disconnected, but the customer-based franchise model, targeting either the patient or the physician, is more efficient and easier to access."

Many big pharma companies have seen a dearth of innovation, with pipelines thinning out as marketed products fall off the patent cliff, and costs spiral for the development of new products. There also have been changes in physician practice and consumer demand, as well as sweeping U.S. and worldwide healthcare reforms. But Urbaniak says diabetes is still an area that needs innovation, explaining that by 2050, one in three Americans could have diabetes. "To meet that challenge, we need to change how we look at its treatment. Many companies have focused on simply providing drugs or devices, but we have realized that these are just a component, and we need to seek more of a solution from the patient's perspective. And this solution will be different for everyone. There are already a lot of great drugs on the market, so what is needed is a new approach, not a new drug," says Urbaniak.

> "Many companies get carried away, and you end up with change simply for change's sake."
>
> Dennis Urbaniak, VP U.S. Diabetes, Sanofi

This new mindset has required a change in how companies look at innovation – how they use it and where they find it, as it's never as simple as just being able to say to researchers "go innovate." Change and innovation are incremental as well as disruptive, so it's important to look for the small ideas as well as the big ones. Facing up to this, Sanofi has created a centralized innovation group, which is looking at new ways to run the business. For example, patients are becoming increasingly vociferous, particularly through social media such as Twitter, Facebook, and LinkedIn, and through patient groups. Sanofi has decided to use this to its advantage by creating a non-brand-specific social media group. The company is using this group to "crowdsource" answers to questions such as, "What matters most to you in diabetes?"

"Monitoring social media gives us the opportunity to hear what the market is saying and provide our customers — both physicians and patients — with what they really want. Two-way communication is just as vital here to manage change in the market as it is with employees, when trying to facilitate internal change."

The Sanofi U.S. Data Design Diabetes Innovation Challenge is an example of how the company changed the way it approaches innovation. The first challenge, launched in 2011, promised prizes of up to $100,000 for innovators to develop a data-driven project that could improve life for patients or caregivers in the diabetes community. "In six months, we had more than 100 responses. It would have taken us maybe four or five years to develop that many proposals in-house," says Urbaniak.

The outcome from the 2011 challenge was the Ginger.io app, which tracks how people are feeling by analyzing changes in their location and cellphone use patterns through "machine learning." People with diabetes are almost twice as likely to suffer from stress, anxiety, and depression, which can interfere with diabetes management. When the app spots this kind of behavior, it sends out "caregiver alerts" to friends, family, or healthcare professionals, to suggest that they check in on the patient. Ginger.io carried out its first patient study in people with inflammatory bowel disease (IBD), and the company plans a month-long diabetes study for 2013, to see if the app does have an impact on disease management.

The success of the project has sparked change in how innovation is perceived in other parts of the company, and similar programs in other divisions may soon be developed. This project also proves that, in addition to patients and caregivers, there is also a role for government in developing innovation. For the challenge, the U.S. government helped Sanofi tap into a network that the company could not have reached alone, as well as provided open access to the data sets on healthdata.gov.

"I hope more companies will see that change is a fundamental aspect of business — you need to feel comfortable with being uncomfortable. However, it's important to remember — the best ideas come from customers, employees, and partners, not from you. Your role is simply to provide support and coordination," concludes Urbaniak.

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Continued Progress In Continuous Processing For Bioproduction

By William Whitford

It's been years since the FDA articulated, in its PAT (process analytical technology) guidance, the goal of "facilitating continuous processing to improve efficiency." Since that time, many have invested in establishing continuous processing (CP). Janet Woodcock, of the Center for Drug Evaluation and Research (CDER), recently commented "continuous manufacturing is going to become a reality." However, despite some early successes in particular unit operations, we have seen little application in biopharm manufacturing. But this is changing, and from seed stock expansion to fill and finish, we now see the development of a number of CP operations for biopharm.

The power of continuous processing (or production) has been recognized since its application to chemical manufacturing in the late 19th century. Its popularity stems from advantages in efficiency, economy, and product quality. Beyond its practicality, CP is consistent with the goals of QbD (Quality by Design) and is supported by results from PAT. In continuous processing, materials constantly flow from operation to operation, in and out of specialized equipment. While batch processing is a current standard in bioproduction, the significant limitations of such a discrete and discontinuous format have been well catalogued — and range from scale-factor issues in development to the consequences of interruptions and delays in production.

CP ADVANTAGES

In CP, materials and intermediates experience a more consistent condition in a steady state. Reactions are not "warmed-up," materials are not exhausted in gradients over time, and a bolus reaction (or culture) is not run to the point of inefficiency. CP's heightened processing parameter consistency provides improved product uniformity and quality. Quality also can be improved by CP's simplified control strategy and its close control of operating parameters around one (optimized) point. It's simplified and shortened process stream, lower reactor residency times, and more concentrated intermediate product also contribute to improved quality. CP can reduce both the amount of, and operator intervention in, process intermediates. Not only can process capability be heightened, but chemistries and procedures unavailable in batch can be presented. CP provides advantages in facility design and construction through reduced footprint and increased facility utilization. Its equipment is inherently easy to clean, provides a shortened production train, and an easy product changeover. A number of sustainability methods are supported as CP's methods provide reduced service and energy consumption. The online monitoring and real-time quality assurance supported makes it amenable to such goals as continuous quality verification as well as parametric and real-time release (see the EMA [European Medicines Agency] new bioprocessing-relevant guideline). Process development and technology transfer is eased, both because development can be accomplished at the final scale of manufacturing, and because CP approaches support numerous "hybrid" technologies (e.g. between classical and single-use systems).

REGULATORY ISSUES

Surprisingly, relevant regulations and guidance are silent on designating the manufacturing mode to be used, yet some considerations for CP approaches are presented. The ICH (International Conference on Harmonization) notes in its Q7 guidance, "In the case of continuous production, a batch may correspond to a defined fraction of the production," and the IPEC (International Pharmaceutical Excipients Council) states "For continuous processes the batch and its records should be defined." It is also

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noteworthy that drug product manufactured by continuous process is specifically defined in 21 CFR 210.3(b)(10).

Quality and safety are reasons for the designation of manufacturing lots, as it has implications on such activities as material rework, process deviations, recalls, and pharmacovigilance. Lot definitions in batch processing are rather clear and intuitive, but in CP significant issues arise in their designation. A CP lot may be delineated by such means as time-stamp, volume, or mass-determined portions of the entire batch.

PHARMA CP CONCERNS

There are a few financial, engineering, and regulatory concerns slowing the uptake of CP in pharma. Some still have concerns regarding the FDA's reception in general, or just how CP-specific approaches will look in a design space concept or failure analysis methods. CP does require some new in-process testing and release approaches, as well as new, more robust adaptive and closed-loop control systems. Some new strategies will be needed as well in such areas as regulatory applications and knowledge management. While some unit operations can be very readily converted to CP right now, for others the means of monitoring some required parameters are not yet adequate. Often both the definition and frequency of measurement of CPPs (critical process parameters) are yet to be determined. This is notable because a clear definition of both critical product quality attributes and process parameters is required for transition from an existing batch to a knowledge-based CP approach. Well-founded or not, process-related concerns include start-up and shut-down material losses, achieving the robust throughput balancing required and fears regarding equipment cleaning — as well as the fact that when any unit op in CP is down for any reason, the whole process is down. Finally, because of existing batch process capacity, others see potential business case issues.

CP IN BIOTECHNOLOGY

While not common, successful examples of continuous procedures in biopharmaceutical production do exist and such unit operations can be thought of as "building blocks" toward a fully continuous manufacturing line. Modern enablers to this approach are the gains afforded by the PAT and QbD initiatives, as well as the rapid uptake of single-use technologies (SUT). The modularity and flexibility of SUT can aid in reducing process steps and facilitate adaptability in a CP flow and layout. Single-use technologies support hybrid reconfigurations where required, and easily accommodate novelty in process design. Beyond the general concerns noted above, there are a few bioprocess-specific concerns in CP for such major production applications as recombinant protein secretion or viral vaccine production.

CP IN UPSTREAM BIOPRODUCTION

Methods supporting continuous or semi-continuous manufacturing include distinct implementations of intermittent harvest, repeated-batch, and perfusion culture. In perfusion, cells are separated or retained (by one of many distinct means) while the culture medium is continuously exchanged. Perfusion culture applications in bioproduction were established, with limited adoption, decades ago —but have lately been growing in popularity. Centocor (now Janssen Biotech) has long been employing perfusion culture in the production of approved product. Genzyme manufactures such products as Lumizyme in CHO-based perfusion culture, and its continued commitment to perfusion is demonstrated by a recent expansion of such capacity at its Geel, Belgium plant. At this spring's ACS meeting in San Diego, Bayer HealthCare presented on methods for operation of steady state perfusion bioreactors during production in mammalian cells. Practical implementation of the perfusion mode has been facilitated by increased process understanding, innovation in real-time measurement and improved control technologies. Maybe a dozen distinct perfusion-like approaches for both research and production scale culture have been commercialized in recent years, including alternating tangential flow, and number of packed-bed and hollow fiber bioreactors.

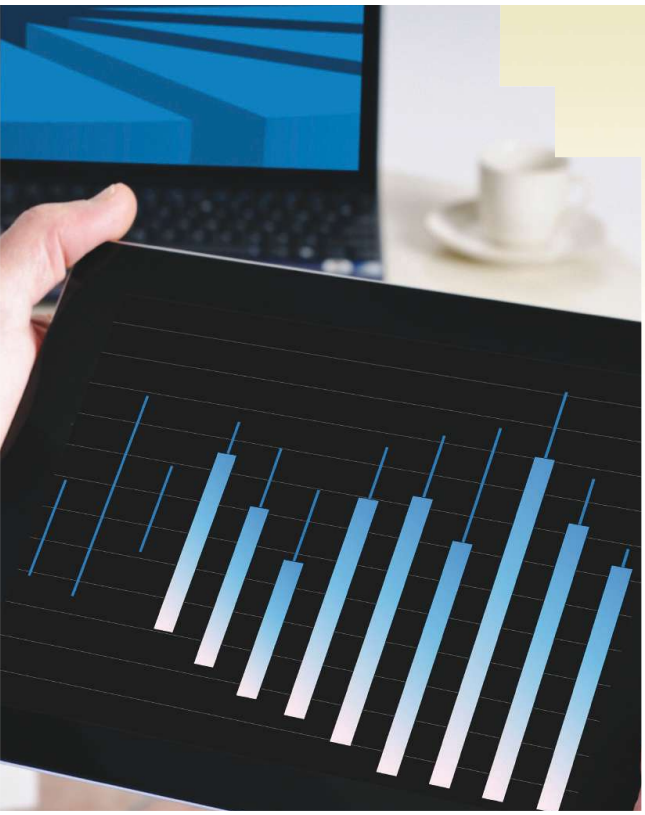
CP IN DOWNSTREAM BIOPRODUCTION

Bulk harvest from large-scale production traditionally undergoes processing operations in employing stainless steel tanks for process fluid and product storage. We've recently heard much regarding downstream bottlenecks, and CP is actually one way of addressing them. Use of such adsorption media as Protein A resins are easily envisioned in a batch mode, however they can be implemented in more continuous processes. Examples of this range from simulated moving bed to countercurrent tangential flow chromatography appearing in entirely disposable flow paths. Because of the higher volumetric product titers and reduced contaminates of serum-free culture, a number of novel chemistries and "flow-through mode" chromatographys supporting CP are now appearing. Surprisingly, the "topping-up" of large-scale containers with a newly prepared buffer providing a virtually unlimited supply has been validated for cGMP manufacturing. Continuous buffer preparation using in-line dilution of concentrated stock solutions has been attempted for years. Lately, this is being realized by advancements in dilution instrumentation, monitoring technologies, and feedback control methods based upon such criteria as component concentration, pH, conductivity, or mass balance.

Equipment and systems supporting continuous processing in operations from seed-stock expansion to fill and finish are appearing. As contiguously combined with such other enabling technologies as single-use mixers and storage systems, the design of flexible, disposable, and continuous biomanufacturing systems is finally being realized.

About the Author

William Whitford is senior manager for the bioprocessing market in Thermo Scientific Cell Culture and BioProcessing at Thermo Fisher Scientific.



Making Regulatory Information Management Pay

By Gillian King and Joel Finkle

At a time when the pharmaceutical industry sorely needs to be focusing on product innovation and market expansion, life sciences companies find themselves weighed down by increasing regulatory burdens and the large volumes of data they must generate to comply with each new requirement. While there are no shortcuts to meeting those important regulatory stipulations, there is a way pharma organizations can turn the requirements to their advantage: by using that same data to streamline internal processes and improve planning.

Pharmaceutical companies depend on data to bring products to market, yet many struggle with managing all that data and information cohesively and coherently. Regulatory information management (RIM) can add real value by bringing order to chaos and by giving transparency to complex and diverse business operations. RIM is a method of bringing together all of the pieces of information and data that tell the complete story of a product — from conception to market entry, to ongoing marketing — so that a company can meet the regulatory authorities' national and international demands.

Once such management is being performed systematically, the process of bringing new products to market is less onerous for everyone involved because it eliminates repetitive, manual information capture and reporting processes and makes it easier to monitor, plan, and influence chains of events. RIM has the potential to even allow individual products to be tracked at a discrete level as they get made and distributed, thereby both improving the responsiveness of product recalls and improving patient safety.

MORE STANDARDS, MORE HOOPS

As health and safety requirements have increased in recent years — leading to changes in the regulatory and commercial landscapes — companies have come to appreciate the need for a better way to track and manage critical compliance data. In the worst case, failure to meet regulatory requirements could result in products being refused approval or being withdrawn from the market.

In response to product scares and growing patient awareness around issues of drug safety, the health authorities have become a lot more risk averse, introducing higher standards and inserting additional hoops for pharmaceutical companies to jump through to prove those companies' robust processes and attention to detail. One of the most recent and prominent examples is the European Medicines Agency's (EMA's) EudraVigilance Medicinal Product Dictionary (EVMPD) mandate, designed to provide regulatory agencies with more-extensive pharmacovigilance information so that individual batches of product can be traced to their source, associated information dissected, and appropriate action taken without delay.

The EVMPD is the EMA's central database telling where specific products are registered. From July of 2012, companies will be required to submit detailed EVMPD data for every authorized medicinal product they sell or otherwise distribute in the European Union. This is a mandate with wide-reaching implications. It requires that marketing authorization holders send to the agency all product and substance information that ordinarily would have been stored and gathered by the individual market companies or affiliates and that would therefore not be in one place. Similar information is needed for U.S. Structured Product Labeling listings and registrations, though the U.S. system is less complex for companies to navigate because the United States is a single regulatory market with a single language.

Efficiency and productivity improvements are additional goals of improved RIM, because today's difficult economic environment takes its toll on the administrative capacities of both the health authorities and the pharmaceutical companies. Having eliminated redundancies and curbed new recruitment, pharma companies must now manage their opera-

tions with fewer resources. This has increased their interest in automated processes supported by reliable content management and workflow solutions whose primary goal is to make users more efficient.

DOING MORE WITH LESS

Forward-thinking organizations have found that they can accomplish several things at the same time if they make the right investments in technology. By looking beyond the basic requirements of regulatory compliance and more closely aligning software with their own internal business strategies — doing more with less, focusing resources on R&D and innovation, and getting products to market faster — organizations are finding they can enhance the returns on their investments, achieving a great deal more for their money.

Once data is being captured systematically and electronically, that data is much easier to find quickly by whoever needs it and at the point of need. This gives companies unprecedented insight into their operations, which they can now exploit in their planning and commercial decision making. Equipped with the right software, companies' internal teams are given a 360-degree overview of everything that's happening with a particular product at a given time. At a glance, they can pick out themes and trends in given regions, enabling them to make strategic decisions about their portfolios for the future.

Consider the fact that most large or midtier pharma companies have numerous products registered around the world in different ways, under different names, and with a range of formulations. When a new product is about to be launched, commercial teams want to know about specific markets in order to determine how best to establish or promote the new product therein. Turning to their regulatory affairs colleagues, they may ask whether they can market the new product in a particular country from legal and regulatory standpoints. The response will depend on regulatory affairs having access to information about already existing products in those markets.

From a purely commercial standpoint, RIM is probably the most important means by which a company can visualize its business and develop its strategy — because of the complete profile that such management represents of a company's exist-

ing and planned activities. RIM also provides a means of assessing the knock-on effect of one decision on lots of other activities. For example, a pharma company that changes the manufacturer for an inactive ingredient must be able to plot the updates it now needs to put in place across, say, 14 products in 27 countries. A RIM tool enables those involved to see exactly which submissions would be affected and to plan accordingly. In short, RIM puts more information at a company's disposal so that decision makers are better prepared to decide how to move forward.

LOGISTICAL CHALLENGES

Achieving effective RIM is rarely straightforward, especially when organizations have long-established products on the market that must be mapped retrospectively. Trying to piece together a comprehensive product history is potentially overwhelming. Companies will need to decide whether it's worth collating information on products that might have been on the market since, say, the 1970s. A more pragmatic approach might be to implement regulatory IM for activities that go back no further than five years, for example.

The first decision a company needs to make, then, is where to start. The decision will depend on where the company is in its own history and where its products are in their life cycles.

A company also will need to acquire a thorough understanding of how it currently gathers and manages information. For example, are there centralized or decentralized points of control? Where is the information held, and who maintains it? Sometimes a company decides to acquire a RIM system without even considering who will be using it and who will be updating it, yet those are the most important criteria to operating such a system: knowing who the users will be, what their needs and goals might be, and who is going to keep the data current.

At the start of a company's RIM project, the biggest challenge involves moving into a single, central repository all of the information that exists in databases and spreadsheets and solutions across the enterprise and then using the same terminology for the same data. Another challenge is that, because RIM needs to be implemented as an internal project, a life sciences company typically lacks the standards that are available for, say, managing submissions. Moreover, as yet, too few comprehensive RIM solutions have been implemented in the industry for best practices to have evolved. Nor is it possible to produce a one-size-fits-all RIM solution, since the needs of a widely dispersed company will differ significantly from those of a geographically compact company or from those of a virtual company. The reality is that each company has its own way of viewing RIM and therefore its own needs: Some might take a project management approach, others might come at the requirement from a pharmacovigilance perspective, and still others might consider it a means of improving registration tracking.

THE BROADER THE SCOPE, THE BIGGER THE IMPACT

Regulatory information management can touch every aspect of a company's business, from product management (keeping track of which products are available where, the current licensing status, whether safety update reports are due and so on) to submission management (e.g. where the company's products are registered, any actions that are due and when, and the status of agency correspondence).

The opportunity to store information in a central repository — thanks to the development of virtual private networks and the cloud — leads to further efficiencies by facilitating remote data access and collaboration. This, in turn, makes RIM more tangible for dispersed organizations.

As these broader benefits become better understood and appreciated, companies will find themselves better able to effectively manage their pipelines around the globe for commercial gain, and the demand for, and the sophistication of, RIM solutions will continue to grow exponentially.

In time, the discipline of regulatory information management will only grow in importance, and tight integration between related systems will help increase the impact. By aligning submission authoring and publishing tools (e.g., electronic Common Technical Document systems) with RIM tracking tools, organizations will become able to move information more naturally between systems, turning raw data into decision-supporting knowledge. As ever, the devil is in the details, and the trick is to harness those details and make them pay.

About the Authors

Gillian King is head of global consulting, global professional services, CSC Life Sciences, and has more than a decade of regulatory experience in the life sciences industry.

Joel Finkle is senior strategist, regulatory informatics, CSC Life Sciences, and a member of the Health Level Seven International Regulated Clinical Research Information Management working group dedicated to development of Regulated Product Submission standards.

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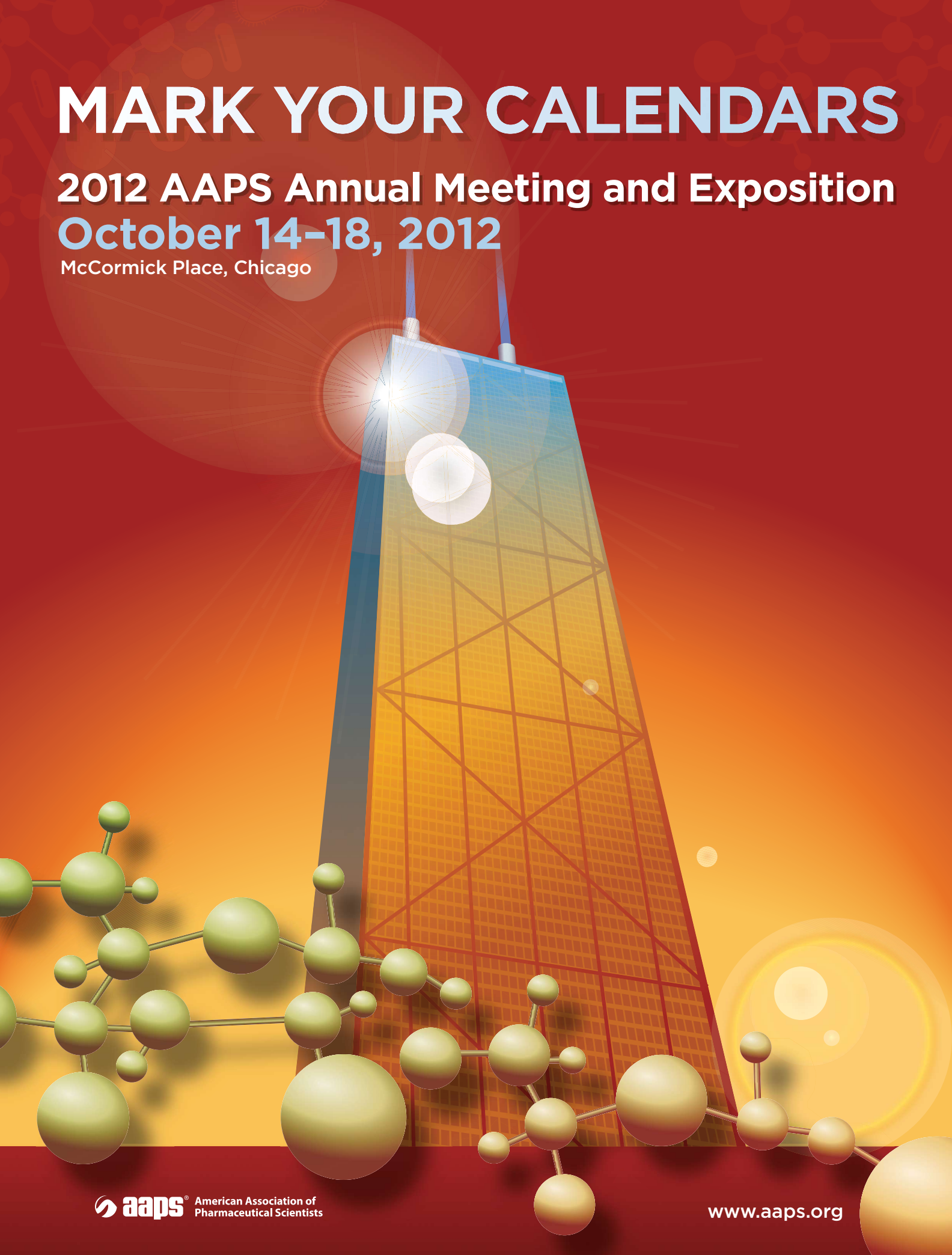

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Tips For Selecting A 3PL For A Life Sciences Supply Chain

Many life sciences companies are outsourcing their supply chains to 3PL (third party logistics) providers. It seems that everyone is getting into the 3PL business from public warehousing firms to trucking companies. When a life sciences company decides to outsource its supply chain, it needs to ensure that the 3PL understands the complexities of the business. Yes, life sciences is different from manufacturing and high tech. When selecting a 3PL, it is important to understand if the 3PL is committed to the life sciences vertical market and has the experience in managing the life sciences supply chain. Many 3PLs become extensions of the life sciences company's staff. Here are some general questions that need to be considered when evaluating a 3PL for the life sciences supply chain. How was the 3PL formed? Did the 3PL acquire a smaller life science logistics company or are they part of a larger drug wholesaler? How many individuals on the staff have deep experience in the life sciences industry? Did they previously work for a wholesaler or a pharma company?

THREE AREAS TO FOCUS ON

QA is a critical area that needs an in-depth analysis when considering a 3PL. Is the 3PL committed to a quality assurance program? One telling trait is to look at an organization chart and determine where QA reports in the organization. QA should not be a part of operations; its staff should report directly to the president or CFO. One key area to review is what the annual budget is for QA and the number of people who are involved in the organization. A small QA organization may mean that the organization is not committed to the QA process. Business needs and requirements change, requiring CAPA (corrective action and prevention), SOPs and WIs (work instructions) to be updated. This takes an organizational commitment in time, money, and people across the organization.

Information technology is another area that must be considered. Does the IT staff understand the additional level of effort for documentation, testing, and implementation, and is it committed to maintaining a validated system? It is extremely important that the 3PL IT department understands 21CFR11 and cGMP. In addition, can the IT department provide visibility to product and shipments throughout the supply chain? Does an IT roadmap exist that summarizes the direction of the major IT projects over the next two to three years? Does the organization have a plan and budget for evolving technologies such as RFID, e-Pedigree, and serialization? Operations is another area that needs proper due diligence. Most 3PLs that truly understand the life sciences industry will have separate dedicated facilities and a separate workforce for their life sciences business. Life sciences products are high-value, temperature-sensitive goods that require someone who understands the processes, procedures, and work instructions. In addition, individuals need to be able to take the right corrective action when something happens.

Last, but not least, the financial health of the 3PL (ascertained by reviewing the company's financials, Dunn & Bradstreet reports, annual audit report, etc.) must be a part of the due diligence process. Does the 3PL have the financial resources to be in the life sciences supply chain business? Do not underestimate the importance of having the right level of insurance (e.g. Who is their insurance carrier? Are they self-insured? What is their claims ratio? Have they paid out any large [$1 million or more] claims?). A lost shipment or spoiled product can cost millions of dollars. Whether we like it or not, accidents will happen, and it is not enough to meet the minimum requirements. For example a shipment may contain 10 cartons of a vaccine. The data loggers indicate five of the cartons were outside the ambient temperature range. The other five were in the questionable range. The minimum requirement would be to pay a claim on the five cartons. The right course of action would be to scrap all 10 cartons and pay a claim on the 10 cartons.

Those 3PLs that go above and beyond and take the right course of action when an error or accident occurs are the kind of partners you want to manage your supply chain. Overall, when selecting a 3PL to manage your supply chain, it is always better to spend the extra effort on due diligence.

James Bisaha

James Bisaha is the managing partner of Logistics and IT Consulting. He has spent 30 years in the transportation and logistics industry.

Visit That's Nice at booth **#2822,** BIO International Convention.

PROFILE INFORMATION

Nice Insight survey respondents were comprised of people who work at the following types of companies:

- Biotech 28%
- Emerging Biotech 8%
- Specialty Pharma 17%
- Big Pharma 27%
- Emerging, Niche & Start-Up 19%

niceinsight QUARTERLY INTELLIGENCE

Do you know how your business is perceived by the biotech market?

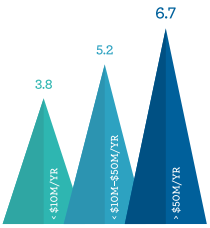
Within Pharmaceuticals and Biotechnology, survey respondents work in the following departments:

- Manufacturing 16%
- Regulatory 7%
- Operations 21%
- R&D 40%
- Purchasing/Procurement 7%
- Quality (QA/QC) 10%

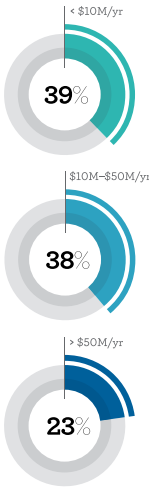
Average Number of Services Outsourced by Expenditure

5.1 Q1 Overall

As outsourcing budget size increases, so do the number of different services outsourced.



Annual Outsourcing Budgets



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OUTSOURCING TRENDS

Attributes of Outsourcing Partners Ranked in Order of Importance

QUALITY
RELIABILITY
PRODUCTIVITY
REGULATORY
AFFORDABILITY
INNOVATION

QUALITY

When selecting partners, survey respondents ranked quality as their number one priority.

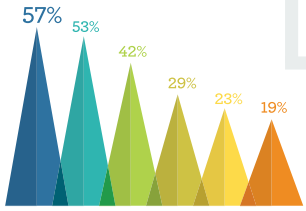
Methods Used for Selecting Outsourcing Partners:

- Consultants 57%
- Referrals 53%
- Industry Events/Trade Shows 42%
- Periodicals/Publications 29%
- Web Searches 23%
- Online Directories 19%

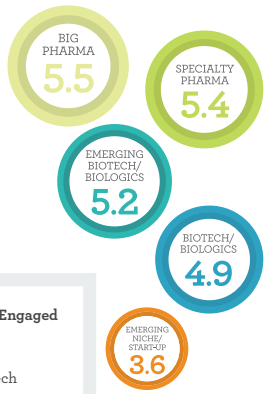
Q1 Results N=3,523

1 CONSULTANTS
2 REFERRALS
3 TRADE SHOWS
4 PUBLICATIONS
5 WEB SEARCHES
6 ONLINE DIRECTORIES

2.3 Average number of methods used to select an outsourcing partner



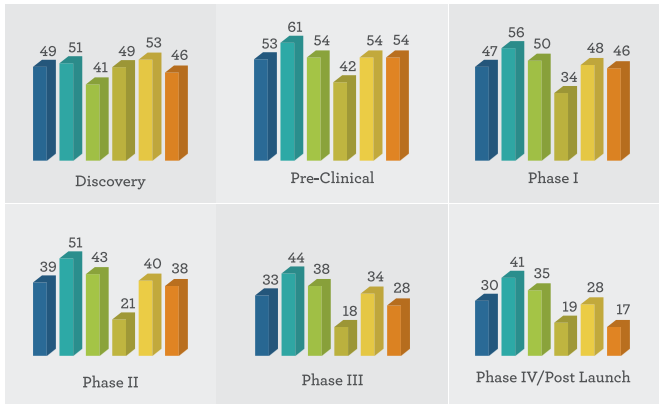
Average Number of Services Outsourced by Company Type



Phase Of Development When Outsourcing Partners Are Engaged

- Overall
- Big Pharma
- Specialty Pharma
- Emerging Pharma
- Biotech
- Emerging Biotech

% engaging partners at each stage

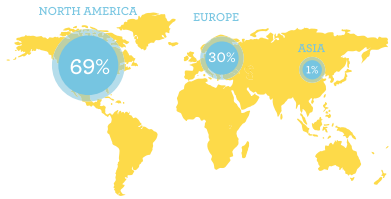


Buyers do.

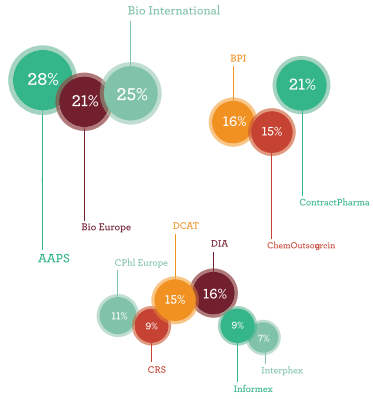
Breakdown of Services: By Therapeutic Area of Focus

- Cardiovascular
- CNS
- Endocrine
- Infectious
- Metabolic
- Oncology
- Respiratory
- Other

Respondents' Business Location By Region



% of Respondents Who Plan to Attend the Following Industry Events



Q1 Outsourcing Trends

18%

of survey respondents reported their company will outsource Packaging Projects in 2012.

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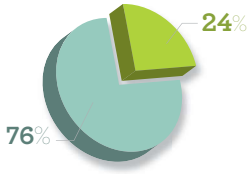
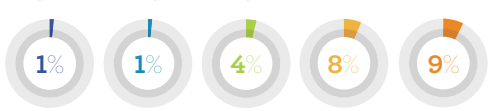
MARKETING COMMUNICATION UPDATES

71 different companies had marcom changes

- No Marcom Changes
- Marcom Changes



Companies that changed marketing between Q4 2011 & Q1 2012



Q1 Outsourcing Trends

41%

of survey respondents reported their company will outsource Consulting Services Projects in 2012.

Q1 Outsourcing Trends

14%

of survey respondents reported their company will outsource Cytotoxic Projects in 2012.

The Role Of Transgenic Animals In Preclinical Safety Testing

Dr. Ali Faqi

Ali Faqi, DVM, Ph.D., DABT, is senior director of developmental and reproductive toxicology and senior principal study director at MPI Research. Before joining MPI Research, Dr. Faqi was a senior scientist at Allergan Pharmaceuticals and a research toxicologist at IIT Research Institute.

Transgenic and genetically modified animals are being increasingly used in the study of diseases and for safety assessments of new compounds. They are a powerful tool for developing a more detailed understanding of the role specific genes play in biological pathways. The Federation of European Laboratory Animal Associations defines a transgenic animal as an animal in which there has been a deliberate modification of its genome.

The first transgenic mouse was created in 1974 by Rudolf Jaenisch, a biologist from MIT. He created this transgenic mouse through micro-injection of Simian virus 40 to explanted mouse blastocysts and early embryonic exposure to retrovirus. The technology to create transgenic animals broke new ground in the scientific community and enabled scientists to seek new ways of treating diseases and developing new drugs. The ability to introduce new genetic information into the germ line of complex organisms has completely changed and enhanced the study of all aspects of biologic processes.

The primary uses of transgenic mice models in toxicology have mainly been to screen for genotoxicity and carcinogenicity and to understand the mechanisms of toxicity. In preclinical safety testing, two-year mouse and rat bioassays are traditionally employed for predicting the potential risk of drugs/chemicals to induce cancer. These assays are time-consuming, use many animals (n=70/sex), and cost more than $1 million per study. Moreover, these traditional assays do not provide insight into the mechanisms of action nor explain key events leading to tumor formation.

The use of genetically modified mice for carcinogenicity evaluation began more than 20 years ago, when researchers found that different strains of genetically engineered mice demonstrated that cancer incidence is increased and tumor latency is decreased in mice whose germ line, the Ha-ras oncogene, has been inserted. Evaluation on carcinogenicity of newly developed pharmaceuticals using genetically modified animals has been performed since the adoption of ICH (International Conference on Harmonization) S1B guidelines on carcinogenicity testing of pharmaceuticals in 1997 and has increased greatly over the past 20 years, following this regulatory acceptance.

IMPROVING SCIENTIFIC UNDERSTANDING

Conducting studies on transgenic animals provides an exclusive opportunity to improve scientific understanding of the mechanisms of carcinogenic compounds. Several transgenic mouse models (Tg.AC mice, ras transgenic mice, p53 knockout mice, Pim-1 mice, p27-deficient mice, and Xpa mice) have been studied for their usefulness as replacements for the lifetime bioassay in carcinogenicity testing. These mouse models could reliably predict the carcinogenic potential of compounds and significantly reduce the number of false positives. However, when applied as single assays, the transgenic models are unable to identify all known human carcinogens. Therefore, using a short-term transgenic mouse assay in combination with a two-year rat lifetime bioassay could eliminate the occurrence of false negatives.

Generally, TgrasH2 and p53+/- are mice models identified as acceptable for use as alternatives to the mouse long-term study together with a rat two-year bioassay; however, currently available data does not suggest that one model is more appropriate than the other for a particular class of compounds. This combined approach could further increase the overall accuracy of detecting carcinogens and non-carcinogens in comparison to using only the lifetime bioassays.

Incorporating a six-month transgenic mouse model into safety testing strategies for new drugs/chemicals makes valid scientific, ethical, and sound business sense, since these assays are shorter in duration, use fewer animals, and the cost is well below the traditional two-year mouse bioassay.

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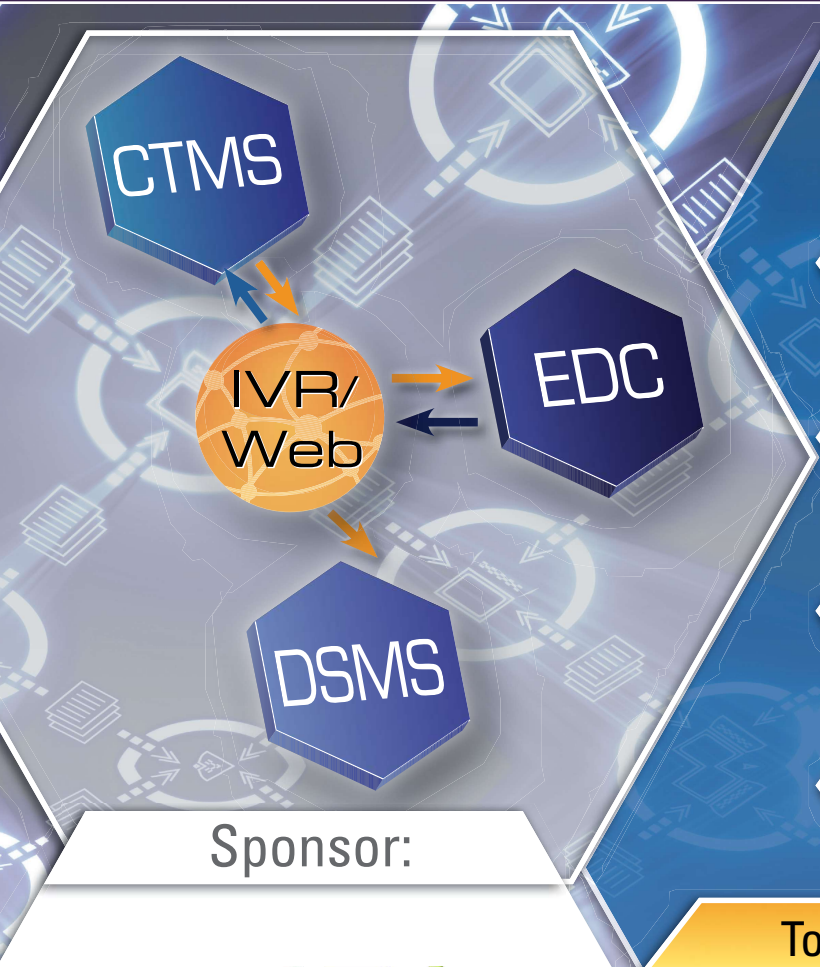

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Life Is Planned Opportunism

Vijay Govindarajan

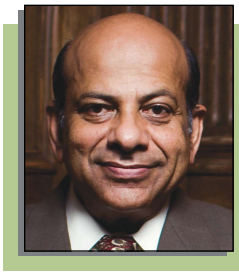
I have a personal philosophy to guide my career — planned opportunism. When I present this philosophy to senior executives, they readily relate to it — both for personal strategy as well as for driving organizational strategy.

Any major change in one's life is always the result of chance events. This is the "opportunism" part. But, how one responds to a chance event is anything but chance. That is the "planned" part. Planning is about knowing yourself, your strengths, your aspirations, and your competencies. The more you know yourself, the more you can take risks and harness and leverage the chance event. Life is neither completely planned, nor is it completely random. It is an interplay between chance events and intentional choices. This is the essence of planned opportunism. Let me give an example.

I did my chartered accountancy degree in India. (They call it a CPA in the United States.) The course prescribed "required" texts which every student must read. But, the course had optional readings, not necessary for the exam. I used to read the optional texts. Many such texts were filled with dry numbers and abstract concepts. There was one such reference book by a Harvard Business School professor named Bob Anthony. In it, Anthony articulated a view of accounting that was a total revelation to me. Accounting, according to him, was not a technical subject but influences human behavior. I still remember the day I read that book. I told myself: "Wow, accounting is not the boring subject that I thought it was. It can change people's behaviors." On that day I decided I must come to Harvard and study under professors who thought so differently. A chance event — stumbling upon Bob Anthony's book — changed the trajectory of my career.

Similarly, corporate strategy cannot be completely planned. Neither is it completely random. It, too, is a happy marriage between intentional choices and random events. So much in the industry changes in unpredictable ways. No company can predict how the future will unfold. There are likely to be dramatic shifts in technology, customer preferences, entry of new competitors, lifestyle and demographic changes, and so on. These changes are random. This is the "opportunism" part. What a corporation needs to do is to build the right set of capabilities and set big audacious goals. This is the "planned" part. The key is to leverage your company's capabilities to capture future opportunities, whatever they may be.

Reverse innovation is any innovation adopted first in an emerging market. In 2005, GE did not know all the opportunities it could pursue in India. What the company did that year was to build a variety of capabilities in India — including R&D, supply chain, and marketing. With the right set of capabilities, GE was able to innovate a portable $500 electrocardiogram (ECG) machine for rural India — a huge success. (In the United States, ECG machines cost between $3,000 and $10,000.) No company can predict the future, but planned opportunism can help you to effectively prepare for it.



Vijay Govindarajan is the Earl C. Daum 1924 Professor of International Business at the Tuck School of Business at Dartmouth College. His latest book is *Reverse Innovation: Create Far From Home, Win Everywhere*, HBR Press.

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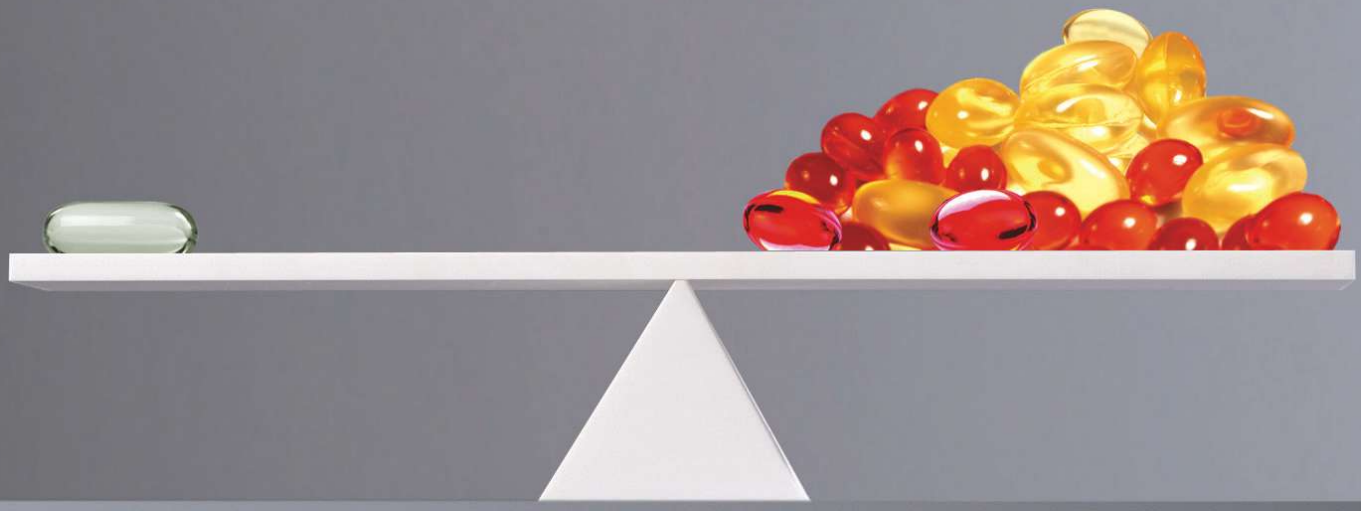

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