Life Science Leader
The Industry's Essential Business Source

A Successful Model For Life Sciences Research Funding

p. 18

An Unlikely

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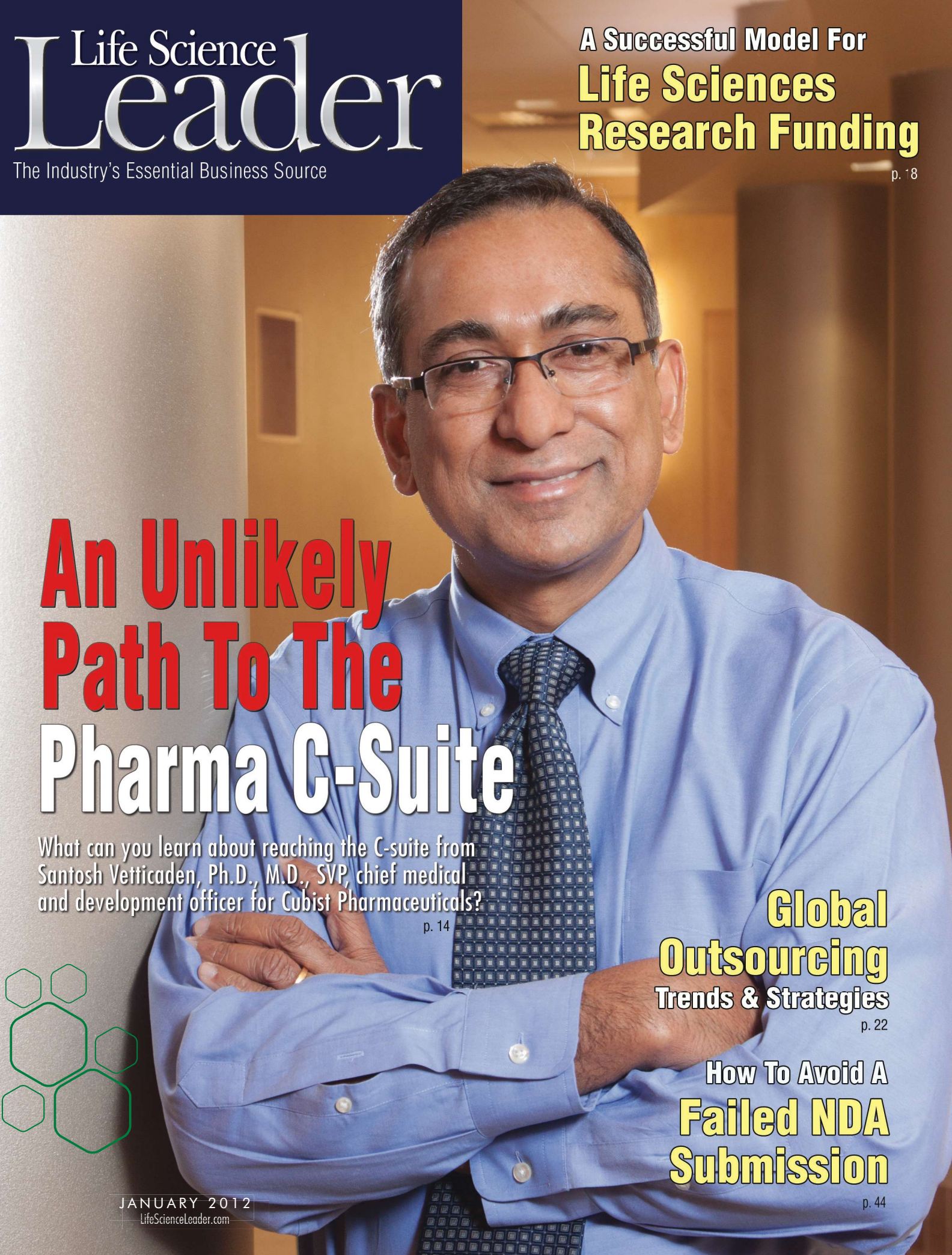

An Unlikely Path To The Pharma C-Suite

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14 FEATURE: CUBIST

"It's really about galvanizing the team around a common need and vision," explains Santosh Vetticaden, Ph.D., M.D., SVP, chief medical and development officer, Cubist Pharmaceuticals.

January 2012

Welcome to *Life Science Leader*

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EDITOR'S NOTE

No Guts, No Glory

In November I had a wonderful opportunity to participate in two end user groups as a moderator for roundtable discussions. Both were inaugural events. The first event was the Sentrx End User Group in Orlando, FL, the brainchild of Sentrx CEO Michael O'Gorman. The second was the CryoPort Frozen Shipping Summit in San Diego, hosted by Larry Stambaugh, CEO of CryoPort. Sentrx is in the business of pharmacovigilance, while CryoPort focuses on cold chain shipping. What I learned by participating and attending these events is how the attendees and sponsors are truly focused on patient safety. Both companies play key roles in the process. What really impressed me about both events is how these CEOs made the decision, in just a few short months, to put on these programs. No, they didn't wait until next year to get the ball rolling. They didn't put off until tomorrow something they could start today. I admire their gumption to begin the process of building a foundation for future events. It seems in business we often get in the habit of procrastinating on making a decision. Sometimes we allow ourselves to be trapped by the data, waiting for enough information to feel we can make a foolproof decision. Guess what, folks — there's no such thing.

I recall hearing a speech by Colin Powell, retired United States Army General and former Secretary of State. He had several pearls of wisdom. The first was to gather enough information to be beyond 50% confident you are making a good decision. The second was to sleep on big decisions as things always look different in the morning. The last suggestion was to trust your gut. Both of these CEOs must have heard the same speech, because they both seemed to be following his advice.

In "An Unlikely Path To The Pharma C-Suite" (p. 14), I had the opportunity to interview Santosh Vetticaden, chief medical officer for Cubist. Vetticaden made a variety of decisions that, on the surface, might have seemed unwise. For example, he quit a job without having another one lined up, and he started medical school at an age when most other doctors have finished and begun to practice. In the article, "Bringing a Billion-Dollar Drug to Market" by Cindy Dubin, on page 32, Gene Haley, CEO and founder of Wilmington Pharmaceuticals, states, "Bringing a drug to market is not an exercise in imagination." I sense a theme here among all of these leaders — no guts, no glory. I expect big things from all of these executives and am humbled they were willing to share their stories and events with *Life Science Leader* magazine.

The first half of 2012 looks to be busy, as I am planning on attending 11 different shows. You may find it interesting that nearly all of the executives I had the opportunity to write about this past year, I met attending shows. Unfortunately, I cannot attend each and every show. So, if you have a story to tell or know someone who does, don't be afraid to reach out to me via an email or a phone call. Some of these electronic introductions have led to some great editorial as well, such as articles in previous issues with John LaMattina and Francis Collins. Keep your ideas coming so we can continue to provide relevant, best practice, and actionable editorial you have come to expect in *Life Science Leader*.

Rob Wright
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CHIEF EDITOR'S BLOG

Have you checked out the blog from our Chief Editor, Rob Wright? He writes about a variety of issues such as recent shows attended, conversations with industry experts, and irritating business buzzwords. He has even been known to incorporate reader emails into his blogs. In fact, some of his favorite topics have started with a question sent for our monthly "Ask the Board" feature. So keep those opinions and questions coming to atb@lifescienceconnect.com.

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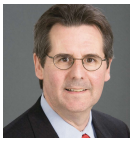
ASK THE BOARD

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

Q: What is one way you can demonstrate leadership to your team?

Think small! Senior leaders are challenged to think big and to take the long view. That is wholly appropriate when it comes to setting strategies that complement the vision and mission of the organization. But, sometimes thinking big can make you forget to focus on what is in front of you — namely, your people. First, find ways to develop your direct reports individually. Give them assignments that force them to dig deep into their talents. Second, challenge them to think and act creatively. Innovation may be a difficult concept to nurture, but it is an easy thing to kill. Give folks permission to do things differently. Third, inform your direct reports that you want them to find ways to develop the talents of the individuals on their teams. It is positive reinforcement for them and for you. Only when you allow people to think and do differently will they begin to find solutions to the obstacles you face.



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: Is PES becoming the ultimate polymer for sterilizing-grade membrane filters?

There have been 20 sterilizing-grade filter launches since 2000; 19 of those were with PES (Polyethersulfon) membranes. This is probably a trend due to the fact that PES as a membrane polymer has properties (e.g. pleat designs, pleat packing, asymmetric structure of the membrane, as well as wetting and unspecific adsorption properties) which makes it easier for membrane manufacturers to optimize the product. Overall, one can say the benefits of PES as a sterilizing-grade filter membrane polymer are too beneficial to neglect. Having said this, other membrane polymers most certainly have their justification, especially since sterilizing-grade filters are chosen to fit optimally to specific applications. These other polymers will stay for the long run, though PES will probably dominate of them all.

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

Q: What would the impact be of the federal budget deficit reduction process to our industry as a whole and to Big Pharma?

For pharma companies that are profitable or nearing profitability, increases in tax rates or reductions in tax credits, net operating loss carry-forward options, or other tax incentives could reduce earnings and distributions to shareholders. In an industry struggling to find sources of profit and where expenditures benefit from tax shelters, drops in earnings would reduce the sector's attractiveness versus other industries as we compete for investor dollars and would decrease R&D investment as tax offsets are unwound. For emerging and development-stage companies, reductions in tax credits and government funding could reduce innovation and spending on early stage products, as well as cause venture investors to flee from risk capital. Clearly deficit reduction is critical, but there could be some important near-term consequences for pharma.

Mark Pykett, Ph.D.
Pykett has more than 15 years of pharma industry executive management experience. He has been a senior exec at multiple companies, including CEO at Talaris Advisors, president/COO of Alseres Pharmaceuticals, president of CyGenics, CEO of Cytomatrix, and executive director of Oramax.

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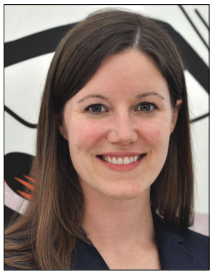


OUTSOURCING INSIGHTS

Optimizing The Partner Selection Process For Drug Developers

By Kate Hammeke, research manager, Nice Insight

By the close of 2011, two prescription drug stories had picked up so much momentum that even people outside the pharmaceutical industry had heard about them in the news. One of these topics was the end of the patent life for a blockbuster drug and how the availability of generic versions means savings for drug consumers but comes at a cost for the drug developer. The second story, however, is good news for both consumers and the drug development industry. In 2011, the FDA approved 35 new drugs, which represents the second highest approval number in the past decade, following 37 approvals in 2009. This high number may be a sign that some of the efforts the FDA has made to expedite new drug approvals, like establishing the priority review, accelerated approval, and fast track approaches, are becoming more effective.

Speeding up the process of bringing new medicines to market remains a key goal for the pharmaceutical and biotechnology industries. Engaging external partners with resources and expertise that complement internal capabilities has been effective in accelerating drug development, yet the process of selecting external partners can be time-consuming and costly. Finding ways to streamline this time-intensive process and to reduce the expense and time commitment involved in partner selection will further progress toward the goal of bringing drugs to market more quickly. Accordingly, Nice Insight developed a quarterly survey to track how sponsors pick partners and to gather feedback on specific performance measures in order to facilitate subcontractor selection and improve collaborations in the drug development industry.

By sharing highlights from the reported behaviors among outsourcing peers in the life sciences industry, Nice Insight aims to offer guidance on how to optimize the partner selection process. Some of the key findings from 2011 involve data on how companies choose partners and which markets they look to for different services. For example, businesses that outsource drug development tend to use a combination of three different methods to select a partner. Survey respondents indicated they are most likely to seek advice from consultants (68%), followed by referrals (53%), and visiting trade shows/ industry events (41%) when they need to subcontract a project to a new partner.

Outsourcing budgets among respondents stayed consistent throughout 2011 and are anticipated to remain steady for 2012. Efforts to reduce spending may not take shape in the expected ways, as respondents indicated a strong preference for outsourcing to businesses in established markets. When it comes to specific services, for each of the sixteen listed in the table, the majority (51%+) of respondents indicated they would look for a business in an established market to fulfill the need. Overall, CROs or CMOs in the United States and Canada were awarded the largest percentage of projects outsourced amongst the respondent group, at 36%, while Western Europe received a share of 11%.

Sixty-nine percent of respondents chose a CRO in an established market for analytical testing projects, which likely reiterates the importance of subcontracting this service locally. Two-thirds of respondents said they outsource within the established markets for product characterization, bioanalytical testing, consultants, and regulatory support. Only one in ten respondents indicated they would consider an emerging market first for their analytical testing projects. Similarly, regulatory support (13%) and consulting services (14%) were seldom sought from emerging providers.

WHAT IS BEING OUTSOURCED TO EMERGING MARKETS

However, respondents indicated that chemical synthesis was the service most often outsourced to emerging markets, at 27%. Additionally, approximately one in five blending, custom manufacturing, and packaging projects is typically outsourced to an emerging market. When CROs and CMOs from emerging markets are engaged, China is the most popular market, receiving 17% of projects, followed by India with an 11% share. Argentina and Brazil combined carried a share of 9%, and Eastern Europe acquired 7% of outsourcing projects.

Reviewing how and where outsourcing dollars are spent helps to establish baseline measures for whether the process and procedures of sponsors are working efficiently and effectively. Evaluating existing practices, including everything from where and how new partnerships are formed, to whether a local or

international business makes the most sense for the project under consideration, will help identify the type of contract organization that will make the best long-term partner. In 2012, Nice Insight will continue to share information on the best practices and further assist drug developers in avoiding pitfalls in partner selection to help facilitate the process of bringing new medicines to the patients who need them.

Spending by customer base by quarter

Based on spending in **16 service sectors** covering all **four quarters**

Market Size: Q1 1.933B, Q2 1.992B, Q3 2.143B, Q4 1.935B

Big Pharma (IN MILLIONS)		Biotech		Emerging Biotech		Specialty Pharma		Niche or Start-Up	
Q1 690		Q1 483		Q1 114		Q1 432		Q1 214	
Q2 689		Q2 524		Q2 185		Q2 328		Q2 267	
Q3 666		Q3 642		Q3 187		Q3 312		Q3 337	
Q4 662	-$28M	Q4 489	+$6M	Q4 163	+$49M	Q4 322	-$110M	Q4 299	+$85M

Average # of services outsourced by company type

Big Pharma		Biotech		Emerging Biotech		Specialty Pharma		Niche or Start-Up	
Q1 3.74		Q1 3.90		Q1 4.95		Q1 4.54		Q1 4.93	
Q2 4.82		Q2 4.35		Q2 5.79		Q2 4.04		Q2 3.27	
Q3 4.27		Q3 4.17		Q3 5.52		Q3 3.98		Q3 2.83	
Q4 5.08	+1.34	Q4 4.00	+0.10	Q4 4.80	-0.15	Q4 4.20	-0.34	Q4 3.05	-1.88

Selected Services Outsourced in 2011

Services	Q1	Q2	Q3	Q4
Analytical testing ↓	50%	29%	33%	40%
Bio-analytical testing ↑	33%	23%	27%	34%
Blending ↑	12%	10%	13%	17%
Chemical synthesis ↓	26%	14%	18%	24%
Consulting services ↓	66%	44%	43%	48%
Custom Manufacturing ↓	35%	20%	23%	23%
Fill & finish ↓	27%	15%	18%	22%
Lyophilization ↑	12%	6%	7%	13%

Services	Q1	Q2	Q3	Q4
Packaging services ↓	23%	14%	15%	19%
Formulation/Pre-Formulation ↓	22%	10%	11%	15%
Product characterization ↓	19%	10%	10%	13%
Process optimization ↓	21%	10%	11%	12%
Regulatory support ↓	32%	21%	22%	24%
Stability, storage, & testing ↓	28%	14%	15%	20%
Sterile compound ↓	14%	6%	9%	11%
Toxicology ↓	29%	13%	15%	18%

Survey Methodology: The Nice Insight Pharmaceutical and Biotechnology Survey is deployed to 40,000 outsourcing-facing pharmaceutical and biotechnology executives on a quarterly basis/four times per year [Q3 2011 sample size 3,021]. The survey is composed of 1,200+ questions and randomly presents ~30 questions to each respondent in order to collect baseline information with respect to customer awareness and customer perceptions on 406 companies that service the drug development cycle. Over 1,600 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, Accessibility, Regulatory Compliance, Pricing, 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.

BIO DATA POINTS

Change On The Horizon For Biomanufacturing

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

A leading indicator as to where the global bio industry is headed, geographically, is where its global vendors are setting up shop. In our *8th Annual Report and Survey of Biopharmaceutical Manufacturing*, along with 352 biomanufacturers, we also surveyed 186 suppliers to the industry.

This year, more than half of the industry's suppliers are actively selling products and services in both China and India (51.2% each). The percentage is up from just three years ago when 38.7% of vendors were actively selling in India and 37.7% in China. This mirrors the global optimism associated with these large markets. It also suggests that vendors recognize the strategic importance of establishing a presence within domestic foreign markets. We also found this year that there is modest growth in the percentage of suppliers selling to these geographies: South America (41.1%), the Middle East (36.7%), and Central America (35.7%).

This growth is also seen in our analysis of global biopharmaceutical manufacturing concentration, at our industry WIKI site: www.top1000bio.com. Here, we find that as of Dec. 1, 2011, Chinese biomanufacturers made up 8.6% of the concentration of biologics production (aggregated capacity, employment, and pipeline products).

DIFFERING REASONS FOR WORLDWIDE BIOPHARM GROWTH

While the United States and other major biopharmaceutical markets tend to grow by rapid adoption of new products and new indications for existing products, growth in most of the rest of the world tends to be driven more by overall economic improvement, including the development of a middle class, and other broad economic and social trends supporting improved healthcare in these countries. The majority of biopharmaceutical manufacture and consumption in emerging markets currently involves biogenerics or other copies of products developed by Western innovator companies, as most lesser-developed counties are not able to afford costly Western innovator biological products.

Even so, developing markets, although still relatively small, are growing at a more rapid pace than major Western markets, and most major biopharmaceutical companies either have established or are establishing a presence in these foreign markets. Some are forming joint ventures and collaborations with local companies. Other collaborations can involve outsourcing of R&D, the licensing of manufacturing rights to developing countries, or establishment of local clinical research operations, all of which drive industry growth and opportunity in local geographies.

We measure these market developments into manufacturing clusters that compete with the traditional powers — United States and Western Europe — using our constantly updated *Top 1,000 Global Biopharmaceutical Manufacturing Facilities* index.

Our index currently shows China at 8.6% of global concentration, India at 8.1%, and Japan and other Asia at 9.7%. Almost two-thirds of worldwide biomanufacturing (based on cumulative facilities index scores) remains concentrated in the United States (36.7%) and Europe (26%). Indeed, our index shows that relatively few of the top-ranking facilities exist outside of the United States and Western Europe.

Despite the current scores, in the short term, developing regions such as China and India will have trouble narrowing the considerable gap in facility types, complexity, and capabilities that exist in the United States and Europe. Eventually, though, biopharmaceutical manufacturing will be done by outsourcing partners in developing countries at GMP-level quality and in areas that require greater skill and expertise.

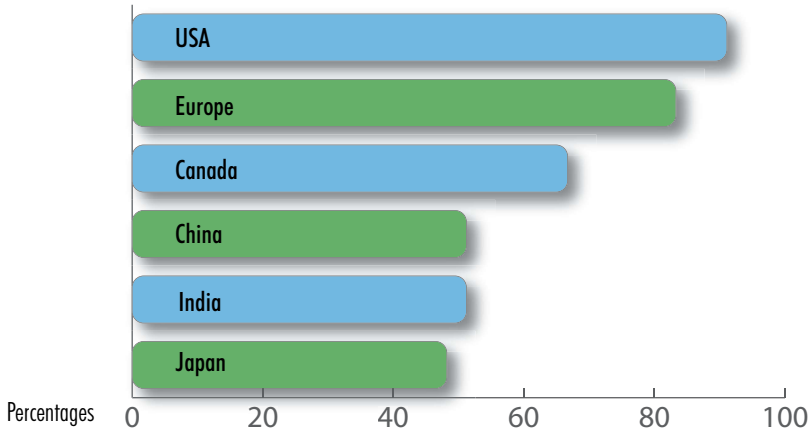
Certainly, as local industries in lesser-developed countries continue to develop, they will attract more world-class facilities and make inroads into our top facilities index. These will be in addition to local companies developing commercial-scale biopharmaceutical manufacturing facilities to serve domestic and regional needs, a trend that is already being seen with vaccines, as some foreign companies develop their own fully innovative biopharmaceuticals. And when regulatory barriers fall, Asian markets, in particular, will become powerful centers within the biomanufacturing market. India provides an excellent case in point — with several Indian vaccine manufacturers having gained prequalification from the WHO, the country is now estimated to account for 60% of the world's vaccine production and 60% to 80% of annual United Nations vaccine purchases.

This much is clear: globalization is firmly entrenched in the biopharmaceutical industry. Stay tuned to our index for more.

Geographic Locations In Which Vendors Currently Actively Sell Products And Services

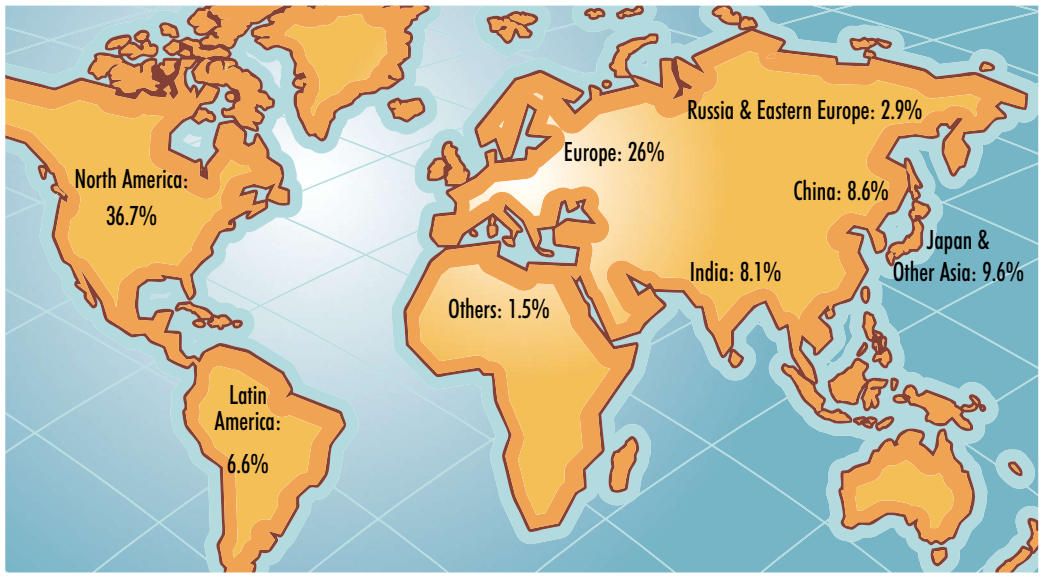
(geographical sales, all respondents)

(As indicated in BioPlan Associates' 2011 Eighth Annual Report and Survey of Biopharmaceutical Manufacturing, April 2011)



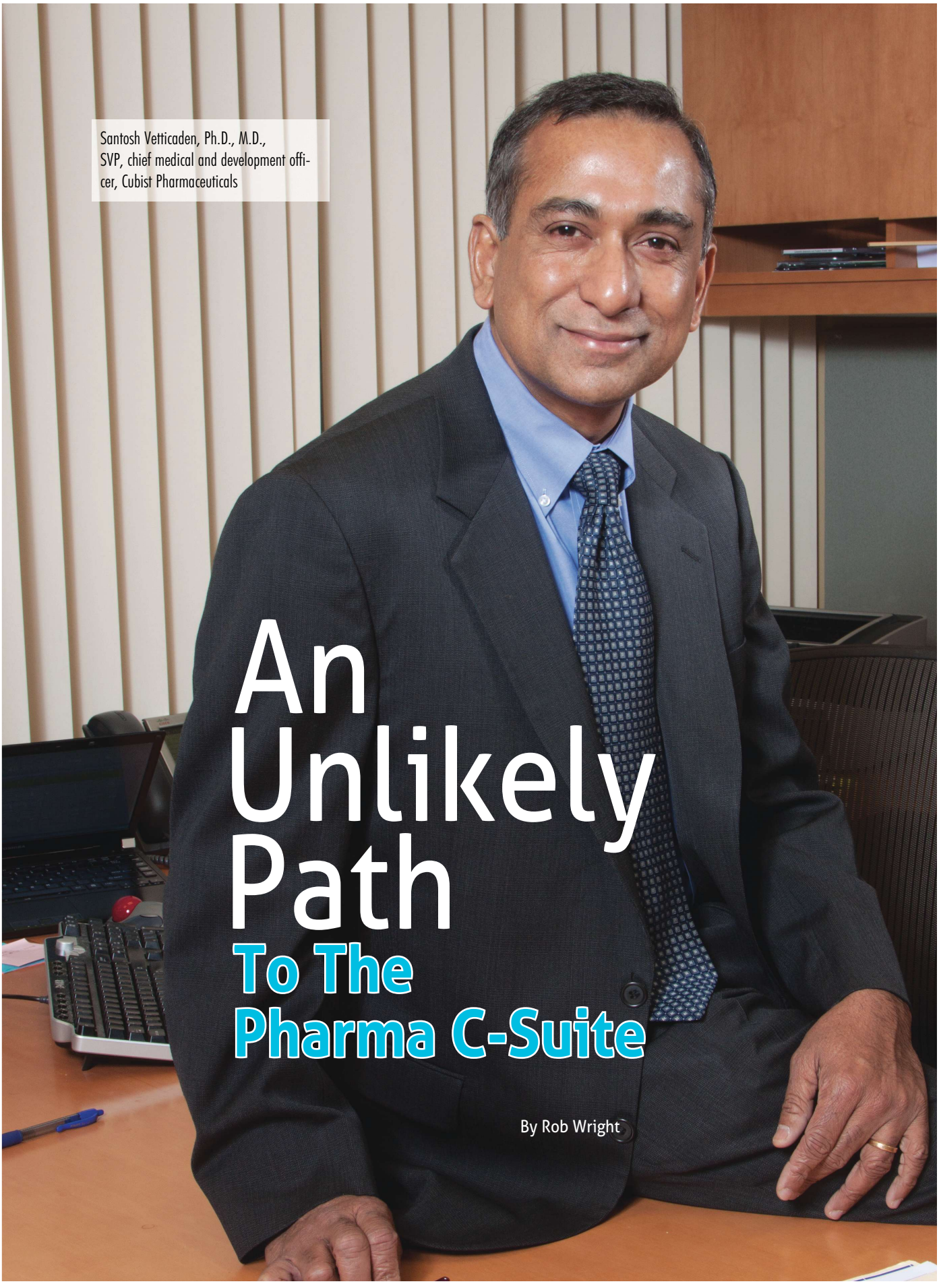
Concentration Of Global Biopharmaceutical Manufacturing

(% of vendors engaged)



Survey Methodology: This eighth 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.



Santosh Vetticaden, Ph.D., M.D., SVP, chief medical and development officer, Cubist Pharmaceuticals

An Unlikely Path To The Pharma C-Suite

By Rob Wright

Santosh Vetticaden had an unconventional approach to getting to the c-suite. With the ink barely dry on his Bachelor of Pharmacy degree, in 1980 he emigrated from India to Richmond, VA, to begin the pursuit of a Ph.D. in pharmacy and pharmaceutics. According to a 2009 report issued by the National Science Foundation, the average age of life sciences doctoral program graduates is 31.5. Vetticaden completed his in 1985 at the age of 26.

After working for about five years for a consultancy which evolved into a CRO, Vetticaden realized he wanted to gain a greater understanding of the drug development process and enrolled in medical school at the age of 32. When he arrived in the states, he thought he would finish his Ph.D. and return to his home country. Thirty-one years later, Santosh Vetticaden, Ph.D., M.D. — U.S. citizen, husband, and father of three — is the SVP, chief medical and development officer for Cubist Pharmaceuticals (NASDAQ: CBST), one of the fastest-growing companies according to CNN Money. Vetticaden attributes Cubist's success to having strong fundamentals, i.e., leadership, cash position, a promising pipeline, and disciplined business development activities. At the time of this writing, Cubist has Michael Bonney in his seventh year as CEO, a cash position (i.e. cash, cash equivalents, and investments) of over a billion dollars, two antibiotics with positive phase 2 result announcements, and reported growth of 21+% in the United States alone. Vetticaden's own success, however, has come via what he describes as calculated risk taking, which is what I would describe as a nontypical, challenge-seeking career path with a great deal of self-confidence in his abilities for achieving his goals and aspirations.

NOT YOUR TYPICAL CAREER PATH

Only 10% of American Ph.D. life scientists land tenure-track academic jobs after completing their training. So it should come as no surprise that when faced with the decision of choosing between industry and academia, Vetticaden landed in industry. What is surprising is where in the industry he landed. For most newly anointed Ph.D.s with a similar background, the path is to start out with a midsize to large pharmaceutical company, spend a few years at the bench, and slowly begin working your way up the corporate ladder. This was not the case for Vetticaden, though. He says he had considered pursuing jobs in academia or large industry, but ultimately felt that a riskier, more challenging, entrepreneurial environment would be the best fit — a consistent theme even in his future career choices. Thus, his first job was working for Biopharmaeutics Research Enterprises — a small regulatory consultancy group started by a couple of former members of the FDA.

According to Vetticaden, "It was great exposure because they were a big consultant to all of Big Pharma. Here's a guy, 26 years old, fresh out of completing his Ph.D., now sitting around a table with VPs of Big Pharma getting exposed to a variety of drugs in varying stages of development and deciding or discussing everything from strategy to implementation." Because they were a consulting company, a lot of times they would subcontract necessary studies to various CROs. Before long, the company realized that instead of subcontracting the work, they could provide better service by setting up their own CRO with analytical services via their own Phase 1 unit. Here Vetticaden was exposed to the nitty-gritty of how to set up a CRO, trial design, and its subsequent implementation. "I was exposed to everything from Phase 1 to Phase 4," he says.

This experience also exposed him to a personal realization. "I lacked the clinical skill set in the drug development process to completely and adequately assess drug safety and efficacy in patients," he contends. Thus, after working in industry for five years, he decided to go to medical school, a highly unusual step when one considers that most M.D.s complete their Ph.D. after finishing their medical degree, not the other way around. Another reason it was unusual is he was starting medical school at an age when most students are finishing their residency programs. Upon completion of his internal medicine residency program, Vetticaden would be just shy of 40 — a bit late to be starting one's career. Undaunted by these prospects, he took the plunge, reentering the drug devel-

opment and discovery workforce with M.D. in hand, mid-1997.

The takeaway is this — if you lack a necessary skill set to move up in your desired field, go get the necessary credentials and experience to improve. This might not require as dramatic a move as Vetticaden's decision to go back to medical school, though. For example, he is in a very senior leadership position, yet has never had any formal business training or been part of a leadership mentoring program. Much of the leadership techniques, such as the skill of persuasion, providing vision, driving and executing on strategy, making sure people follow up, and knowing when to intervene and escalate appropriate issues, he picked up by observing fellow colleagues who he felt had skills sets more advanced in certain areas than his own.

THE BENEFITS OF TACKLING NEW CHALLENGES

Many of Vetticaden's current leadership techniques also can be attributed to his penchant for taking on new business challenges. For example, his first job upon completing medical school was working as a clinical research director for Whitehall-Robins Healthcare, a division of American Home Products. In this role his focus was on the OTC side of the business with an emphasis on preparing prescription drugs for the OTC space. The whole reason he went to medical school was to gain a better understanding of patients. Now, here he was, creating medicines which most often did not require a physician's prescription for the patient to use. Vetticaden found this process to be very beneficial in his career development. "It extended my understanding of safety and efficacy considerations for these medications, where the standards had to be even higher than those on the prescription side."

After spending three years at Whitehall-Robins, Vetticaden left to join Aventis Pharmaceuticals to gain global exposure to drug development, which he lacked. He considers his experience at Aventis to be the job where he learned the most and the key to developing his current leadership style.

As a global project team leader, he was in the unique position of managing a global team with no direct reports for a drug he would help grow to be a blockbuster — Lovenox. "When building a high-performing team, there arises a variety of situations — from strategic to execution — which each require you to adapt your leadership skills in order to achieve your desired results," he says. For example, with the Lovenox team, he found he had to lead by influence, considering none of the members directly reported to him; some of the team worked on more than one project or had other priorities. Leading by influence involves using persuasion, inspiring a shared vision, fostering collaboration, recognizing contributions, and celebrating accomplishments. He had to rally the team behind challenging initiatives, such as the new indication for the drug, while also convincing team members to relegate some of their other activities to a lesser priority. "It's really about galvanizing the team around a common need and vision," he affirms. The initiatives he implemented and the results his team achieved got the attention of the heads of development and R&D — Sol Rajfer and Frank Douglas. Being only a senior director at the time, Vetticaden found it very beneficial to have two senior members of management backing him to provide indirect influence over the team.

If involved in a corporate change initiative, Vetticaden emphasizes the importance of being able to develop and articulate a clear vision so every member of the team knows exactly what they are signing up for, understands where the company is going with the initiative, feels important, and wants to take part. With Lovenox, the message was the development of a new indication in acute myocardial infarction that would save lives and reduce the number of repeat heart attacks. Not only would this impact millions of patients' lives, it would have a significant impact on cardiology since Heparin had been used for decades. A victory would also ensure the drug's trajectory toward a multibillion-dollar product. The drug continued on a successful trajectory and became a greater than $4 billion product over time.

OVERCOMING ADVERSITY & ACHIEVING GOOD LIFE/WORK BALANCE

Overcoming adversity is nothing new to Santosh Vetticaden, SVP and chief medical and development officer for Cubist Pharmaceuticals. As a youngster, Vetticaden suffered from childhood asthma. For many, this would result in a lack of participation in athletic competitions. Vetticaden's parents took a different approach, getting him involved in sports at a young age, which helped immensely in overcoming what can be a very debilitating ailment. As a result, one of the hobbies he enjoys today is physical fitness, and he is an avid jogger.

And as with most top executives, achieving a good life/work balance is important to Vetticaden, who strives to maximize the time he spends with his family. "Since my kids are between the ages of 5 and 10, I feel it's important that I try to maximize my time with them," he asserts. "As an example, I wake up quite early and tend to work when they are asleep or out of the home on other activities. If I work at home while my kids are around, I try to have them be with me in my home office working around me doing their activities, whether it is reading, drawing, or something else."

Some Impactful Books

One of the books Vetticaden states as having the greatest impact on his life is "Winning through Innovation – A Practical Guide to Leading Organization Change and Renewal" by Michael Tushman and Charles O'Reilly III. "It is a wonderful book which is a guide to leading organizational change and renewal," he reflects. Another book he recalls as important in his life is "Freedom at Midnight" by Larry Collins and Dominique Lapierre. "It is an epic about India's road to freedom, and each time I read it different parts of it fascinate and appeal to me," he states. "For example, the different styles of leadership with Gandhi and Nehru, the different tactics employed by the leaders to realize common objectives, and the trade-offs to achieve the goal, just to name a few, are fascinating."

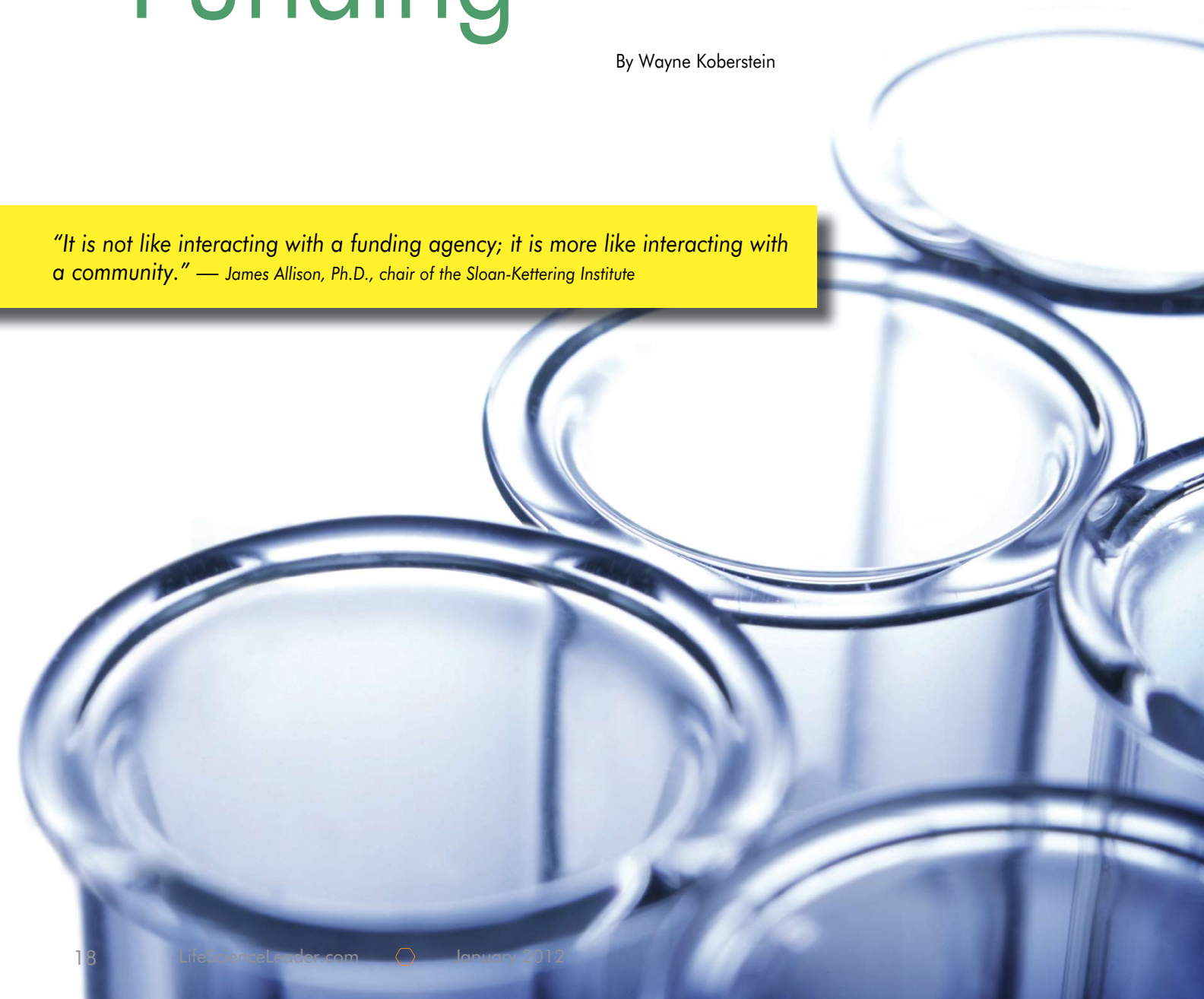
THE CONSUMMATE OPTIMIST

While at Aventis, Vetticaden was limited to leading a team focused on one drug in one therapeutic area. He began to yearn for the greater challenge of being able to lead drug development in a broader sense. "I wanted to utilize my skills, have a greater impact on developing drugs and making a difference," he explains. He also wanted the opportunity to learn additional skills in leadership by managing people directly. He felt the best opportunity to do this involved moving over to a small biotech. There was just one problem; the small biotech for which he was interviewing, Scios, became the acquisition target of Johnson & Johnson. Nonetheless, he took the opportunity, relocating to the West Coast. Within three years, J&J decided to restructure its operations on the West Coast and essentially shut down Scios. "What I wanted for myself, being in an entrepreneurial environment and having a greater impact, was not something I saw as being possible within J&J following the restructuring," he explains. Vetticaden took a position as SVP & chief medical officer with Maxygen, and after a year and a half, in his most senior position to date, did the unthinkable — HE QUIT — leaving without having another job lined up. He explains that when he started, Maxygen was a great fit. "I was hired to get drugs developed and move them through their pipelines." As the company grew, Maxygen's leadership team recognized that the clinical drug development process can be very risky and expensive and made the strategic decision to license out the process. It became clear to Vetticaden that the process he so much enjoyed, developing drugs and getting them out in the marketplace and having an impact in the medical community, was not something he would be able to do if he stayed at Maxygen. As a result, he decided to create his own company, Global Drug Development Consulting. "The timing was not great," he admits. "But in retrospect, I made the right decision." By consulting with VCs and biotechs, he was exposed to a variety of prospects. Opportunity came knocking in the form of Cubist Pharmaceuticals, and hence, relocation of his spouse and three children back to the East Coast. "I'm very fortunate in having an incredibly supportive family," Vetticaden states. Through their trust and support and his own self-confidence, he survived restructuring, starting his own company, and more than one coast-to-coast relocation to again arrive at a position he would find fulfilling — the SVP and chief medical and development officer for Cubist. Vetticaden's advice is have confidence in yourself and your abilities and don't waste time second-guessing past decisions which cannot be changed.

A Model For Life Sciences Research Funding

By Wayne Koberstein

"It is not like interacting with a funding agency; it is more like interacting with a community." — *James Allison, Ph.D., chair of the Sloan-Kettering Institute*



Ever wonder where the money goes when you donate to a large "Fight This Cancer" campaign? How does such a donation translate into productive research? What are the chances it will help yield a breakthrough treatment or "cure," which many campaigns proclaim as their goal?

Similarly, if you run a life sciences company or plan to start one, do you know for certain that the vast sums raised by megacampaigns are distributed to researchers in a rational way? Do the funding organizations systematically ensure meaningful results? And do they present a clear route by which companies can obtain access to the funded research for commercialization into products that benefit patients?

One funder that can arguably answer yes to all of those questions is the Prostate Cancer Foundation (PCF). It not only does an effective job of research funding and coordination in prostate cancer, but also inspires emulation outside its immediate sphere. With its strong science-driven focus, tight research timelines, and unique role as a community of academic and industry researchers, the foundation stands as a new model for other funding agencies in the life sciences.

OFFERING MORE EFFICIENCY AND PRODUCTIVITY IN RESEARCH

The PCF approach may seem like an implicit criticism of the larger charity drives or "megafunds" such as Susan G. Komen for the Cure, but more accurately it is an alternative. Rather than covering every possible base with a vast universe of fundraisers, donors, scientists, marketers, and administrators, the PCF model assumes that a smaller-scale, more hands-on organization, run by physician scientists, offers more efficiency and productivity in research. Its commitment to fast decision making and effective funding also promotes quicker outcomes and analysis of funded research and, therefore, course corrections. Greater coordination and targeting of research may result.

In an era when pharmaceutical companies admit throwing money at research is no guarantee of positive results, it is appropriate to assess the nonprofit funds not just by how much they invest in research but how and where they invest it.

"Philanthropy is more than giving out money; you have to show results," says Howard Soule, the PCF's chief science officer. Soule emphasizes that "every one of our awards is science-based, selected to help patients in the short term."

Did the PCF founders see such accountability lacking in other, traditional funds and intentionally design it into the organization? "There are two answers to that question," PCF president Jonathan Simons replies, "Yes, and hell yes!"

Like other funds such as the American Heart Association, says Simons, the entire PCF board consists of people who have been touched in one way or another by the targeted disease. Chief founder Mike Milken also brought business principles to the plan, setting up what is essentially a nonprofit venture fund "laser focused" on bringing down prostate cancer morbidity and mortality rates in the shortest possible time frame. "Venture philanthropy" is now a new player in the VC-starved world of the life sciences industry.

REAL RESULTS

The Prostate Cancer Foundation and its partner, the PCF-Department of Defense Prostate Cancer Clinical Trials Consortium (PCCTC), have supported research leading to five novel FDA-approved treatments for prostate cancer in the past three years—an extraordinary record.

Zytiga (abiraterone)
Approved May 2011 for metastatic, castration-resistant prostate cancer
Abiraterone is a new targeted therapy in the class of androgen production blockers. In total, PCF invested $8.2 million in research (PCF Creativity and Challenge Awards 2007-2010) for fast-forwarding treatment science research around abiraterone.

Xgeva (denosumab)
Approved September 2011 for bone loss in non-metastatic prostate cancer
Patients undergoing androgen deprivation therapy (ADT) tend to be at high risk for fractures, including fractures of the spine. Denosumab injections increase bone mass to reduce the risk of such fractures. Since 1997, the PCF has invested more than $1.8 million on the work of the Genitourinary Malignancies Program at Massachusetts General Hospital Cancer Center on denosumab and treatment sciences on improving survivorship.

Yervoy (ipilimumab)
Approved March 2011 for melanoma
Research on this CTLA-4 agonist by UCLA's James Allison, Ph.D., was largely funded by the PCF since 1999 and approved by the FDA in March 2011 for the treatment of melanoma. Phase 3 trials are now underway for ipilimumab in prostate cancer (BMS).

Provenge (sipuleucel-t)
Approved March 2010 for advanced prostate cancer
Sipuleucel-t is a therapeutic vaccine. Since 1993, PCF has invested nearly $2 million as venture philanthropy to support dendritic cell vaccines and immunotherapy research including Provenge by Dr. Eric Small at UCSF beginning in 1999.

Virtually no effective research in treating prostate cancer was taking place when the PCF started up in 1993. Thus, the group has directly pushed almost all significant advances against the disease since then, including five novel drugs approved by FDA in the past three years — a feat no other nonprofit funder can claim. (See "Real Results.") Meanwhile, prostate cancer rates fell much faster than most other solid-tumor cancer tumors. All that is related to PCF efforts to "create an exchange or marketplace for extremely good vetting and evaluation," according to Simons.

Although it is not a patient-support organization of a Komen's scale and variety, the PCF supports research into better prevention, detection, and the range of early to late treatment, with related programs in nutrition, genetics, disease mechanisms, tumor metastases, and diagnostics. All are superficially similar to the research areas of Komen and other cancer groups, were it not for the much tighter timelines and coordination of the PCF system.

"Looking at small companies and start-ups, and at how innovations get to the patient, we are very interested in what we can do as a nonprofit," says Simons. "We never put a philanthropic dollar into a company, but we often put a lot of money into university science that can open up or amplify a technology for companies. So, we are constantly curious about where the best research ideas are in government, in universities, nonprofits, and for-profits. And, we are constantly talking to companies, trying to introduce them to the scientists who have those ideas."

The PCF's first purpose is not to be an economic development force, but it does help companies by funding preclinical studies, "de-risking" technologies prior to commercialization and by personal diplomacy and networking — it bridges between academia and industry. It also aids companies directly with services that support product development, from funding trials to expert guidance, according to Simons. "We can assemble a scientific advisory board for any company in about a week, on almost any topic, with experts from around the world."

TWO WAYS TO GET THE PCF's ATTENTION

A researcher enters the PCF community in one of two ways — by writing a tight paragraph stating the purpose and value of the research to be funded or by receiving a tap on the shoulder from PCF scientists on the hunt for programs that fit its goals and the "human capital" they contain.

"If you can say, in four sentences or less on a piece of paper, how a relationship with us can get science to the patient and then how the patient could benefit, it presents an easy value proposition for us to be involved in," Simons explains. Most other organizations use an NIH-like application procedure that may start with a summary letter but ultimately requires all the bureaucratic skills of a good grant writer.

Plenty of examples abound of the "shoulder-tap" route into

the PCF family. Two investigators who answered the foundation's call and have since become leaders in the group are James Allison, Ph.D., chair of the Sloan-Kettering Institute, and Matthew Smith, M.D., Ph.D., at Massachusetts General Hospital.

Now on the PCF scientific advisory board, Allison was a researcher at UCLA who had not yet focused on prostate cancer until Howard Soule approached him in 1999 regarding his early publication on the potential of anti-CTLA-4 strategies. The PCF subsequently funded Allison's mouse models and further work that eventually led to the approved immunotherapy ipilimumab and others in development.

"They track interesting things in the literature and try to bring people into the prostate-cancer community. That's certainly what they did with me," Allison says. "They took note of my work and helped steer me into prostate cancer, and they stayed with it the whole way — helped fund clinical trials, helped two companies launch two drugs together, and helped me understand the business side. It is not like interacting with a funding agency; it's more like interacting with a community. It has a common goal."

PCF applicants receive a funding decision within 60 days, and successful applicants obtain funding within 90 days of applying. From there on, everything is geared for synergy and rapid results. All funded researchers enter a network of collaboration, culminating annually in a retreat where they report on their progress and exchange insights with peers, interact with industry researchers and executives, and plan groupwide priorities and goals for further research.

The invitation-only annual retreat reflects the organization's overall approach. There it gathers the "best and brightest" in prostate-cancer research worldwide to sit in one big room for presentations with ample discussion. Over the two days, the PCF defines a set of critical research questions, develops the research agenda for the coming year, and then funds the research, either alone or in cooperation with other funders such as the DOD and the NCI (National Cancer Institute).

PCF does not support basic bench science; all funded projects must have the potential to initiate clinical trials within two years. That admittedly difficult timeline, compared to the decade-long vista more common among the megafunds, tends to focus minds and resources on the goal of bringing benefits to patients. At the same time, and along with a suite of special grants to "young researchers," the foundation often funds an investigator over an entire career, as it has with Allison and Smith. It also funds a handful of institutions to do specific but large "challenge" projects, each designed to answer one of its critical research questions.

A BEST PRACTICE FOR RESEARCH FUNDING

Several good reasons exist to see the PCF model as a best practice for coordinating funding and research. If accountability for the results is important, the model appears designed to ensure it. The PCF emphasizes accountability and transparency in numerous ways, from its lean structure to its concentration on science over marketing and administration. At least two other disease-research campaigns, the Melanoma Research Alliance and the Michael J. Fox Foundation, both founded since the PCF, share many aspects of the same model.

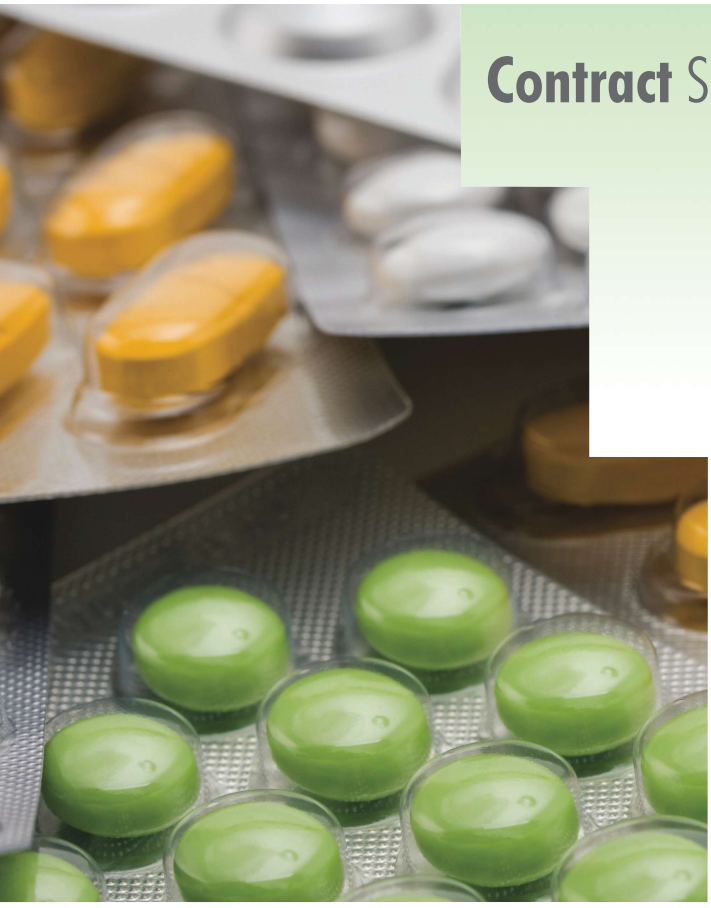
But what about fundraising? The megafunds have set records — Komen alone raised more than $4 billion last year, with fundraising events in almost every U.S. city and town. The PCF also raises funds from major donors and local events, about $40 million last year and $475 million since its inception. But PCF revenues go mainly to science, according to Simons. "Of course, we work hard to raise money, but the purpose of fundraising is to drive more human capital into research."

"Of course, we work hard to raise money, but the purpose of fundraising is to drive more human capital into research." — *Jonathan Simons, president, Prostate Cancer Foundation*

The PCF also "amplifies" its own grant money by attracting additional private and public investment. The group cites a total of more than $10 billion in financial capital it has attracted to prostate-cancer research from government, VCs, pharma and biotech companies, academic centers, and others. It also counts among its "results" $100 billion in "human capital" — supporting more than a thousand new scientists and 9 out of 10 publications in the field — as well as "incalculable social capital" in its overall impact on research and treatment.

A final note: Like global warming looming over the natural world, one eminent and common danger all disease philanthropists face is radical reductions in public research funding, especially by the NIH. Congress seems bent on hitting science on many fronts, but has singled out basic medical research as one of its preferred targets for federal cutbacks — exactly the area least covered by any other funding.

"Severe NIH cutbacks would obviously affect the PCF research enterprise," says Simons. "We would naturally have to work to fill in the gap as much as possible. Government research needs to be viewed as an investment, not an expense. In the end, it is research and science for patients that creates the real value."



New Global Pharmaceutical Outsourcing Trends

By Jim Zhang

It has been widely recognized that the global pharmaceutical industry is currently experiencing dynamic change. Under high pressure to contain fixed costs, all drug companies are currently reducing their internal capacities in R&D, manufacturing, and even marketing and, instead, increasing their outsourcing. To a large extent, the drug companies, large or small, now rely on outsourcing service providers more than ever to fulfill their tasks, solve their problems, and improve their efficiency and productivity.

OUTSOURCING DEMANDS

In recent years, many major pharma companies have remodeled their traditional drug R&D operations. They now focus on de-risking their R&D efforts via external, outsourced resources. Meanwhile, the global competitive environment also has forced them to constantly streamline manufacturing operations, leading to an increased demand for contract manufacturing of marketed drugs, especially small molecule generic drugs (e.g. intermediates, APIs, finished products).

A much softer outsourcing demand presently exists in the R&D-focused biotech industry. Compared with the time before the financial crisis, the global-funding models of many VC investors have changed. Due to the funding shortage, many small biotech companies that focus on small molecule drug R&D have either reduced the scale of their R&D or cut the number of their programs — or even closed their entire operation. The outsourcing demand by the community of these small, R&D-focused biotech companies has thus been significantly weakened since the global financial crisis.

NEW TRENDS IN EACH SERVICE SECTOR

New outsourcing strategies and types of services are developing in almost every stage of the drug R&D and manufacturing process. For instance, in the sector of target identification and validation, genomics and proteomics research and gene-silencing technology have now been widely used to validate more complex and structurally diverse disease targets. A variety of microarray technologies also are widely used to study the differences in gene expression patterns and gene interactions. Most of this type of work is now performed by either academic research organizations, specialty biotech companies, or professional CROs.

A virtually integrated, cross-functional outsourcing operation of drug discovery research is currently prevailing as the latest outsourcing model, especially for small molecule drug discovery. Chemical synthesis and biological testing work is now almost completely performed by CROs and, to a lesser extent, academic research organizations.

The worldwide outsourcing demand for preclinical research and development is, however, still soft at present. Almost all major pharma companies have publicly announced that their current and near future R&D focus will be on the late-stage drug candidates. Meanwhile, many drug companies also are shifting their research methodologies for toxicology (tox) studies to include molecular biomarkers, imaging, and companion diagnostics, as these new technologies are able to provide better safety profiles of trial compounds.

The clinical trial has now, indeed, become a global process. More and more trials now require the inclusion of global trial sites, with an increasing proportion of patients from the emerging countries participating in trials. Those CROs that are already well-established in these emerging countries appear to be well-positioned for success in the competitive global industry.

Likewise, the global CMO sector also is currently experiencing strong demand for both APIs and pharma intermediates of the marketed drugs, in particular, generic drugs. Moreover, as more drug companies now pursue personalized medicines (which will result in more diverse product portfolios for these companies), it is expected the demand for related outsourcing services will become stronger in the future.

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Major pharma companies also are gradually increasing the outsourcing proportion of their formulation work, especially for small molecule generic drugs. Meanwhile, as drug companies of all sizes are gradually increasing their focus on biologic drugs, the outsourcing demand for R&D and manufacturing of biopharmaceutical products is growing rapidly. However, unlike the outsourcing of small molecule drugs, large-scale outsourcing of biologics did not start until very recently. Most biopharma companies still have not yet established a strategic plan for their bio-outsourcing practice. At present, the majority of bio-outsourcing activities are still centered on low-end tasks such as the development of cell lines, contract manufacturing of developmental biologic drugs to support clinical development at various stages, and bio-analysis and product characterization. Meanwhile, because of the worldwide recognition of the huge future growth potential of the biosimilar market, increasing numbers of global CROs and CMOs are aggressively enhancing their capabilities and expanding their services in this new area.

LATEST NEW TECHNOLOGIES AND SERVICES

Today, major pharma companies are in desperate need to develop better drugs with high success rates. The key bottlenecks include selecting the right therapeutic targets and understanding the cause of severe side effects. That's why pharma companies are focusing more on the basic type of research in genomics and proteomics, primarily through collaboration with academic research organizations, specialty biotech companies, and/or CROs.

To increase productivity and efficiency, both drug companies and outsourcing service providers have been striving to make improvements in every aspect of the drug R&D and manufacturing processes. Consequently, new technologies such as biomarkers, molecular imaging, and companion diagnostics as well as new services such as antibody library construction and screening, genomic testing, and cell-line development have been developed.

FOCUSING ON EMERGING MARKETS

The new model of "more achievements for less cost" has forced many drug companies to think about the possibility of moving some of their operations to low-cost emerging markets. These companies are focusing not only on expanding their market space in these regions, but also outsourcing more costly R&D and manufacturing work to these markets, especially for small molecule drugs. The recent financial crisis has further strengthened this trend.

Most emerging markets possess a number of attractive factors to all global pharma companies. For instance, one such factor is the availability of a large talent pool that earns a wage still relatively low compared to Western countries but that has nearly comparable technical capabilities and skills. This situation is especially true in China and India.

To realize their goals, the global drug companies are currently looking for partnerships with local companies or research organizations in the emerging countries that possess the desired technical capabilities. Meanwhile, to meet these demands by the global drug companies and to have a firm position in the fast growing regions, almost all major CROs and CMOs have put a significant amount of their investment into these emerging countries, including building up their service capabilities and capacities through either vertical growth, partnerships (including joint ventures), or acquisitions of local service providers.

FUTURE OUTLOOK

As almost all major pharma companies have reprioritized their therapeutic focuses, including abandoning a number of programs in their pipelines, it is expected that global drug R&D spending will remain flat or even slightly decrease in the next couple of years. However, in the meantime, as they are cutting the fixed cost and improving productivity and efficiency, all these drug companies are aggressively increasing the outsourcing of core drug R&D and manufacturing.

Based on the past growth trend and the future growth drivers of this industry, it is believed the global pharma outsourcing industry will still experience fast growth in the next five years (2011 to 2015). We forecast that the global pharma outsourcing market will likely grow in a CAGR of about 12% during this time period, and the market value will likely climb from about $85 billion to as much as $150 billion by 2015.

The CROs and CMOs each presently make roughly equal contributions (CRO:CMO = 48:52) to the total global pharma outsourcing market value. Of the total CRO market value, which is about $40.5 billion, chemistry-based drug discovery research service accounts for about 25% (about $10.7 billion), whereas the biology-related services, which include preclinical and clinical development, account for about 75%.

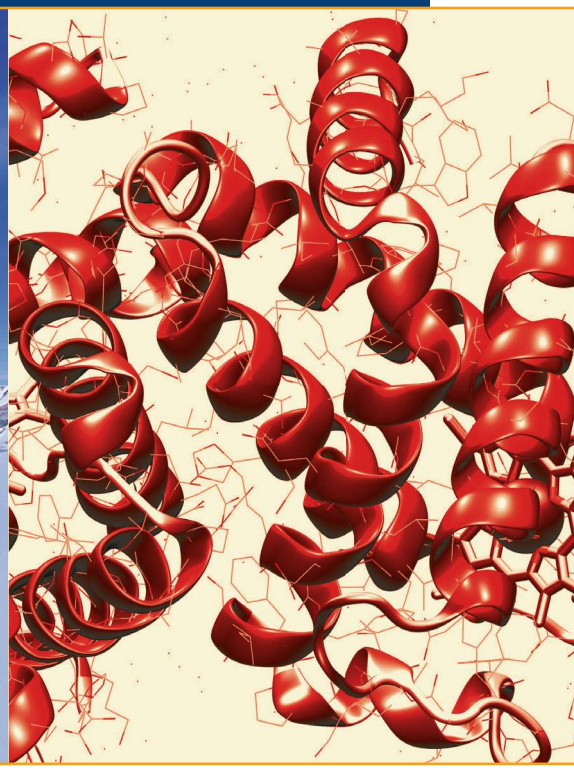
On average, the current R&D outsourcing penetration in the global pharmaceutical and biotech industries combined is estimated to be around 37%. Based on the current outsourcing strategies drug companies are taking, the outsourcing proportion will still rapidly grow and reach close to 67% by 2015 or so, representing a CAGR of about 12.5% between 2011 and 2015. In other words, by around 2015 the proportion of the fixed operation cost out of their total operation cost for most drug companies will be only about 1/3, decreasing from the current rate of about 2/3.

In addition, as all major pharma companies are currently narrowing their service provider pool to only a couple of preferred CROs in the key service sectors, it is expected that fiercer competition will occur in the global pharma outsourcing industry in the next couple of years. As a result, an industrywide wave of CRO consolidation is expected to take place in the very near future.

About the Author

Jim Zhang, Ph.D., is president and managing director of JZMed, Inc., a market research company specializing in research on the Chinese pharmaceutical outsourcing industry. The company also provides consulting services for pharmaceutical outsourcing in China.

Value through Innovation



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Match Your CRO To The Clinical Study

By Cindy Dubin, contributing editor

The success of companies that rely on outsourcing for the development of new pharma products can be intrinsically linked to the partnership with the CRO. Savvy life science leaders recognize this and, thus, revenue for U.S. CROs is set to soar from a total of $11.43 billion last year to $20.09 billion in 2017, forecasts a new report from Frost & Sullivan. While the economic downturn did take a toll on most markets in 2009, the CRO sector managed to buck the trend, growing 8.5%, says the study.

While the slowdown in funding for early-stage projects has dampened the CRO market's prospects for the next three to four years, this lack of funding also has restricted companies from investing in in-house clinical trials, creating opportunities for CROs. Analysts are optimistic about continued growth due to interest shown by new sponsors, especially biotechnology and specialty pharmaceutical companies that are demanding full services from their CROs, from the preclinical to postcommercialization stages.

GETTING THE RIGHT FIT

Selecting a CRO is not a one-size-fits-all proposition. The CRO should be specific to the project, have access to the correct patient demographic, be knowledgeable about the therapeutic area, and exhibit a level of expertise in project management.

These were the qualities that Galena Biopharma, Inc. (formerly RXi), a Portland, OR-based biopharmaceutical company, sought as it set out to begin a Phase 3 clinical trial. Galena develops targeted oncology treatments that address major unmet medical needs to advance cancer care. The company is developing NeuVax, an off-the-shelf peptide vaccine based on the concept of active immunotherapy. NeuVax targets patients who achieve a remission with current standards of care, but have no available adjuvant treatment for maintaining their disease-free status. The intradermal injection is given once a month for six months, followed by a booster injection once every six months. Based on a successful Phase 2 trial, which achieved its primary endpoint of disease-free survival, the FDA granted NeuVax a special protocol assessment (SPA) for a Phase 3 clinical trial in adjuvant therapy of women with low-to-intermediate HER2+ status. An SPA is a declaration from the FDA that a prospective Phase 3 trial's design, clinical endpoints, and statistical analyses are acceptable for FDA approval.

According to the National Cancer Institute, more than 230,000 women in the United States are diagnosed with breast cancer annually. The currently approved Herceptin (trastuzumab by Roche-Genentech) monoclonal antibody treatment is indicated in women with tumors that over-expressed (3+) HER2, which represent 25% of patients, while NeuVax targets the remaining patients with low-to-intermediate over-expressing (1+/2+) HER2 tumors — representing a targeted personalized therapy for about 40,000 to 50,000 patients annually. NeuVax attempts to harness and boost the body's immune system to seek out and fight off cancerous cells. Herceptin had revenue of more than $5 billion in 2010, approximately half of which was in the adjuvant setting. Mark Ahn, Ph.D., president and CEO of Galena Biopharma, expects NeuVax to satisfy an unmet medical need and that the drug has blockbuster opportunity.

THE NUANCES OF AN SPA

Ahn admits Galena needs a little help achieving the goal of becoming a blockbuster. So while Phase 1 and 2 clinical trials of NeuVax were performed in-house, the management team at Galena decided that outsourcing the Phase 3 trial, expected to commence in the first half of 2012, was necessary. Much of this decision was based on the multinational nature of the study. One hundred sites will participate in the United States, Canada, and Europe.

As clinical trials become ever-increasingly complex and global, the competition for access to patients, new investigators, and fresh studies is heating up. The gap between patient access and trials has been rising consistently over the past decade and could affect future projects, states the Frost & Sullivan report. CROs enable access to an extensive patient pool.

Galena needed a CRO partner with global

reach and locations in sites with the standards of care that would adhere to the protocol. "The results from each site have to be comparable, and the way to ensure that is to be certain the standards of care at all locations are similar," says Ahn.

In addition, all of the 700 patients who will participate in the 36-month study must be appropriately screened, and their data must be easy to electronically access on a timely basis.

The selection process took about six months and included screening about 12 candidates, then whittling the list down to 4 who were sent detailed requests for proposal. "Galena conducted a very professional, rigorous, and thorough evaluation of clinical research service providers to conduct its trial," says Gene Resnick, M.D., chief medical officer of Aptiv Solutions, a CRO headquartered in Reston, VA.

Galena provided a framework of specifications and requests in the RFP. In addition to providing the standard information regarding therapy area expertise, relevant study experience, global footprint, and staffing/resources, Aptiv Solutions provided information specifically focused on the Galena study. For example, the CRO provided detailed analysis of site distribution and enrollment projections, feasibility assessment for the trial, statistical modeling for adaptive design features, and regulatory timelines. These items proved valuable to Galena in study planning and provided a basis for discussions and study implementation.

During the assessment process, Galena also asked questions such as:

- Does the CRO have experience in the same disease indication?
- Is there a proven network of clinical sites?
- Does its project management have a proven track record of handling a similar level of complexity in drug product?
- Can it perform careful patient screening?
- Will it perform CRA follow up?
- Is there a database lock and data safety monitoring board?

Ahn says, "After a careful review of these details and an intensive in-person meeting, we felt Aptiv Solution's knowledge in oncology and its international presence in more than 20 countries participating in the study made it a logical choice for handling the Phase 3 trial called PRESENT (Prevention of Recurrence in Early-Stage, Node-Positive Breast Cancer with Low to Intermediate HER2 Expression with NeuVax Treatment)."

Aptiv Solution's clinical trial team will manage the PRESENT trial start-up and all related clinical trial activities for global implementation, including consideration of adaptive trial design strategies. This includes project management services, data management collection, statistical analysis and reporting, pharmacovigilance, and regulatory filing.

One of the biggest challenges the CRO will face in performing the Galena clinical trial is adhering to the established 36-month deadline of enrolling the right patients. "While breast cancer is unfortunately a common disease, only certain subsets are eligible for this study," says Resnick. For instance, the patients cannot be eligible for treatment with Herceptin, and they also have to exhibit certain markers of potential immune responsiveness.

Galena also needs Aptiv Solutions to handle the study's design nuances as they relate to the SPA. An SPA provides a significant advantage for companies because the rules of assessing safety and efficacy are prespecified, explains Ahn. "It is incumbent on the sponsor and the CRO to carefully adhere to the protocol to maintain the viability of this regulatory pathway," he says.

> "Hiring a CRO is not abdication, but a partnership, born of an assessment that using their operational infrastructure and experience is more efficient and less risky than creating a new multinational team."
>
> Mark Ahn, Ph.D., president and CEO, Galena Biopharma

Adherence to the agreed protocol specifications and processes will be essential. "The protocol is established and set, and no changes can be made during the course of the study," reiterates Resnick. "Galena had to be sure that whatever CRO it chose could understand how to analyze the data of such a study and represent the findings to the FDA in a way that satisfied the protocol."

RELINQUISHING CONTROL ... SOMEWHAT

Because NeuVax was developed at the University of Texas MD Anderson Cancer Center and the Brooke Army Medical Center in San Antonio, these facilities will comprise 2 of the 30+ U.S.-based sites for the PRESENT trial, making them important partners in this project.

Just as important is establishing a collaborative partnership with the CRO, agree Ahn and Resnick. The two groups will meet weekly throughout the study, and while Galena plans to actively manage the study, Aptiv Solutions will take ownership of the project. "Having this collegial partnership relieves the tension and helps work through the bumps that are sure to come down the road," says Resnick. "If we work as a team with the same goal in mind, the relationship will work."

"Hiring a CRO is not abdication, but a partnership, born of an assessment that using their operational infrastructure and experience is more efficient and less risky than creating a new multinational team," says Ahn. "The collaboration of a biopharmaceutical and a CRO shows the best that this industry has to offer."

Protecting Pharma Manufacturing Workers With Barrier/Containment Technologies

By Cathy Yarbrough, contributing editor

Because of recent advances in genomics and other fields of science, biopharmaceutical companies and CMOs are producing medications that are much more potent than their predecessors. As a result, both industry and the federal Occupational Safety and Health Agency (OSHA) are focusing more on the safety of workers in pharmaceutical manufacturing.

However, protecting employees from exposure to toxic drug substances during the pharma manufacturing process began many decades ago, noted Glenn Herring, VP of manufacturing at Halo Pharmaceutical. During the early years of the birth control pill, manufacturing staff members, most of whom were male, worked rotating schedules within the factory to minimize their exposure to product APIs.

Today the therapeutic area requiring the most potent medications — and thereby posing the greatest safety risk for pharmaceutical manufacturing workers — is oncology. "Unfortunately cancer can't be effectively treated with just an aspirin," Stephen Richard, manager, mechanical systems and processors at Bristol-Myers Squibb (BMS), said in explaining the need for powerful, targeted drugs for cancer patients. The manufacture of these innovative drugs requires that personnel work with APIs that are highly toxic, particularly in the large amounts that are stored in liquid or dry powder form in pharmaceutical and CMO warehouses.

"Workers often must scoop these very dusty powders from big drums during dispensing operations," said Richard. To prevent skin and inhalation exposure to these powders, technicians typically wear coveralls, gloves, and boots and use powered air-purifying respirators (PAPRs) outfitted with HEPA filters connected to a hood and shroud. By the time the medication reaches the patient, however, the amount of API in the drug, while based on the therapeutic dose, is relatively microscopic, because the dosage form will typically include one or more biologically inactive substances, or excipients. "Potent therapy drugs can have great benefit for patients when used in proper regimens, where doses are controlled and risks are minimized. But, they also can have serious consequences to the workers who handle, dispense, mix, apply, and dispose of them without proper controls and training," said John Howard, M.D., director of the National Institute of Occupational Safety and Health.

SELECTING BARRIER/ CONTAINMENT TECHNOLOGIES

During the manufacturing process, exposure, even at the lowest levels, to some APIs can produce such toxic effects as cancer, reproductive and developmental problems, and allergic reactions, according to OSHA. The protection of pharma manufacturing workers has spawned a robust industry with numerous companies whose products range from personal protective equipment (PPE) to containment systems that physically separate workers from the drugs' ingredients. One of these companies designed the space suits for NASA and is applying its expertise in safeguarding astronauts to protecting pharma manufacturing employees.

Unlike space suits, barrier and containment systems for pharmaceutical manufacturing "come in different shapes, sizes, and materials," said Herring. Although their primary purpose is employee safety, these systems also reduce human contamination, an increasingly important requirement for the aseptic filling of potent products.

Herring explained that the selection of barrier/containment technologies depends on several factors, chief of which is the potential toxicity of the material being handled and the resultant occupational exposure limit (OEL). API manufacturers will develop a material safety data sheet (MSDS) that iden-

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tifies safe handling practices and disposal of the components as well as an appropriate OEL. The OEL is typically calculated based on data generated during preclinical and clinical toxicology studies.

In pharmaceutical manufacturing, containment structures often are referred to as isolators. But, some industry leaders refer to structures that keep contaminants away from products as "isolators," and use "containment" to describe strategies or systems that keep toxic or potent products from workers. The Parenteral Drug Association (PDA) uses "aseptic isolator" and "containment isolator," respectively, to describe the same technologies.

Isolators come in two varieties: open and closed. In aseptic pharmaceutical filling, isolators enable continuous or semicontinuous ingress and/or egress of materials, while maintaining a level of protection over the internal environment. Open isolators are becoming popular in fill areas because they protect products while allowing vials to enter and exit the workspace.

Closed isolators, according to PDA, are "capable of levels of separation between the internal and external environment unattainable with other technologies." Nothing goes in or out of closed isolators during their operation except for air, whose direction distinguishes aseptic closed isolators from containment closed isolators. While the former uses positive pressure to keep germs and particles out, the latter operates under negative pressure to keep toxic or potent materials away from workers and their workspace.

According to PDA, a barrier technology is "an open system that can exchange contaminants with the surrounding area, and cannot be decontaminated to the extent possible in an isolator." Containment refers to closed isolators such as the physical structures that separate employees from hazardous substances. These include glove boxes that enable personnel to safely handle materials as well as plexiglass windows that allow them to view their work.

Three-sided downflow booths are an example of a barrier technology used in pharmaceutical manufacturing. Equipped with airflow equipment that draws particulates away from the worker's breathing area, downflow booths prevent the inhalation of unsafe levels of dust during material handling. Because they enable workers to move freely, downflow booths are regarded as ergonomically friendly.

Some companies have begun to use downflow booths as the primary engineering control for containment. The amount of time required for cleaning is much less with a downflow booth than it is for containment systems. Thus, downflow booths are regarded as cost-effective.

KEY ADVANCES IN CONTAINMENT TECHNOLOGY

Recent advances in containment or isolation technology include the use of flexible containment materials as an alternative or supplement to the traditional containment structures that are constructed from stainless steel and other hard materials. Flexible containment technologies include bulk bags and super sacks as well as glove bags, isolators, flooring, and soft-wall clean rooms. The containment capabilities of flexible and rigid materials are reportedly comparable.

Flexible containment technologies have two advantages over rigid systems, said Herring. First, the initial purchase price for flexible technologies is lower than the capital investment required for rigid containment systems. Another advantage: These technologies are disposable, while rigid containment requires time-consuming setup and cleanup. Setup, which can take as long as 8 hours for rigid systems, can be reduced to minutes with single-use containment. The time required for changeover from one product operation to another is reduced from days or weeks to hours with single-use technologies.

Restricted access barrier systems (RABS) are also regarded as an efficient alternative to clean rooms and containment or isolator technologies that completely enclose the aseptic working area. RABS are mini environments with rigid walls that provide a physical and aerodynamic barrier between staff and the sterile drug manufacturing process enclosed within the production environment. In both RABS and isolators, materials are introduced and leave through mouse holes, rapid transfer ports, and pass-throughs. Glove ports and half suits also are used to separate staff from the RABS' sterile interior.

A NEW APPROACH TO BARRIER TECHNOLOGY

In collaboration with barrier/containment company Walker Barrier Systems, BMS' Richard has designed and installed a barrier device within a downflow booth as an added engineering control to further reduce dependency on PPE (see photo on page 28). The device, a 3' x 4' adjustable plexiglass screen, is designed to provide a physical separation between the worker's breathing zone and the task being performed — dispensing of dusty powders from large drums. Personnel can manipulate the screen by hand while working in a downflow booth to place it in the most ergonomically effective position. Richard said that his initial studies indicate that the barrier provided a 10x protection factor to workers from inhalation and skin exposure to the APIs, in addition to being operator-friendly. Richard plans to conduct more studies on the device.

"The most impressive step I have noted in containment technology is the change to small equipment isolators and the move away from reliance on clean rooms," said Dr. Wolfgang Kramp, senior manager of quality assurance at Fischer Clinical Services GmbH, at a recent International Society for Pharmaceutical Engineering (ISPE) conference. One application for such smaller containment areas is the solid-capsule filling process, during which the generation of particulates is unavoidable. Isolators enable the biopharma companies and CMOs to minimize the containment area and increase worker protection.

No doubt the dispensing, formulation, filling, and packaging of the next generation of pharmaceuticals will continue to generate new approaches to safeguard the health of the personnel essential to bringing these drugs to patients.

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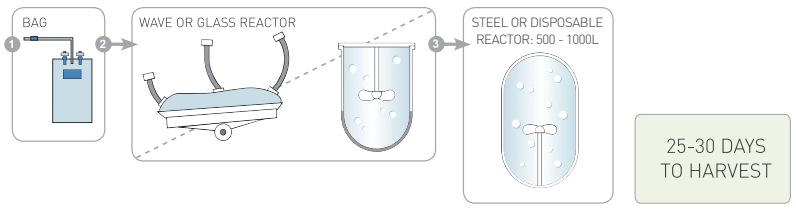

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Bringing A Billion-Dollar Drug To Market

By Cindy Dubin, contributing editor

A report by Deloitte on the world's 12 largest drugmakers shows that the average cost of bringing a product to market rose by more than 25% to greater than $1 billion in 2011, from $830 million in 2010. And, for new drugs, it typically averages 10 to 15 years from discovery to enter the marketplace. With the time and monetary investment, it is no wonder that the number of late-stage drugs in development dropped to 18 from 23, on average, per company, from 2010. And, 10 of the 12 firms actually saw a decline in investment returns from R&D, resulting in an overall drop to 8.4% from 11.8% last year.

But there are success stories: 35 new medications were approved during the FDA's 2011 fiscal year, the second-highest number in a decade. Industry pros say that those who have received FDA approval were careful to dot all their "i"s and cross all their "t"s during clinical studies, communicate with regulatory bodies, and choose the right sales and marketing team.

BEGIN WITH THE END IN MIND

According to Gene Haley, CEO and founder of Wilmington Pharmaceuticals (which develops and out-licenses fast-dissolving formulations for established medicines), a successful process begins with the end in mind. "Bringing a drug to market is not an exercise in imagination but a process that aims to satisfy an unmet need within the market for patients, physicians, and managed care and brings with it economic value." Haley says when you start with the end in mind, it is much easier to communicate the goal and gather a team that has the capability to carry out that goal.

The team should represent a variety of skill sets — formulation, clinical design and trial, regulatory, and manufacturing. "Any drug approval process is more than one person deep," agrees Jim Hauske, Ph.D., president and founder of Sensor Pharmaceuticals, a virtual drug discovery and development organization focused on molecules affecting the nexus of inflammation and metabolic disease. Hauske is not a novice when it comes to bringing a drug to market; he was part of the team associated with discovering and developing Zithromax. "Bringing a drug to market is a team sport that requires all the skills of a highly diversified team."

CLINICAL TRIALS: WHEN TO STOP

To promote the development of innovative new therapies, the FDA has made advances in regulatory science a top priority. For example, the agency is working to improve the science behind certain clinical trial designs. It has issued a draft guidance document on "adaptive trial designs" that makes use of early results of a trial to modify the design, making the study more likely to detect whether a drug works. The FDA also is working on a guidance document on "enrichment designs," studies that make use of patient characteristics to identify people for whom the drug is likely to be effective. These designs allow smaller studies to be successful and target the treatment to patients who will benefit the most.

About 50% of drugs entering Phase 3 trials fail because of lack of benefit and sometimes because of unacceptable side effects that were not seen in Phase 2. "That fact is just amazing to me," says Robert Temple, M.D., CDER's (Center for Drug Evaluation and Research's) deputy center director for clinical science. "The FDA understands that when the drug is exposed to more people during a Phase 3 trial, this opens the possibility to see more adverse events, but a large failure rate for effectiveness suggests inadequate Phase 2 trials. I encourage pharma to take a close look at their Phase 3 failures to identify why a failure occurred."

One area Temple says requires a closer study during Phase 3 is dose response. While no one wants to give more drug than necessary to do the job, studying a range of doses can mean the difference between success and failure. "There was one drug, Alosetron for diarrhea caused by irritable bowel syndrome, that caused severe constipation, which sometimes needed to be treated surgically, as well as ischemic colitis," relays Temple. "During the course of clinical trials, patients were dropping out because of the constipation. One would have thought the drug company would have tried a lowering of the dose study, but no."

The International Conference on Harmonization (ICH) urges that different dosing regimens be evaluated during Phase 3. Often companies study a few dosing regimens in Phase 2 and then study only one dose in Phase 3, which Temple says is often a "terrible mistake."

In addition to studies of more doses, Temple recommends that clinical trials

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encompass a range of patient populations. In addition to relatively healthy patients, seniors and people who have diseases other than the one being the focus of the study should be included. This, says Temple, will provide more and better data related to drug interactions and drug metabolization. It is also important to test various patient populations for drug side effects. A randomized withdrawal study with responders who are randomized to continued treatment or placebo is a very efficient way to test for the persistence of effect over time.

One major difficulty pharma companies face is knowing how much time to spend conducting Phase 2 and Phase 3 trials, says Temple. "Sometimes it is tempting to overinterpret data and perform subset analyses and decide you already have enough information, but this leads to inadequate dose finding and poor Phase 3 studies," says Temple. "The saved time is wasted. Better Phase 2 data, perhaps using careful adaptive procedures and a full range of doses, is often a worthwhile investment."

On the other hand, resist the temptation to overanalyze and collect too much data. "There is no need to collect lab data every month in a Phase 3 study; maybe every three months is sufficient," says Temple.

One way to see if clinical protocols for Phase 3 trials are sufficient is by way of a special protocol assessment (SPA) by the FDA. While not a guarantee of eventual drug approval, an SPA is a way to come to an agreement with the FDA on the design of protocols related to animal carcinogenicity, final product stability, and pivotal Phase 3 trials.

Getting FDA agreement (read: buy-in) on your Phase 3 protocol can be critical to your development plan. It means the FDA is familiar with your program and feels that the protocol is adequately designed to address the endpoints proposed. Having an SPA can give you and investors confidence in your program."The advantages of submitting an SPA seem obvious, yet many companies do not avail themselves of the process, which does not seem prudent," says Temple.

FDA APPROVAL COMES DOWN TO SOUND DATA

The FDA often gets the reputation of slowing down the approval process. Yet, historically, the agency has put many guidelines in place to attempt to do just the opposite. For example, a report by the National Organization for Rare Disorders says the FDA's flexible standards for approving drugs targeted at rare disorders have made it easier for those drugs to reach patients in need.

"Oncological development is presented with fewer hurdles than other therapeutic areas, so the regulatory process is more straightforward," says Habib Skaff, CEO of Intezyne, a specialty pharma firm that was founded in 2004 with the goal of developing better cancer treatments. "Regulators know these patients are terminal, and it is important to get therapies available to them as soon as possible."

Intezyne's work involves substantially changing the pharmacokinet-

ics of already approved drugs, which is unique when it comes to clinical trials. "Our risks in clinical trials are not the same as those associated with the development of a traditional new chemical entity (NCE) because the API in our NCE has already been clinically proven," says Skaff.

But others remain skeptical of how much the FDA can handle and how quick the approval process really is. "The FDA's workload can be an impediment to a rapid review process," says Tom Aluise, CFO, Wilmington Pharmaceuticals. "The process gets delayed because the agency doesn't have the time and people to answer questions. NDA (new drug application) filing used to involve meetings and a Q&A process with the FDA, but now the agency doesn't have the time for personal meetings, so we receive written responses, which can be open to interpretation. Collaboration is largely gone."

Temple adds, "Many pharma companies are knowledgeable and have discussions with us about areas of their studies that might cause trouble. And sometimes, disagreements arise, but we are willing to disagree, and companies should feel free to push the issue with us. Despite what many believe, disagreeing with the FDA won't harm the chances for drug approval."

According to Dr. Ron Hargreaves, VP, regulatory affairs at Ferring Pharmaceuticals, "Gaining FDA approval is, and probably should be, a challenging procedure. While we aim for the smoothest process possible, we expect and are prepared to face the challenges." The challenge Ferring knew it would face is one that faces all companies making a submission to the FDA — the agency's increasing criteria for the demonstration of safety and/or efficacy. This is particularly the case when a new product or a new claim is introduced into an existing class of products. According to Dr. Paul Korner, senior VP, U.S. development at Ferring, "This has to be expected in product development, and studies need to be designed to allow for such rigorous criteria."

It is important to have a thorough understanding of what products have been approved in the area of interest and, if possible, what issues were encountered during the development and approval process. Additionally, communicate with the FDA early and at key points during the development process to ensure a successful program outcome. Finally, the project team must respond quickly, clearly, and completely to FDA questions or comments, particularly in the final stage of the review process.

Treading carefully from drug discovery to commercialization is essential. And once you've been through the process, don't get too comfortable. There will always be an "i" left undotted and a "t" left uncrossed. "When launching a product, you don't know what you don't know," says Hauske.

FutureWatch

EXPECTED TO GROW AT NEXT TWO YEARS

to be $137 billion during the same period. Even with this market boom, there is room to grow. Global markets will be important for smaller generic pharmaceutical companies. The ability to enter these markets quickly will have a major impact on their success.

According to one industry analyst, "the global economic downturn opened the door for generic products, with many patients choosing generics over brand equivalents. As the economy began to rebound, most of these people stayed with generics because of the lower cost and no discernable difference in their effectiveness."

Saudi Arabia Emerges As Pharma Manufacturing Hot Spot

By Sara Gambrill, contributing editor

The World Bank/International Financial Corporation's Doing Business report ranked the Kingdom of Saudi Arabia 12th in the world out of 183 economies for ease of doing business in 2011 — up from 67th in 2005. The speed with which Saudi Arabia has risen through the ranks can be attributed directly to the efforts of the Saudi Arabian General Investment Authority (SAGIA), which aimed to make the country one of the top 10 most-competitive economies in 2010. The country's "10 x 10 program" encompasses all efforts toward achieving this goal.

Saudi Arabia is focused on encouraging the growth of its private sector to diversify its economy beyond petroleum — which accounts for 80% of the country's budget revenue — to include knowledge-based industries. For example, building a life sciences industry is one of the Saudi government's top economic priorities. In addition to transforming the economy and its infrastructure to support knowledge-based industries, the government is supporting the sector's development through a broad range of direct and complementary investments. With nearly 30% of its population under the age of 15, Saudi Arabia is keenly focused on providing private sector employment opportunities for its next wave of working-age citizens and lowering the current rate of nearly 30% unemployment among its youth. Only about 10% of private sector jobs in Saudi Arabia are held by Saudi nationals currently.

As part of an effort to attract foreign investment, Saudi Arabia joined the World Trade Organization in 2005. The following year, SAGIA established the National Competitiveness Center (NCC) to monitor, assess, and support competitiveness enhancement in Saudi Arabia. NCC's recommendations, including the streamlining of business start-up, construction permitting, and property registration, combined with tax incentives entered into the tax code in 2006, have contributed to Saudi Arabia's efforts to increase its attractiveness to industry.

'ECONOMIC CITIES' ATTRACT BIG PHARMA

The most ambitious project SAGIA has undertaken as part of its 10 x 10 program is facilitating the construction of four "Economic Cities." At a cost of more than $60 billion, this development project is expected to promote economic diversification, create new job opportunities and new homes for 4 million to 5 million people, and contribute $150 billion to Saudi Arabia's GDP.

King Abdullah Economic City (KAEC) has attracted the notice of Big Pharma, leading a few companies to strike agreements to build manufacturing facilities there. The most recent one to announce such an agreement is Pfizer. "Triggered by exceptional growth of the Saudi market, Pfizer has joined efforts with SAGIA to set up a legal company entity and establish a manufacturing plant at KAEC," says Guy Lallemand, regional president, Pfizer AfME. "It's intended that the plant will be able to serve both the needs of the Kingdom and neighboring countries. It will also help create new employment opportunities to local manpower in KSA [Kingdom of Saudi Arabia] and develop their skills."

Pfizer's KAEC facility will be operational by the end of 2014 and will include solid dose manufacturing, packaging, and warehousing. The new facility will produce a broad range of Pfizer's best-in-class brands.

KAEC alone will be the size of Washington, D.C. and is projected to have a population of 2 million and create 1 million jobs, according to SAGIA. In 2010, Sanofi-Aventis also announced plans to build a new manufacturing plant there. Its facility will produce oral antidiabetics and cardiovascular drugs.

IMPORTANT PHARMACEUTICAL MARKET, EAST-WEST HUB

Ease of doing business alone can't account for why two Big Pharma companies have recently announced plans to build manufacturing plants in Saudi Arabia and why others already have. The Saudi pharmaceutical market is the largest in the Middle East and accounts for roughly 2/3 of all drug sales in the Gulf Cooperation Council region, which, in addition to Saudi Arabia, comprises Kuwait, the United Arab Emirates, Oman, Qatar, and Bahrain. The Jeddah-based National Commercial Bank (NCB), in its Saudi pharmaceuticals sector review, predicted that the Saudi pharma

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market would grow to SR14.04 billion [$3.75 billion] in 2012.

Saudi pharma market growth drivers include increasing population, aging, and affluence; modernization; and the establishment of more private facilities. According to Espicom, Saudi Arabia's pharmaceutical market "is expected to rise by a CAGR in the high single digits during the 2011-2016 period." The pharmaceutical company in Saudi Arabia with the largest share of the pharmaceutical market in country is GSK.

GSK has had a presence in Saudi Arabia for 50 years. In 1992, the company formed a joint venture with Banaja Holdings, establishing Glaxo Saudi Arabia Limited. GSK has operations in the capital city of Riyadh, Jeddah — where its headquarters are — and Dammam, with nine locations in all, including a manufacturing site in the Jeddah suburbs. The company employs just under 500 people locally.

"We are different from other pharma companies in the country as we are the only one to have a joint-venture pharmaceutical manufacturing company," says Youssry Nawar, general manager and VP Saudi Arabia, GSK. "With regards to SAGIA, we do not directly benefit from any incentives, as we were established before this group was formed. However, it is a great initiative for driving further foreign industry investment in the country, as well as supporting existing ones."

Nawar adds, "Saudi Arabia is an important market for GSK, both in terms of improving medicines for patients and in developing our business in the Gulf. The Saudi Arabia pharmaceutical market is the largest among the Gulf Cooperation Council countries and the whole Middle East. More importantly, economically and politically the country proves to be stable, which will further drive growth of the healthcare business."

In addition to stability, Saudi Arabia has a legal infrastructure that offers industry assurances other emerging markets cannot always provide. "Saudi Arabia has strong legislation addressing areas of IP protection, import licensing, and customs tariffs and fees. Innovative patented medicines are still leading the market growth," Nawar says.

SAGIA's vision is to make Saudi Arabia a "major hub between East and West." The country's geographic location helps make this vision attainable. Pfizer's Lallemand says that in addition to the favorable business environment, competitive advantages, and other investment opportunities offered by the Saudi government, "Our decision to establish a new manufacturing base in Saudi Arabia is also based on its central geographic location and the well-established routes of distribution to all parts of the Middle East and beyond."

GOVERNMENT INVESTMENT IN HEALTHCARE

Saudi Arabia has a population of more than 26 million, which includes about 5.5 million nonnationals residing there. Eighty-two percent of the country's population is urban. Saudi Arabia has five cities with a 1 million+ population: Riyadh, Jeddah, Mecca, Medina, and Dammam. With its growing population, its healthcare needs will rise. The country's healthcare spending is projected to increase.

Saudi Arabia has "a prevalence of disease in areas such as diabetes, which affects 25% of the population, and asthma, which affects 15% of the population," GSK's Nawar says. "Health expenditure in the Kingdom has more than doubled in the past decade. The government has allocated £11.3 billion [$17.8 billion] to health services in 2011, an increase of 12.3% [compared to] 2010."

Saudi Arabia has 400 hospitals, 2,075 primary health centers, and 850 private clinics. "The government's plan is to proceed with the construction of 56 new and 51 replacement hospitals and 750 primary health centers in the coming five years," Nawar says.

The main regulatory authority in Saudi Arabia is the Ministry of Health, and the Saudi Food and Drug Authority was established in 2003 to be responsible for developing and enforcing the regulatory system. Clinical research is a growing component of GSK's operations in Saudi Arabia. The company has conducted several studies there in areas such as oncology and vaccines. GSK is a research partner with National Guard Hospital, King Faisal Specialist Hospital & Research Centre, and the Ministry of Health.

> "Saudi Arabia is an important market for GSK, both in terms of improving medicines for patients and in developing our business in the Gulf." Youssry Nawar, general manager and VP Saudi Arabia, GSK

INVESTING IN THE FUTURE

In addition to the 10 x 10 program and the facilitation of the Economic Cities, Saudi Arabia is demonstrating its commitment to investing in science, business, and the Saudi workforce through the founding of the King Abdullah University of Science and Technology, a graduate research university focused on scientific and technological advancement. It is the first coeducational university in the Kingdom. The university aims to be a world-class research institution for the purpose of educating and training future generations of scientists, engineers, and technologists to be leaders in their respective fields. It also intends to foster collaboration and cooperation with other research universities and the private sector. Its vision includes publishing articles in peer-reviewed scientific journals and making a significant number of scientific discoveries and technological innovations.

With a highly educated and technically skilled workforce, a growing population with an increasingly Westernized disease demographic, significant and growing government expenditure on healthcare, and a hospitable business environment, Saudi Arabia has all the right ingredients to continue to grow in importance as a key pharmaceutical market.

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Logistics Improving In Emerging Markets

By Gail Dutton, contributing editor

Brazil, Russia, India, and China (BRIC) are such promising regions for life sciences companies that it's easy to forget their challenges. Developing markets, including BRIC nations, all tend to have inadequate transportation infrastructures, a limited number of knowledgeable distributors, security issues, and unique bureaucracies and interpretations of regulations.

Whether there for clinical trials, manufacturing, or market share, life sciences companies entering emerging and developing regions for the first time "tend to overlook the challenges associated with security, regulations, and the unique nature of the supply chain," notes Bill Hook, VP of global strategy for UPS Healthcare Logistics.

The UPS "2011 Pain in the (Supply) Chain Survey" cited limited infrastructure as one of the top four barriers to global expansion. Likewise, the DHL report, "Transforming Life Sciences Logistics in India," recommends strengthening the logistics infrastructure, coordinating ground-handling agencies, streamlining the import/export process at ports, implementing best practices, increasing the use of technology to improve supply chain operations, and developing multiuse warehouses. Those concerns extend to most developing regions. "Often, the infrastructure simply isn't there," Hook reiterates.

The infrastructure is improving, though. For example, Hyderabad, India, opened a dedicated cargo handling zone for pharmaceutical products in 2010, and DHL opened its second Life Sciences and Healthcare Competence Center in China in September. FedEx maintains a large Dubai facility as a hub for traffic flowing among nations in the Middle East, Africa, Asia, and Europe.

TRACK-AND-TRACE — THE HOLY GRAIL

Risk management concerns remain high in developing regions. In Brazil and Mexico, for example, DHL takes a comprehensive security approach for its warehouses and during transit. In DHL's Brazilian operations, security includes background checks of all personnel, vehicle safety checks, and GPS tracking. Best practices include transportation escorts and extensive driver training to minimize the risks of hijacking.

"Robust track-and-trace capabilities are the holy grail of global visibility," Hook acknowledges. "As an industry, we're not there yet, but we are making improvements." UPS is evaluating new technology to monitor the condition of products in transit and to note unplanned interventions such as package openings and delays. Such technology is especially beneficial in monitoring temperature-sensitive materials. "The challenge is getting the technology to acceptable costs. The best strategy today is to minimize the number of handoffs in the supply chain," Hook says. He also recommends working with one organization — to the extent possible — to achieve global visibility using the same technology.

THE CHALLENGE OF GOVERNMENT RELATIONS

As an API supplier, LGM Pharma is tapped into Africa, Asia, Eastern Europe, the Philippines, and South America. "The greatest challenge, logistically, is understanding local regulations," according to Robert Hoppes, director of sales. He points to confusion over international commercial (INCO) terms (which should be resolved since the release of new definitions), the interpretation of local regulations, and sometimes obscure permitting processes.

"We get calls from clients who aren't familiar with the requirements for importing certain APIs or who need last-minute documents when goods are held up in customs. Usually the issues are minor and can be resolved with updates or clarifications," Hoppes says.

At UPS, "We have a public affairs group that meets with government bodies to help them understand our objectives and to help us understand their regulatory stance," Hook says. Access to established, international government affairs teams is one of the advantages in working with large, global logistics providers in developing regions. Working with a

logistics firm that already has undergone the process lets life sciences companies leverage those experiences and thereby smooth their own entry into new regions.

Those regulations may affect the distribution network a company establishes. "Who moves goods and how they are moved varies and affects other strategic decisions," Hook says. "For example, in India, product is taxed as it moves across state borders. In China, healthcare is managed through hospitals, not the physicians," so manufacturers deal with fewer, but more powerful, buyers.

In Brazil, the tax system causes manufacturers to ship directly to retailers to bypass wholesalers and one level of sales tax. Brazil also requires warehousing in the same state as the manufacturing facility. DHL began its PharmaShare services in Brazil, with consolidated warehousing and shipping, to help its clients meet those requirements and conserve capital, Jose Fernandes, VP of operations for DHL Supply Chain Brazil, says. PharmaShare is also available in Mexico and is launching in the United States now.

> "We're seeing a sudden interest from medical device and pharmaceutical companies in using simulations to evaluate the economics of drugs in specific markets."
>
> Claire Cordeaux, healthcare practice leader, SIMUL8 Corp.

THE INCREASE IN MODELING & SIMULATIONS

Contract logistics is evolving to integrated logistics so that more aspects of the supply chain are handled by a single logistics provider. UPS and DHL, for example, each work closely with clients to design a network that is most effective for the region of interest and for clients' own particular needs.

Logistics and business model simulations provide a way of smoothing expansions by helping managers identify the right questions, asserts Claire Cordeaux, leader of the healthcare practice for SIMUL8 Corp. "Anywhere there is a flow of events — people, product, process design — simulations can be used to see beyond volumes to identify bottlenecks, timetables, and other factors, enabling you to experience the problems you may encounter before going live," she says. Modeling is used often as a learning device, to enable dialog and work out the real questions that must be answered.

"We're seeing a sudden interest from medical device and pharmaceutical companies in using simulations to evaluate the economics of drugs in specific markets," Cordeaux adds. Economic evaluations, ideally, include the healthcare model, pricing, volume, patient conditions, and access — many of the same parameters that also figure into logistics decisions. Modeling also can become a value-added service for manufacturers to help their own clients develop more efficient business and distribution models.

THE BENEFITS OF SHARED WAREHOUSES

"I see hesitancy among the largest life sciences companies to outsource logistics and transportation to one party," according to Richard Smith, managing director for life sciences specialty services at FedEx Express. The integration trend is growing, though, as life sciences companies and logistics providers expand into the interiors of developing regions. UPS, for example, launched express flights to Chengdu, in western China, last July.

Logistics providers are, increasingly, developing secure, shared warehouse facilities that meet the requirements of life sciences regulators and provide the flexibility that companies need as they enter new markets. For example, "UPS has nearly 5 million square feet of healthcare distribution centers around the world and is continuing to build out. Five or six more facilities are planned for the next year," Hook says. Likewise, DHL has expanded Brazilian warehouses beyond Sáo Palo and Rio to include midwestern and southern Brazil.

PUBLIC HEALTH PROGRAMS: AN ENTRANCE TO EMERGING MARKETS

Chembio Diagnostics Systems, Inc. entered emerging regions by working through public health programs. "Chembio's tests for leishmaniasis, leptospirosis, HIV, and tuberculosis each have FDA approval, but a large percentage of our non-U.S. sales have been in Africa," according to Larry Siebert, president and chairman. There, the President's Emergency Plan for AIDS Relief (PEPFAR) provides Chembio's AIDS point-of-care tests to the various nations' ministries of health from a central distribution point in Africa. The company also works with an Ethiopian distributor that sells directly to the Ministry of Health.

To access the Brazilian market, Chembio works with the Oswaldo Cruz Foundation. Its tests are assembled there under the Foundation's brand. As Siebert explains, "We shipped the components and trained the locals to assemble and manufacture our product there. For us, there's no concern about distribution or quality."

In those emerging markets, track-and-trace requirements are minimal, Siebert recounts. "We have lot numbers," but more

sophisticated solutions haven't been requested. However, "The National Agency for Food and Drug Administration and Control (NAFDAC) in Nigeria required that 'Chembio' be printed directly on the individual pouches and the kit boxes, rather than a stick-on label, to combat counterfeiting," Siebert says.

He adds that even though these are humanitarian products, his company still has to go through the application and perform due diligence. That applies not only to identifying the ultimate purchaser of the product, but to identifying product components. "The life sciences industry uses sophisticated software, radioactive material, lasers, etc. You never know what wlll trip up a company."

> "I see hesitancy among the largest life sciences companies to outsource logistics and transportation to one party."
>
> Richard Smith, managing director for life sciences specialty services, FedEx Express

THE COMPLICATED COLD CHAIN

The cold chain is very challenging, particularly in the emerging market. There are big opportunities there in terms of new technologies, but also in developing the information systems and reporting processes to manage the cold chain.

In North America and Europe, the transportation parameters are well-known. "We know the profile of the temperatures in which we are transporting, from the cold North Dakota winter to the heat of a Texas summer, and what that means for packages," Hook says. That information is less detailed for emerging markets, where maintaining correct temperatures for packages can become complicated.

At Chembio, "We subject our products to all sorts of simulated conditions, including changes in temperature, air pressure, packaging seals, and shelf-life challenges," Siebert says, to minimize the chance that challenges in the supply chain will adversely affect the assays.

"FedEx Express developed its SenseAware monitoring system to provide comprehensive monitoring that is managed on an iTunes-like platform," Smith says. It uses real-time GPS and also monitors temperature, light exposure, relative humidity, and barometric pressure. Partnering with CryoPort, FedEx also offers deep-frozen shipments that are guaranteed to maintain the specimen at -150° C for 10 days.

The UPS strategy uses what it calls "Control Towers" in Asia, North America, and the EU to monitor critical shipments. "If a package misses a log-in window, the team mobilizes local staff to track it, get it moving again, and re-ice or recharge the package as needed. We try to intervene before temperature becomes an issue," Hook stresses. UPS also is evaluating new technology, and has added a new type of air freight container that doesn't require manual intervention.

The cold chain was one of two focus areas when DHL Supply Chain Brazil was formed in 2004. As yet, that operation does not have deep frozen storage capabilities. Instead, "DHL coordinates therapeutics to arrive moments before they are applied to patients. It's very time-sensitive," Fernandes adds. "That's very convenient for clinics and hospitals that often lack the freezers to store deep-frozen product."

Products that don't require deep frozen temperatures are packed in Styrofoam and stored at -20° C in DHL's freezers. "That method maintains temperature for 48 hours. We are investigating a new technology that doubles that hold time," Rogerio Mansur, director of operations, DHL Supply Chain Brazil, says.

THE SEARCH FOR LOGISTICS SKILLSETS

Finding people in emerging regions with the right logistics skill sets is another challenge. "Not having people on the ground to help resolve issues is problematic and, in emerging markets, there are not enough people with the right skills," asserts George Bickerstaff, executive chairman and cofounder of the Global Leader LLC and board member of the International Vaccine Institute. Those skills include knowledge of the international logistics and life sciences industries as well as the local logistics and regulatory environments.

"China is particularly difficult without an in-country presence," observes Karen Etchberger, executive VP for plasma, planning and supply chain, CSL Behring. When it launched its albumin product in China 20 years ago, it found two distributors and has remained with them. Their local knowledge helped CSL Behring navigate the bureaucratic hurdles. For example, she says, "Although there's only one registration required, each Chinese state has different documentation requirements." Other nations also have their own specifications, and even within the same country, interpretations can vary, she cautions.

Bickerstaff recommends outsourcing logistics to leverage the collective knowledge gained by larger teams working with multiple companies in a specific area. "Historically, Big Pharma handled logistics in-house," he says. He sees that changing as blockbuster drugs are replaced by the smaller markets of personalized medicine. "Big Pharmas will call in additional extra expertise, and the number of specialized distributors will increase," Bickerstaff predicts.

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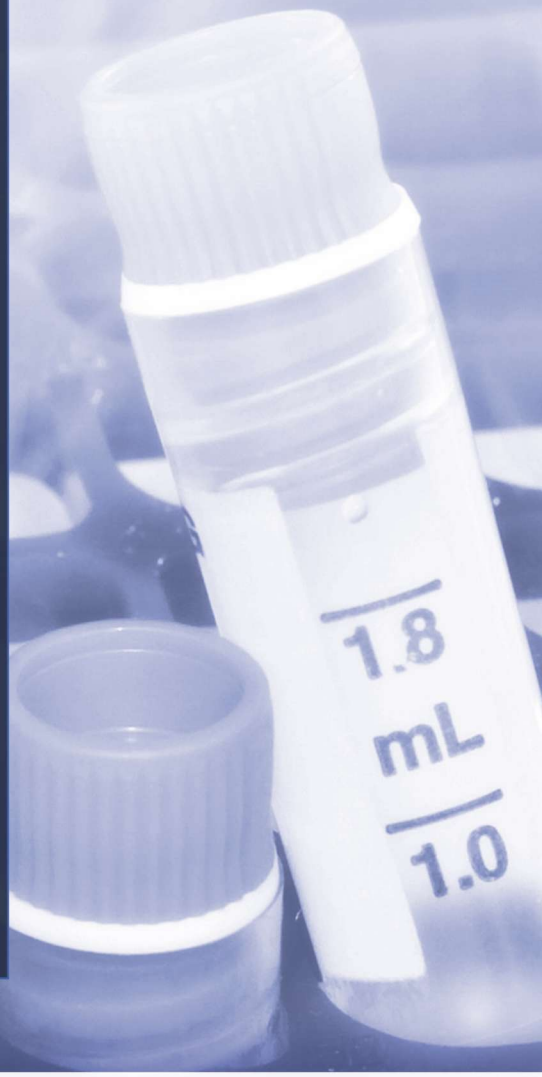

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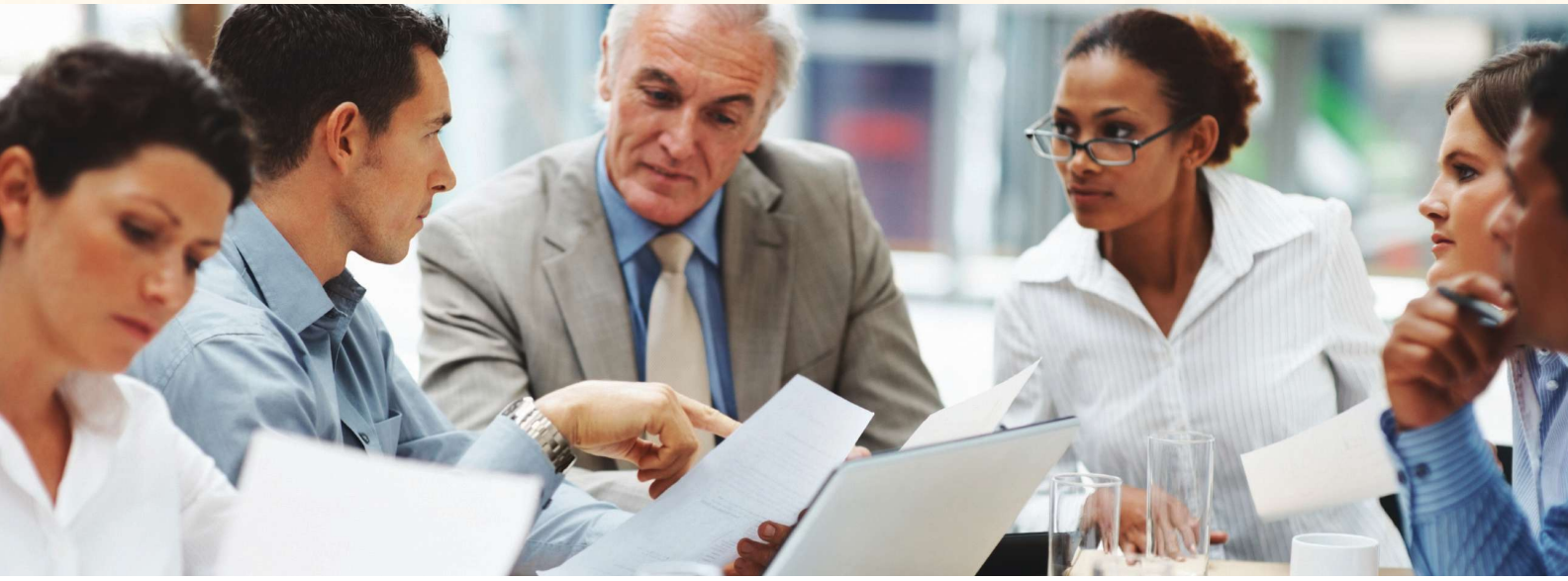
Avoiding A Failed NDA Submission Via A Third-Party Gatekeeper

By Diane Mauriello
and William Cairns



Companies specializing in the development, registration, and manufacture of pharmaceuticals will require no less than flawless management of data and tactical tasks to meet stringent FDA NDA (new drug application) submission requirements. In the supercharged business and highly regulated life sciences industry, your company must engage the best skills and most highly experienced professionals who offer end-to-end solutions to assure that your new products will be brought to market as rapidly as possible, well managed, and with minimal risk.

YOUR IN-HOUSE TEAM WEARS TOO MANY HATS

Your staff is responsible for numerous day-to-day global housekeeping activities. They do not have the time, focus, or experience to manage all aspects of a submission successfully. Submitting an NDA is the conclusion of 10 to 15 years of R&D, clinical development, and scientific discovery, and the cost is in the millions of dollars. Outsourcing these services to industry experts is the best alternative — not only because of the savings involved in every area, but because of the expert subcontractor's in-depth understanding and day-to-day use of the procedures, protocols, and techniques required to reach a successful submission end point.

However, there are negatives and unseen risks. Many people do not do due diligence and spend enough time identifying the correct outsourced expertise and do not work on how to manage the resource. They are mainly concerned with signing a check. Unfortunately, when they get the deliverables, they start to see the problems and deficiencies.

You must consider whom you will engage, how to qualify a prospective expert, how to insert that resource/team into your company, how to keep project management centralized, how to monitor work and quality, and so on. The most successful method for avoiding a failed submission is the engagement of a third-party gatekeeper. This is the high-level project management individual or team who details a comprehensive road map in the form of a master project planner, which includes all components to the project. The gatekeeper serves as the communicator, the leader, the team effort overseer, sponsor, and project participant. They lead the team and manage the issues, timelines, and durations linked to all near-term or downstream activities but not the relationships. It is essential to monitor and QC (quality control) all actions. It is not enough to monitor without quality checks and

controls firmly in place. All deliverables must be checked and timelines verified to determine how each element will impact another in the building of a submission "pyramid." Overlook these steps, and you risk the potential impact of delays to your filing date and you will be faced with very costly daily delays.

Your in-house team can meet a perfect on-time schedule of deliverables, some of which are substandard. The gatekeeper opens the attachments, checks the summaries, verifies a data point at random, and asks for a preclinical report — or better — the appendices. This leader wants to see all FDA or regulatory and compliance correspondence, user-fee receipts, detailed (not summarized) marketing initiatives, and a sample label of a suggested product profile. They will organize the global teleconferences every week, without fail ask the pointed questions, and clearly assign responsibility and accountability — not just sign the agreement and write the check.

For the post-approval and postmarketing processes, more work will be required to monitor and assess the new drug in numerous areas including safety, benefit to the patient, risks, and efficacy, for a 12- to 36-month period.

BE READY TO FILE THE FIRST TIME

Utilizing the gatekeeper for up-front development of a crystal-clear clinical/regulatory submission strategy and strict implementation of the master project planner leads to a successful submission end point. Effective medical writing is essential. It is a must that all data be reviewed for gaps, correctness, and consistency for compliance to CFR (code of federal regulations) and EMEA (European Medicines Agency). The gatekeeper approach will manage the project and your team to provide quality, clear, and pristine data and documentation with the end result being a fileable clinical submission the first time to the agency.

About the Authors

Diane Mauriello, Ph.D., is the president of Dante Resources, a global company of clinical and submission specialists.

William Cairns is the founder and president of BCM Group, an international consultancy working with U.S. and non-U.S. manufacturers of pharmaceutical and medical technologies at the commercial level to create business growth and industry presence in North America.

Applying Lean Principles In The Analytical Laboratory

While Lean principles are typically associated with manufacturing processes, they can also deliver great improvements in the operation and productivity of the analytical laboratory. Even in heavily regulated life science and pharmaceutical laboratory environments where standard protocols can't be modified, Lean principles can help to minimize waste, improve workflow efficiency, and increase throughput. The Lean approach has gained so much attention in the laboratory world that it is routinely presented at analytical meetings and conferences like the annual Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy (PITTCON).

In general, Lean methodology is designed to remove "waste" or inefficiency from a process. In the lab, waste can negatively impact people and product quantity/quality. Waste in the laboratory can take many shapes and forms. For example, lab inefficiencies may exist because tasks are not standardized or operations are not fully understood by lab personnel. Unbalanced workflows can create idle time or redundancies, or cause instrumentation not to be used to its full capacity. An inefficient laboratory layout can cause wasted motion and add unnecessary delays to every step. Even inefficient storage and inventory schemes can create waste. Lean principles are focused on eliminating waste so that all activities/steps add value from the customer's perspective.

IMPLEMENTING LEAN METHODOLOGIES

There are five guiding principles in implementing Lean methodologies:

Specify Value: Each analytical laboratory has a defined objective, whether it be product discovery, quality control, or testing and analysis. The value of the lab must first be understood from the customer's perspective, whether that customer is internal or external. How do the laboratory services impact the customer's value expectation? What happens if the output is late or quality poor?

Map The Value Stream: Map out all of the steps required to bring the product or service to the customer, from the acquisition of raw materials, to the execution of lab processes and the delivery of the final product or service. What are the cycle times and resources required in each step?

Establish Flow: Identify the end-to-end workflow necessary to deliver the final product or service to the customer. Understand the entire process and identify those steps that truly create value. These are where you will want to focus.

Implement Pull: The term "pull" in this case is defined by the customer need. In a Lean-based laboratory, a service is not provided or task performed until the customer signals the need (creates the pull).

Work To Perfection: The goal of the Lean Analytical Laboratory is the complete elimination of waste so that all lab activities are geared towards creating value for the customer. Once the above steps are completed, Lean processes can be slowly integrated into the lab workflows, evaluated, and refined over time.

MANAGING CHANGE

Implementing Lean principles in any environment is challenging. Everyone reacts differently to change, and not everyone is open to change. The key to successful implementation is how the change process is managed. Most importantly, management must visibly endorse the Lean project and clearly communicate the reasons for evaluating and adopting Lean principles. The Lean project team should be composed of contributors from every area that may be affected by changes and empowered to implement the necessary changes. Often there is value in inviting an objective third party into the process to look at tasks and workflows differently than those so closely involved on a daily basis. Finally, it is important to define and outline tangible goals that can be measured during the process and after changes are implemented.

Through implementation of Lean principles, most labs could realize dramatic improvements in sample throughput, process turnaround, and customer satisfaction. In one recent example, a chemical and thermal testing lab employed Lean methodologies to improve the lab's turnaround on work requests after receiving complaints from its internal customers. The Lean project group was tasked with tackling inefficiencies in one area but actually uncovered unexpected issues in other areas that were negatively impacting their level of service. They implemented changes in their workflows and lab organization that reduced their turnaround on testing requests from weeks to days, in some cases.

Derek Lake

Derek Lake is a Six Sigma Black Belt in the Lexan process technology group at SABIC Innovative Plastics. Lake has taught several Lean Six Sigma classes and led numerous Lean improvement projects in laboratory, technology, and manufacturing settings.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The Evidence For Endpoints: PROs And Beyond

On October 19, 2011 the FDA hosted a workshop that will change how developers of medical products select, evaluate, and provide evidence to support endpoints for their clinical development programs. Dr. Janet Woodcock, director, Center for Drug Evaluation and Research (CDER), started the day with clear statements regarding the instruments used to measure the efficacy, and sometimes safety, of new medical products.

Woodcock cited FDA regulation 21CFR314.126(b)(6) requirements: "The methods of assessment of subjects' response are well-defined and reliable. The protocol for the study and the report of results should explain the variables measured, the methods of observation, and the criteria used to assess response."

WHAT DOES THIS MEAN?

In December 2009, the FDA released the final guidance on how patient reported outcomes (PROs) will be evaluated to meet the standard of "well-defined and reliable." Woodcock made it clear to those in the audience that the requirements for developing evidence to support PROs as outcomes equally apply to other outcomes, including: clinician reported outcomes (ClinROs), which are those collected by a clinician evaluating a patient and recording the results; and other observer reported outcomes (ObsROs), such as parents observing and rating children. In other words, the same "yardstick" for evaluating evidence will be used for all outcomes. Taken together, the FDA is now referring to all types of outcomes in trials as clinical outcomes assessments (COAs).

WHY IS THE FDA TAKING THIS POSITION?

The release of the PRO draft guidance in 2006 and the final guidance in 2009 articulated scientifically appropriate standards for PROs and for other outcomes. The workshop was the FDA's signaling to sponsors that the basic evidence needed to evaluate one type of endpoint applies to all others. FDA staff made a clear distinction between direct measures of patient benefit and indirect measures, which include various types of ClinROs, ObsROs, and biomarkers. The workshop participants also discussed how the appropriate endpoint for a given trial varies depending on context of use. For example, in measuring pain in a mentally competent adult, a direct measure of pain obtained from the patient using a PRO instrument may be the most appropriate. However, in mentally impaired adults or small children who cannot self-report, a ClinRO or ObsRO reporting patient behaviors that reflect pain may be appropriate. Sponsors would have to provide the evidence that shows the indirect measures reflect the direct concepts. The FDA, and specifically Woodcock, charged the workshop leaders to not discuss surrogate endpoints that day, and instead strongly encouraged discussion of the use of other forms of evaluation of efficacy of products. However, these endpoints must be compelling and interpretable — that is, they must be well-defined and reliable, as required by 21CFR314.126(b)(6). As Woodcock commented, the outcomes must have an evidentiary basis to support that they are appropriate for their context of use.

Jean Paty

Jean Paty, Ph.D., is cofounder and senior VP of scientific, quality, and regulatory affairs for invivodata, inc., and chief scientist and regulatory advisor of PRO Consulting.

HOW DOES THIS AFFECT MY CLINICAL TRIAL PLANNING?

Following Woodcock's initial address, the rest of the workshop day was spent discussing what this meant for clinical trial planning. What emerged was that the implication of the FDA's position is that any ClinRO, ObsRO, or PRO implemented in a clinical program with the goal of supporting the product labeling must have evidence to support that it is fit for purpose (previously referred to as "validated") for the context of use in the specific patient population. This kind of evidence includes content validity (demonstrating that an instrument measures what we think it measures), reliability (or showing the instrument will give consistent results if the patient is not changing), sensitivity to change (if treatment works, we can detect it), and that the results from an instrument are interpretable (or, being able to assert that a change is clinically meaningful). These criteria, which are standard in the world of instrument development and evaluation, will need to be met and reported in evidence dossiers for COAs. Such dossiers are separate and distinct documents from those on the efficacy and safety of the product.

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Why Foster Optimism In The Workplace?

By Shawn Murphy

Workplace optimism isn't about training employees to see the glass half-full through rose-colored glasses. Fostering workplace optimism focuses on three outcomes:

- renewing hope in the company's future
- adapting to the changing nature of work and expectations employees have of their employer
- repairing fractured relationships between management and employees.

To bring about these outcomes, leaders can use three leverage points to foster optimism in the workplace.

Know your leadership brand. We've seen too many executive scandals exhausting trust. Leaders in the 21st century need to have crystalline clarity in their personal values. It's not a matter of personal development to know your values. It's a matter of doing work that matters to you and having a source from which you can draw to inspire others to contribute their talents. It's a personal matter and a competitive advantage.

Tap into the need to make a difference. Trusted leadership expert Ken Blanchard recently published findings on employee work passion. Nearly 60% of employees said it was their responsibility to do meaningful work. Leaders tap into our human nature to do work that matters, to live a life that matters. Give employees meaningful assignments. No more tolerating the usual suspects trap (i.e. turning to the same employees to do high-profile projects). That type of activity signals an unintended message that favoritism and politicking are okay.

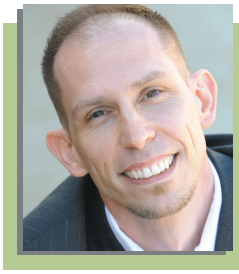
Repair relationships with employees. Organizations across industries and of all sizes had to take cost-cutting measures to survive this economy. It's time to begin repairing the damage done to the relationship with employees.

Senior leaders can signal to the entire organization the shift by publicly acknowledging how difficult it has been. Then, follow up with actions that reinforce that the shift is genuine:

- Share financials in ways employees understand. The goal is to authentically enlist their support for the company's future growth.
- Share successes and missteps related to the company's growth plans.
- Invite influential employees to participate in strategy setting.
- Stop rewarding senior executives with large bonuses while reducing or eliminating employee pay increases and perks like holiday parties.

Business Value of Workplace Optimism

In our knowledge economy, leaders who can create an environment of optimism create a competitive advantage. When employees work in an environment that lets them contribute their talents, engagement goes up. In high-engagement companies, Gallup has found that companies have seen a 19.2% increase in their 12-month operating income, and these companies outperform low engagement companies in customer loyalty and profitability.



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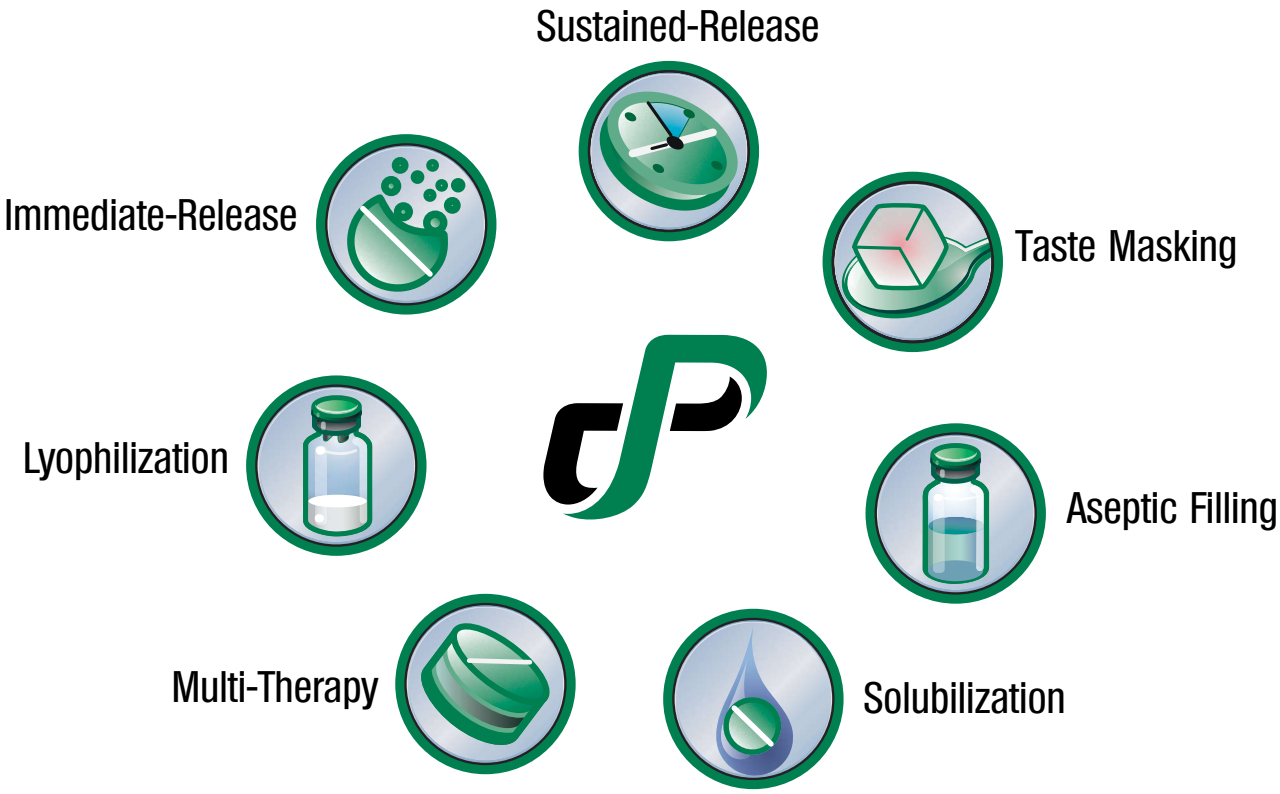

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