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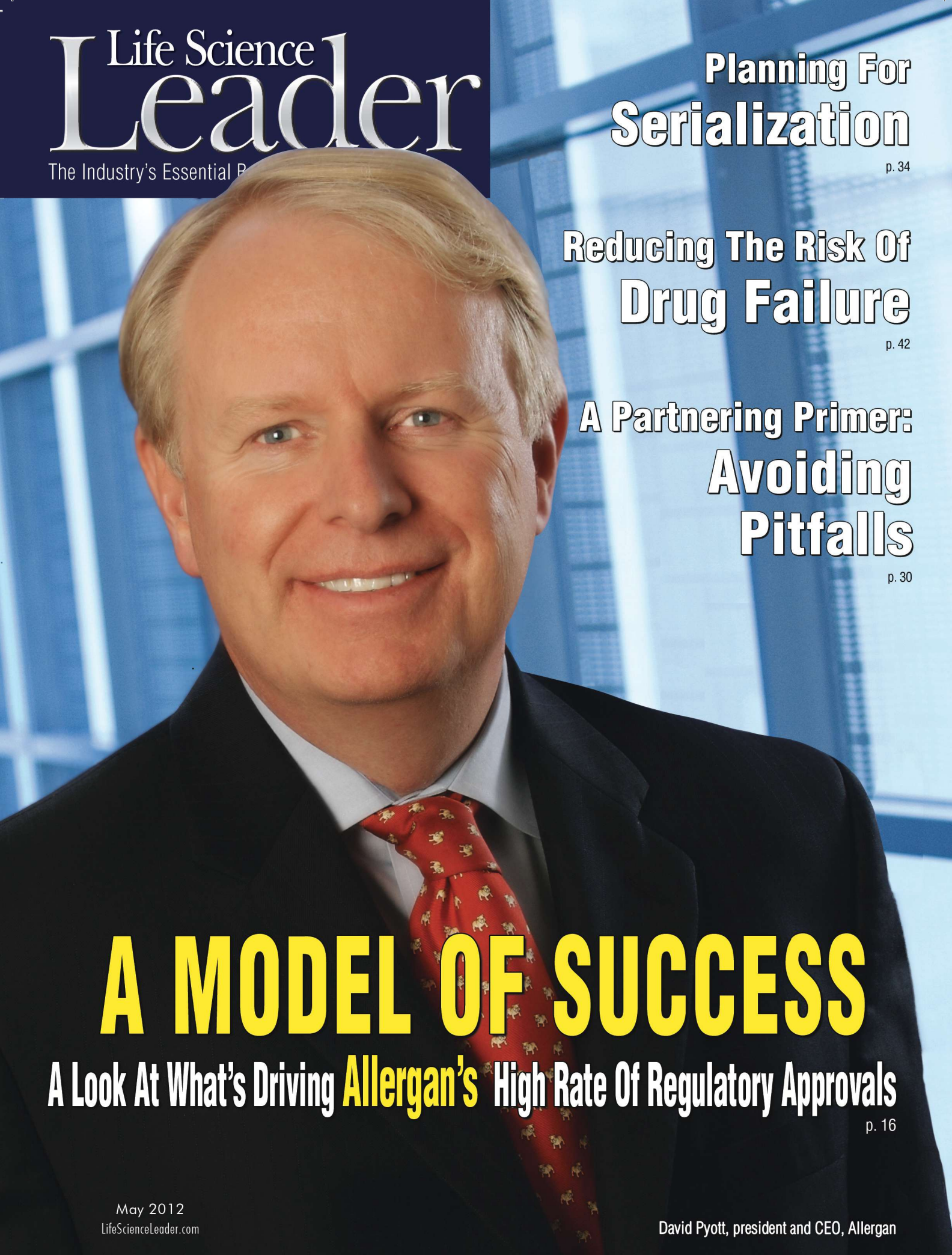

A MODEL OF SUCCESS

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May 2012
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David Pyott, president and CEO, Allergan

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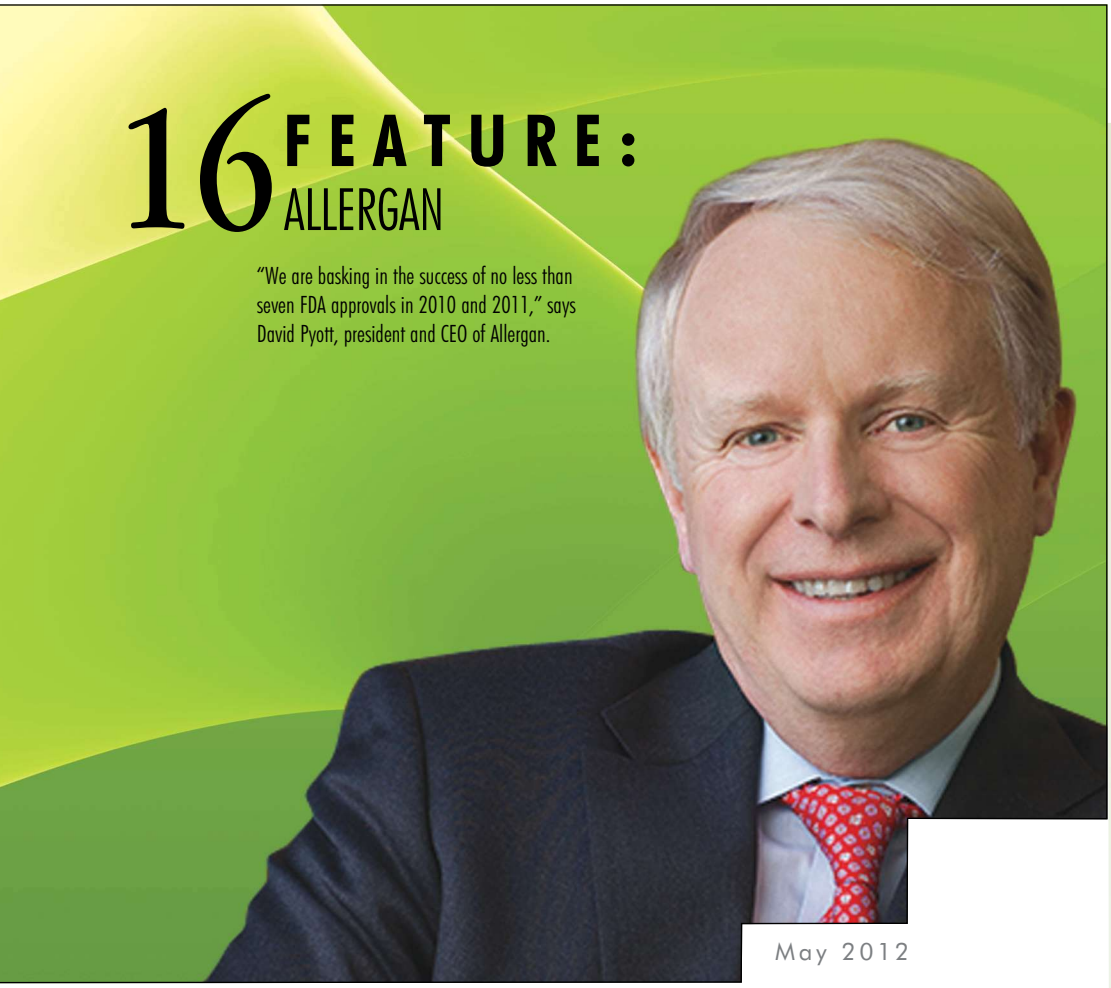

16 FEATURE: ALLERGAN

"We are basking in the success of no less than seven FDA approvals in 2010 and 2011," says David Pyott, president and CEO of Allergan.

May 2012

DEPARTMENTS

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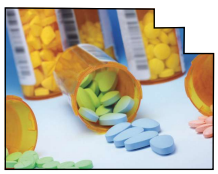

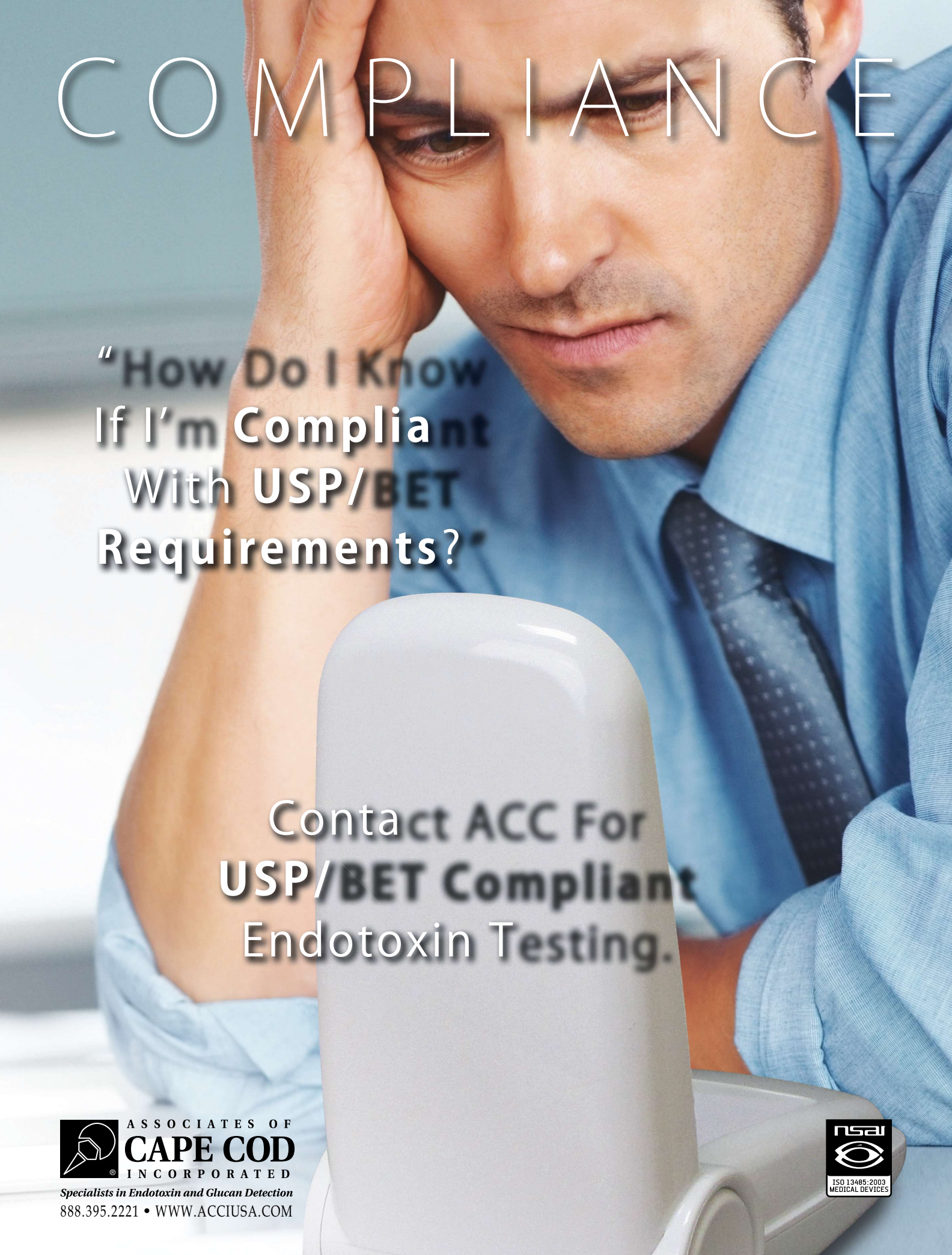
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EDITOR'S NOTE

Serialization Is Doomed Unless We Implement A Big-Picture Approach

As I reviewed the articles for this month's issue, one in particular got my attention to the point that I felt compelled to give my own opinion. Gail Dutton wrote an excellent article on page 34, "Planning For Serialization" — part two of a four-part serialization series. Dutton compares the issue of serialization in the pharmaceutical industry to Y2K back in 1999, with the difference being that the pharmaceutical industry has no defined parameters, whereas the computer industry did. In her article, she quotes an industry executive as saying that an industry consortium is appealing to both state and federal regulators for a single, national standard. When I read this statement, I was struck by the notion of this being what I can only describe as small-town thinking. The pharmaceutical industry is global, and as such, requires global standardization and interoperability. There are two models which could be used to demonstrate a solution — one comes from logistics and the other from banking.

Thanks to the International Civil Aviation Organization (ICAO), various airline functions have been standardized, such as Aeronautical Message Handling Systems (AMHS), machine readable passports, and three-letter airport codes. Imagine if these types of issues hadn't been addressed? Pilots would be guessing if, how, and where to land a plane without the guidance of air traffic controllers. Your luggage would probably never get to its final destination, and getting through security screening would be even more unpleasant than it already is. In my opinion, if serialization is as big an issue as I have been hearing, then perhaps we should be looking to create an organization which would fall under the United Nations. We already have the WHO and the International Conference on Harmonization (ICH), but if we really want a global solution, we need a global authority for total industry buy in.

The banking industry has the other example I mentioned, and it pertains to the evolution of the credit card. Some people argue that the world needs an international currency. But, thanks to the credit card companies, we already have one. MasterCard is accepted by 28 million merchants in 210 countries, and Visa is accepted by about 30 million merchants in 170 countries. Global expansion of the credit industry has been fueled by the availability of global electronic networks which allow for distribution of funds and real-time management information systems with interoperability. Imagine if a retailer had to have a different machine to read every different type of possible credit card. The system would not function very efficiently.

These two examples represent standardization via two different models — push-down (airlines) and pull-through (banking). The banking model was successful because customers demanded the ability to have greater utilization of credit cards and industry accommodated, and everyone benefitted. Regulatory bodies, not customers, are clamoring for serialization. As such, I believe the only way we will see successful serialization on a global scale is for a unified, government-backed initiative. Think big picture.

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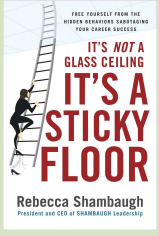

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ASK THE BOARD

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Q: What are the most important skills for leadership development, and how can they be obtained?

My top five list of essential leadership skills starts with the ability to see and share a vision that motivates others to follow you. This is closely followed by superior communication to clearly articulate your vision and why someone should follow you. Build a strong team with a diversity of experience and knowledge, and encourage them to actively contribute their thoughts, not just listen to yours. Provide unwavering support allowing your team to take calculated risks. And when there are missteps, which *will* happen, treat them as moments for growth, not punishment. Last, and importantly, create a positive environment with mentoring, recognition, and celebrating progress along the way.

Laurie Cooke
Laurie Cooke is the CEO of the Healthcare Businesswomen's Association (HBA), the leading nonprofit professional association in the women's leadership space in healthcare globally.

Q: How do you prepare for being a speaker or moderator at an industry event?

The first step is to clarify the expectations regarding objectives, scope, format, and target audience. Delivering repurposed content for a new venue will often fall flat if it does not meet the unique needs of the congress and its audience. Once the direction is clear, I determine whether I have most of the materials necessary to draft a presentation or set of speaking points, or whether I need to seek input from various experts across my organization or externally. Invariably, advice from other experts is helpful to ensure that I have a balanced and comprehensive perspective to share. If I am moderating a panel discussion, I typically draft and socialize a set of likely questions for the panelists and convene a conference call ahead of time to align on the approach. This eliminates surprises and helps to ensure a focused and informative session.

John Orloff
John Orloff, M.D. is the chief medical officer and SVP global development at Novartis Pharma AG. He also serves as chair, Pharma Portfolio Stewardship Board (PSB), overseeing safety and risk management plans for pharmaceutical products.

Q: What are the important skills companies are looking for from pharma/biotech employees?

Innovative thinking, nimbleness, and entrepreneurial spirit are the key drivers of success in the new pharma/biotech model. Employees who have varied experience and exposure in a mix of large and small companies add significant value, bring a very different perspective, and have a good balance of risk-taking mindset. It's also essential to have translational thinking where ideas are operationalized into a product that makes a difference. Necessity is the mother of all inventions — a big reason why a lot of innovation happens in smaller companies. "Zero-gravity" thinking, such as high risk-taking and not being weighed down or biased by negative experiences, is also critical for innovation to thrive. A good mix of these attributes is what makes a successful organization, and more companies are emphasizing this approach.

Sesha Neervannan, Ph.D.
Dr. Neervannan is VP of pharmaceutical development at Allergan. In his current role, he oversees the CMC (chemistry, manufacturing, and controls) activities related to developing the drug product from discovery to commercialization.

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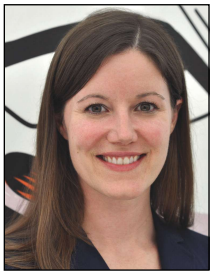

OUTSOURCING INSIGHTS

Data Management And Information Technology — Do The Benefits Outweigh The Risks?

By Kate Hammeke, research manager, Nice Insight

Data management, or the entry, verification, validation, and quality control of data gathered during clinical trials, is one of the many challenges of drug development. Clinical data, which will later form the basis of the safety and efficacy analyses, comes from hospital labs, nurses, and patients and through input from physicians, chemists, and biologists. These disparate information bases make standardization a challenge, even in the days of mobile computing devices and the widespread use of technology. Consequently, an industry known for innovation has been slow to shift entirely away from paper, when it comes to record keeping.

At present, Big Pharma is the primary purchaser of Data Management services, making up roughly 1/3 of the market (31%), followed by biotechs, which account for another 26%. According to Nice Insight survey respondents, these two groups spend upwards of $225M each year outsourcing data management. Catering to these customer groups is likely part of the challenge in shifting to a fully computerized platform for data management, considering the risks may not seem to outweigh the benefits in the eyes of sponsors. It makes sense to take a conservative attitude toward software solutions, considering how much easier it is to err when entering information onto a touch screen or keyboard than it is when writing with a pen and paper. The pressure to reduce costs conflicts with concerns about data entry errors causing a trial — or worse a project — to be invalidated at a huge financial setback.

On the other hand, electronic data collection and management can be designed to help reduce potential errors by building in alerts indicating when the information entered falls outside of an acceptable range. It can also significantly reduce setup time for new studies because the standards will have already been established during the initial software setup.

Nice Insight survey results indicate that the CROs that allocated the largest market share for data management services are businesses that have developed their own technology or are using third-party software to facilitate the process. The top five companies with respect to data management market share are PharmaNet/i3, Covance, Quintiles, Parexel, and ICON.

One of the greatest concerns that correspond with data management is whether electronic records (which lack a paper trail) will stand up to FDA scrutiny. As such, Nice Insight looked to see how the leading data management companies scored in regulatory compliance in comparison with the data management benchmark for regulatory as well as against the CRO regulatory benchmark. Among the top five, the average regulatory compliance score was 78%, which is 3% higher than the data management benchmark and 4% higher than CROs at large. This finding bodes well for sponsors who choose to outsource data management, as it may help alleviate the concern of mishandled information.

The leading data management companies also tended to excel in the productivity category, which should come as no surprise, considering one of the major reasons to employ electronic data management is access to near real-time information across all trial sites. Among the leading data management companies, the average productivity score was 76% — 2% higher than the data management benchmark and 3% higher than the CRO industry benchmark for productivity.

In addition to having better scores for regulatory compliance and productivity, the businesses with the greatest market share for data management were perceived as more affordable — with an average score 2% higher than the data management benchmark for affordability as well as the CRO affordability benchmark, both of which were 69%.

These companies illustrate how information technology may be integrated into data management while positively impacting productivity and affordability customer perception scores and, at the same time, maintaining solid regulatory compliance scores. Optimistically, results like these will help pave the way to embracing technology, but what may be more effective is if CROs come together in open collaboration to develop a standardized system. After all, cloud technology is the result of collaboration in the information technology industry.

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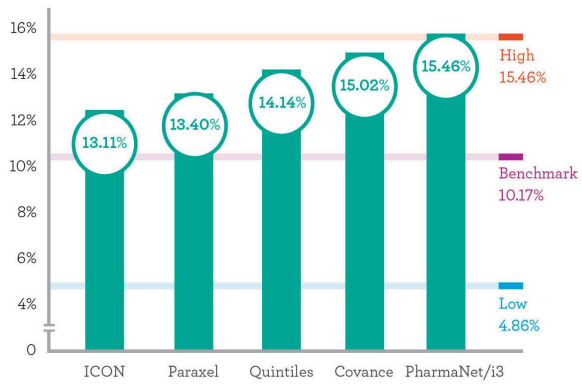
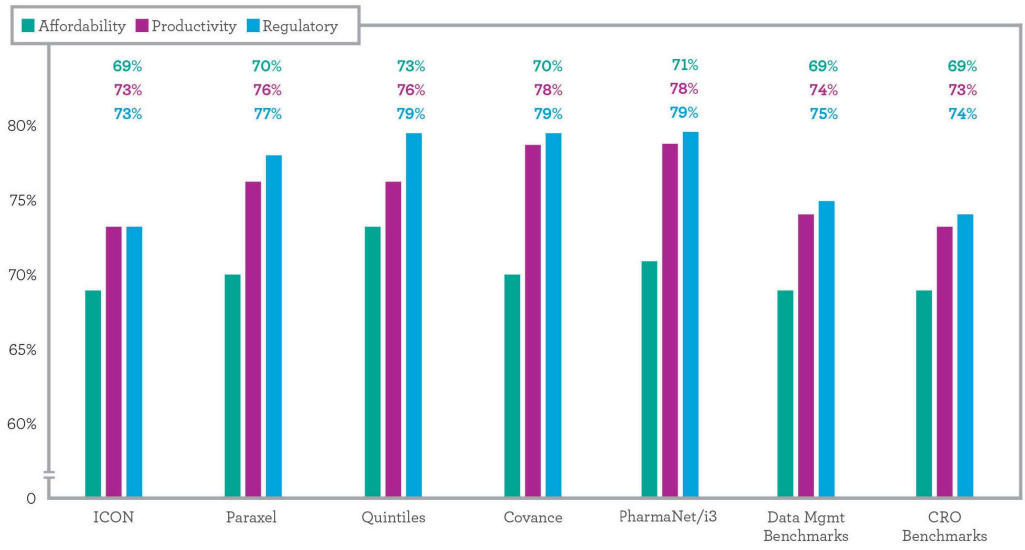


Customer Awareness & Perception	CA Score	CP Score
ICON	43%	71%
Parexel	47%	74%
Quintiles	46%	74%
Covance	57%	76%
PharmaNet/i3	48%	75%
Benchmark	46%	72%
High	57%	77%
Low	38%	63%

NI Breakdown of Customer Perception Measures



Survey Methodology: The Nice Insight Pharmaceutical and Biotechnology Survey is deployed to 40,000 outsourcing-facing pharmaceutical and biotechnology executives on a quarterly basis [Q4 2011 sample size 2,619]. The survey is composed of 1,000+ questions and randomly presents ~30 questions to each respondent in order to collect baseline information with respect to customer awareness and customer perceptions of 300 companies that service the drug development cycle. More than 1,200 marketing communications, including branding, websites, print advertisements, corporate literature, and trade show booths are reviewed by our panel of respondents. Five levels of awareness from "I've never heard of them" to "I've worked with them" factor into the overall customer awareness score. The customer perception score is based on six drivers in outsourcing: Quality, 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.

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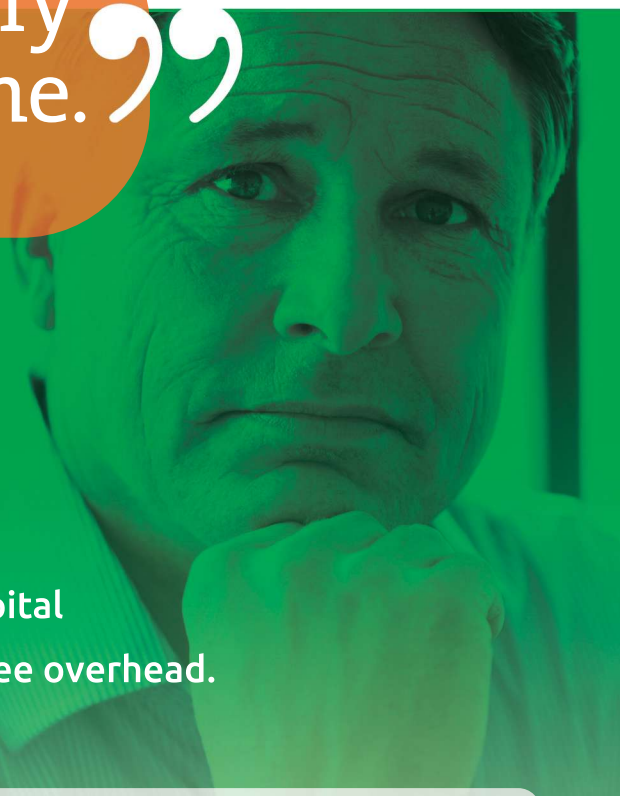

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BIO DATA POINTS

Majority Of Vendors Increasing Budgets For Big-Ticket Items

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

Biopharmaceutical industry suppliers (i.e. anyone that sells services, instrumentation, or raw materials to the industry) are increasing their budgets in a number of key areas this year, according to data from our newly released *9th Annual Report and Survey of Biopharmaceutical Manufacturers*. And, these increases won't be limited to smaller items, either. In fact, nearly half (44%) of vendors are planning to increase their budgets for new capital equipment, including 6% who will be making large increases of 20% or more. This contrasts with just 11% planning any decrease in spending in this area, the majority of which are small decreases. Similarly, a third (33.3%) of vendors are forecasting greater dollars spent on new facility construction, including 8% making large increases.

This is a significant reversal from previous years, when the economic downturn forced many suppliers to retrench and reduce spending. The increased budgets are likely a leading indicator that industry suppliers expect long-term growth in relation to their customers' — biopharma manufacturers — budgets.

Although big-ticket items such as new capital equipment account for some of the biggest areas of spending, other areas are signaling growth, too. Nearly half (45%) of our respondents are boosting their marketing budgets, and more than half (54.5%) will increase their sales budgets. This may indicate short-term expectations for more rapid growth. As yet, advertising budgets remain generally flat this year. Hiring also figures into the equation. A majority of respondents are increasing budgets for hiring new operations staff (43%) and close to two in five (38%) will be boosting new scientific staff budgets.

Although big-ticket items such as new capital equipment account for some of the biggest areas of spending, other areas are signaling growth, too.

We measured 11 areas of budget changes among our 186 vendors surveyed this year. When we average out the planned increases and decreases across respondents, outside of marketing or sales budgets, we find that vendors are again planning relatively large increases for new capital equipment (3.4%), hiring new operations staff (2.8%), hiring new scientific staff (2.4%), and new facility construction (1.4%). While these numbers may not appear substantial, when shown as cumulative over the past three years, the budget increases (aside from new facilities construction, which has shown sluggish growth the past three years) have generally far outpaced the budget slashing that occurred during the economic downturn in 2009.

SUSTAINED INDUSTRY GROWTH IS EXPECTED

The increase in sales budgets of suppliers to the biopharmaceutical production industry is a positive sign and indicates current growth among vendors. Perhaps more importantly, it shows that vendors expect sustained growth in the overall industry. Budget changes for operations staff (2.8%) are lower than those reported for sales (4.3%); however, these increases do show recognition that inventory levels must be increased to support sales of current products. Interestingly, budget increases for advertising were significantly less than for sales. This may be a cause for concern, but it is offset by a relatively strong growth forecast for marketing budgets.

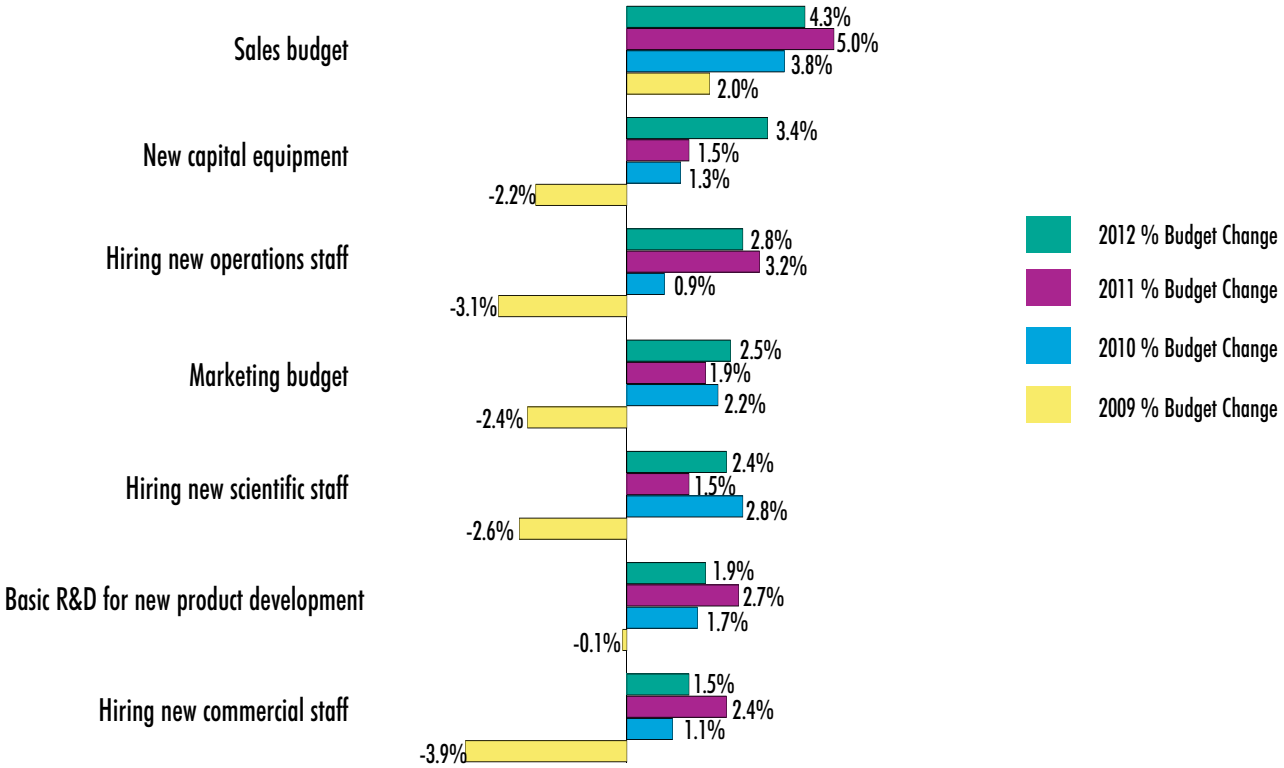
We compared annual budget changes from 2009 through to this year. Budgets during the economic downturn in 2009 were down in all departments except for sales, and by as much as 6.7% for new facility construction. In 2010, the environment generally improved, with all areas except new facility construction and in-licensing seeing their budgets recharged. That trend continued last year, with almost all areas getting bigger budgets, led by sales.

This year we see the trends continuing. Sales budgets, which led the list last year at 5%, get an average increase of 4.3% this year. Keep in mind these increases are cumulative, year-over-year. So, a drop in budget increases is not unexpected. Some of the biggest changes from last year include budgeting for new capital equipment, marketing budgets, new scientific staff, and new facility construction. In fact, each area of the 11 areas we studied is slated for at least some budget increase this year, including basic R&D and in-licensing (which was up only slightly).

With budgets up across the board and increases seen in almost all areas from the past three years, the overall picture is one of optimism.

Answer Options	Large (>20%) or moderate increase (10-20%)	Small increase (1-10%)	No change	Small decrease (1-10%)	Large (>20%) or moderate decrease (10-20%)
New capital equipment	17.6%	26.4%	45.3%	6.9%	3.8%
Hiring new operations staff	12.7%	30.3%	47.3%	6.7%	3.0%
Hiring new scientific staff	9.8%	28.2%	53.4%	5.5%	3.1%
New facility construction	18.2%	15.1%	56.6%	3.8%	4.4%
Sales budget	17.4%	37.1%	36.5%	7.8%	1.2%

Vendors' Approximate Average Change In Budget 2009-2012



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

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

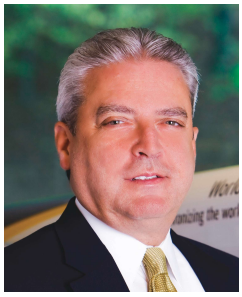
David Pyott, president and CEO of Allergan, led his company to 2011 sales increases of 22% in Asia/Pacific; 17% in Europe, Africa, and the Middle East; and 25% in emerging markets.

Accelerating The Drug Approval Process

By Rob Wright

When David Pyott took the reins of Allergan (NYSE: AGN) as president and CEO in 1998, the stock was trading at just under $8 a share, and the company reported annual sales of $716 million. Thirteen years and two stock splits later, the company has grown — significantly. At the close of 2011, Allergan reported product net sales of over $5.3 billion, and in March 2012 the stock was trading in the neighborhood of $95 a share.

Based in Irvine, CA, the company has had growth beyond just increases in sales and stock price. For example, from 2007 to 2011, Allergan was granted nearly 1,600 patents worldwide and ranked tenth on the Patent Board's list of the top 50 pharmaceutical industry innovators, based on the number of patents issued and the strength of its patent portfolio. Pyott attributes some of Allergan's growth to the company's extreme success at securing a high proportion of regulatory approvals around the globe. He says that success is due to three things: Allergan's business model, expertise through specialization, and an enormous attention to detail, using what he describes as the "flywheel effect."



Mark Davis
HEALTHCARE LOGISTICS
PRODUCT MANAGER
UPS

The Benefit Of A Logistics Provider With A Healthcare Focus

Because of the sensitive nature of healthcare products and the industry's complex business and logistical needs, UPS developed a focus specifically designed to address the needs of this industry. Mark Davis, healthcare logistics product manager for UPS, shares his insights on the challenges and solutions related to shipping and distributing time- and temperature-sensitive products.

What are the biggest challenges or gaps for healthcare manufacturers when it comes to protecting temperature-sensitive products?
Understanding Controlled Room Temperature (CRT) remains a constant challenge because it has no universal definition. From a Parenteral Drug Association (PDA) perspective, CRT is 20–25 degrees Celsius. Yet, many manufacturers may still consider CRT to be ambient or room-temperature and therefore may not believe their CRT products need any special packaging. These manufacturers need to be aware of how the potency and stability of these products can be affected in the supply chain.

I don't think the industry has been focusing on that particular product line in terms of packaging protection. There is very little regulatory guidance for CRT in the supply chain, but this is clearly a space in which more and more manufacturers will need to pay closer attention. It's an area that UPS is prepared to help manufacturers handle.

How are UPS's global network and broad range of capabilities in transportation, distribution and logistics an advantage for healthcare manufacturers who need to manage temperature-sensitive products?
One of our biggest strengths is having 30 dedicated healthcare-compliant facilities around the world. They are fully cGMP-compliant and include capabilities for frozen, refrigerated and CRT storage. This allows us the flexibility to move products into our multi-client facilities and not only maintain and control the temperature, but also feed into our integrated transportation network for fewer hand-offs.

More than just physical space, UPS has experts who understand temperature-controlled logistics and can help companies with evolving regulations and putting the right solutions in place. For example, we can help with technology for better shipment visibility and build in risk-mitigation strategies to protect products while in-transit. UPS manages more than 800 licenses in the United States alone to ensure compliance and help healthcare companies plan ahead to avoid surprises in the supply chain.

At UPS, we find building partnerships with our clients brings about the most success. This way, we not only understand their product, its temperature requirements and the best packaging to do the job appropriately, but we have an understanding of their larger business objectives and the needs of their customers.

PharmaPort 360

What's next in temperature-sensitive supply chain management?
UPS recently announced a very unique air freight container called the PharmaPort™ 360, which is specifically designed to transport temperature-sensitive pharmaceuticals, vaccines and biologics required to stay within 2–8 degrees Celsius. The PharmaPort 360 is really a game changer, offering a new level of in-transit product protection. The unit maintains a strict 5 degree Celsius set point within the container, plus or minus two degrees. And, it can do so for upwards of 100+ hours, depending on the ambient conditions. PharmaPort 360 is powered by an AC rechargeable battery and its technology eliminates the need for dry ice and the hazards and fees associated with its handling. This super-insulated container has an R factor of 70 and includes built-in GPS/GSM (Global System for Mobile Communications) capabilities which enable near-real time visibility and monitoring. Data is monitored by UPS's global network of control towers to not only track location, but more importantly to enable UPS to act on shipment alerts in-transit such as low battery life or temperatures that are going out of range, which helps protect against product loss.

Together with UPS Temperature True®, our air freight service, we're providing a whole new level of shipment protection and monitoring of temperature-sensitive products throughout the supply chain. Our service gives companies precise, measurable operating procedures backed by dedicated support and contingency plans for unexpected situations. With UPS, they feel confident that products are being handled with care and under the right conditions.

4 WAYS LOGISTICS CAN IMPROVE YOUR HEALTH.

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2) GAIN GLOBAL ACCESS UPS serves over 220 countries and territories, and has 30 dedicated healthcare distribution facilities worldwide.

3) KEEPING YOU COMPLIANT The movement of medical products triggers costly compliance issues. UPS's team of experts maintains hundreds of geographically specific regulatory licenses and registrations that can help keep your supply chain cost efficient and compliant.

4) PROTECTING TEMPERATURE-SENSITIVE PRODUCTS Many healthcare products require special handling. That's why UPS Temperature True® provides proactive global monitoring to help keep your shipments within strict temperature ranges and prevent costly excursions.

For healthcare industry insights, go to **thenewlogistics.com/healthcare** or snap the QR code.

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THE ALLERGAN BUSINESS MODEL

When Pyott arrived at Allergan, he sought to improve the company's business model to that of being a global, multispecialty healthcare company with portfolios in eye care, neurosciences, medical dermatology, medical aesthetics, obesity intervention, and urologics. Clarifying, Pyott states, "Most of our products are topicals, or in the case of BOTOX, extremely focal injections. The benefit of being primarily a topical-based company is that most regulatory agencies are very quickly able to get beyond the issue of drug safety with many of Allergan's products and can then focus on whether or not the product really works for its indication." As an example, Pyott cites the FDA's approval of RESTASIS, the only therapeutic treatment to increase tear production in patients with chronic dry eye due to ocular inflammation. Based on cyclosporine, a compound originally used for the suppression of organ transplant rejection, RESTASIS was able to take advantage of the well-known liver toxicity data in addition to that which Allergan generated. When evaluating RESTASIS for approval, the FDA first looked at the drug toxicology data and then at its concentration, which with eye drops is typically low. "We are basking in the success of no less than seven FDA approvals in 2010 and 2011, which starts with our business model of being primarily topical," he concludes.

UNREASONABLE EXPECTATIONS

David Pyott, president and CEO of Allergan, has guided his company to significant growth during the past 13 years. During this same time period, he has witnessed the evolution of greater analytical capabilities that have enabled both the life sciences industry, as well as the regulatory agencies, to constantly raise the bar with regard to requesting data for clinical tests to approve a product for an additional indication — a prospect that is both good and bad. "The good part is that you have higher sterility standards," says Pyott. The bad part is that raising the bar results in additional costs and increased spending on the part of the drug company with minimal benefit to the patient. "At some point the system is going to break because we just can't afford it," he affirms. Pyott believes that some of the new regulatory requirements resulting from the utilization of greater analytical capabilities have resulted in the FDA developing what he would characterize as "unreasonable expectations."

According to Pyott, once a regulator has set a requirement to do something, e.g. the FDA requiring a pulmonary function test to approve BOTOX for cerebral palsy (CP) in the United States, it is very difficult for them to undo. "When somebody rules on something, how do you do a 180-degree turn?" he asks. "I think to be fair to the agency, they are particularly concerned that once they have made a pronouncement and clinical sponsor companies have relied upon it, all other sponsors will often complain if the rules are changed." The example of requiring a pulmonary function test to approve BOTOX for Juvenile CP seems unreasonable to Pyott given that it affects approximately 3 of every 1,000 children, making it difficult to recruit and test. "At some point they need to realize that this is impossible and negotiate a pass," says Pyott. This certainly seems reasonable when you consider that BOTOX is approved for Juvenile CP in approximately 60 other countries around the world, including Japan, but not the United States.

SPECIALIZE IN A LIMITED NUMBER OF THERAPEUTIC AREAS

Allergan's second key to accelerating the drug approval process, according to Pyott, is what he describes as "having an almost extreme specialization in a very limited number of therapeutic areas." Allergan focuses on 24 products in 6 therapeutic categories. Interestingly, Allergan's most well-known product, BOTOX, is being developed or has been approved for indications in five out of the six therapeutic categories. Compare this to Merck, which has more than 100 products including vaccines, prescription, consumer, and animal health products spanning 12 therapeutic categories.

With its 24-product focus, Allergan approaches clinical development similarly to the manufacturing process. "First, develop a protocol which answers the specific question you wish to address and execute," Pyott states. "If you develop protocols which attempt to answer everything, you will have a difficult time recruiting patients." Next, Pyott advises to gather metrics on everything, such as, but not limited to, time to draft a protocol, time to get through IRB (institutional review board), time to first patient enrolled in a trial, and time until last patient out. By having a significant level of metrics, companies develop an enormous attention to detail. This attention to detail is just one of the reasons why BOTOX has 25 individual indications around the globe.

USING THE FLYWHEEL EFFECT FOR REGULATORY APPROVALS

Lastly, Pyott advises using what he refers to as the flywheel effect to accelerate the regulatory approval process. A flywheel is a rotating mechanical device that is used to store rotational energy, has a significant moment of inertia, and as such, resists changes in rotational speed. Pyott and his team apply this physics principle of creating momentum to accelerating the drug approval process. "Once you have regulatory approval in one of the major jurisdictions — typically the United States or one of the members of the EU — you need to figure out how to continue that momentum and get approval in other countries in an expeditious way," he explains. "We have gotten better at identifying the first 'court' of regulatory approval for a product, which is the first step in the flywheel effect." For example, according to Pyott, in the area of ophthalmology, the FDA is usually the first agency from which they seek approval. Canada and Australia are usually the first countries they go to for approval of additional BOTOX indications, followed closely by the United Kingdom. "Unfortunately for BOTOX," Pyott explains, "the United States is usually second to last for approving additional indications, and Japan is almost always last." By knowing which is the first court of approval for a given indication, you can better determine the best place to apply first when seeking regulatory approval. From there you can also determine where to apply for approvals in other countries, the second phase of the flywheel

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regulatory approval process.

For example, Brazil, like many countries, accepts the common technical document (CTD), which is a standardized format for describing the quality, safety, and efficacy information related to a drug. The CTD is maintained by the International Conference of Harmonization (ICH) and eliminates the need for customized submissions to many ICH regulatory agencies. Thus, you can accelerate the approval process in other countries by knowing which ones accept the CTD. Other countries do have a review process, but this can be accelerated if you have a solid data package and approval from one of the more rigorous approval bodies. "Once we get approval from the United States or Canada, we then go to Brazil, because we manufacture ophthalmology products there," Pyott explains. "We can then use the Brazilian documentation to go to Argentina, Colombia, Venezuela, Chile, and on down the line. That is how you operate the flywheel. Get it started, and turn it up into a bigger gear."

"If you develop protocols which attempt to answer everything, you will have a difficult time recruiting patients."

David Pyott, president and CEO, Allergan

Another key aspect to executing the flywheel is developing relationships with particular regulatory agencies. Pyott advises to focus not only on the agency, but the reviewers as well, so that you know what they are comfortable with and what they would consider as the logical next step. For example, Ireland plays a very important role historically with BOTOX for two reasons. First, BOTOX is made in Ireland, and second, Ireland is a reference member state of the European Medicines Agency (EMA). According to Pyott, "The EMA allocates you an agency. No longer are you able to pick which agency to review your application." He prefers this because the EMA has demonstrated a pragmatic tendency to assigning the regulatory agency with the most experience. Since the Irish Medicine Board has more than 20 years of experience in reviewing BOTOX files, it is often assigned to review an additional BOTOX application for the EMA.

Many small companies often struggle with building relationships with agencies around the world as a result of having limited resources, being first-time filers, or having just one or two programs in development. Pyott thinks it would be wise to hire a consultant who does this for a living rather than hiring someone to manage the process internally, unless you anticipate a significant amount of ongoing work. When hiring a consultant, look for ones who have past experience with big companies, as they will most likely have had the benefit of doing many filings. By tapping into somebody else's expertise, smaller companies can avoid making common first-time filer mistakes and thus enhance their chance of gaining approval.

Some have described BOTOX as being a pipeline within a drug, given its ability to be successfully utilized across a variety of therapeutic categories. However, as Pyott points out, there's more to the company's success than just one product. And, evidently the company's plan is working, considering last year Allergan had sales increases of 22% in Asia/Pacific; 17% in Europe, Africa, and the Middle East; and 25% in emerging markets. Not bad when you consider these numbers were achieved during one of the worst global economic recessions on record.

WE WEREN'T LISTENING

According to David Pyott, president and CEO of Allergan, there have been times of regulatory failures when "Our biggest problem was we needed a hearing aid." Elaborating, he states, "We have a product called Tazorac, a topical for acne and psoriasis. We had a program for oral Tazarotene, for the same indication. I still think today that we had a much better product than Roche's Accutane." Pyott believes that the product Allergan had developed really worked and, as a result, prevented the company from being able to effectively listen to the FDA's concerns. "Because of the history of isotretinoin and retinoids in general, the FDA was just terrified," he says. Isotretinoin's best known and most dangerous side effect is birth defects. "If you know the regulators have every card stacked against you, it is probably not the best competition to get into," he observes.

Pyott wishes he had sought and listened to regulatory advice earlier on. "I always recommend to people that if you are unsure of your pathway, getting a special protocol assessment (SPA) is a very smart way to go," he states. "In this way, you have at least defined what tests you are doing and what needs to be done versus throwing yourself at the regulators' mercy later on." According to Pyott, an SPA wouldn't have solved the problem, but listening would have, and Allergan could have saved a lot of money in the process.

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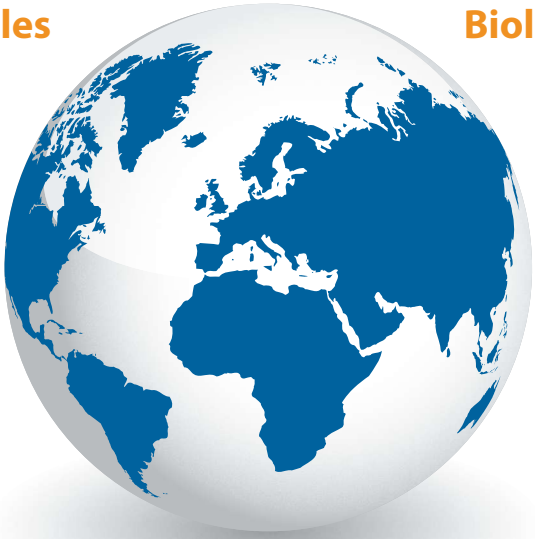

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The Quest To Reinfuse Innovation And Creativity Into Biotech Funding


Stelios Papadopoulos, Ph.D.

By Sara Gambrill, contributing editor

Longtime biotech industry observer Stelios Papadopoulos, Ph.D., remembers exactly where he was when Genentech had its initial public offering (IPO) in 1980 — defending his Ph.D. thesis in biophysics at New York University (NYU). Struck by the excitement among his fellow scientists about the event, he realized he had found his true calling. "Thirty years ago, scientists didn't talk about the stock market," Papadopoulos said. "As I was finishing my Ph.D., I was growing curious and interested in doing something other than conventional research. When Genentech hit its IPO, right

then and there I knew this was an exciting opportunity and that I could play the role of go-between, interpreting science for businesspeople and business for scientists."

He earned his MBA while working on the faculty of the Department of Cell Biology at NYU School of Medicine, then in 1985 joined Donaldson, Lufkin, and Jenrette as one of the biotech industry's first analysts. Two years later he became an investment banker, first for PaineWebber, then Cowen and Co., from which he retired as vice chairman in 2006. Along the way, he also invested in and cofounded several biotech companies. He is still very active in the industry as an advisor, investor, and member of several boards. With a Wall St. career that spans nearly 30 years, Papadopoulos has just about seen it all when it comes to the world of biotech financing, and he shared many observations with me about the current investment climate, how it compares to that of decades ago, why it has changed, and why Big Pharma needs to take a brand-new approach to investing in early-stage biotech companies for the health of their pipelines, the industry, and, ultimately, patients.

INVESTMENT CLIMATE CHANGE FOR BIOTECH PUTS DAMPER ON INNOVATION

Privately owned biotechs have always largely depended on venture capital for their survival, so the change in the way VCs invest in them has had a significant effect on the development of innovative technologies and drug therapies. "In the 1980s and 1990s, venture capital was a business that tried to identify exciting science and great people, put them together, help them through funding, and help them grow to develop their own products," Papadopoulos said.

But, the investment climate for biotechs has changed dramatically in the past 10 years, in terms of the funds available and what types of companies get those funds. "By any historical comparison, the amount of money available for biotech companies in the past few years is meaningfully larger than the money in the 1980s and 1990s. However, the bulk of this money goes into very large, established companies that have products to sell," Papadopoulos said. "The huge proportion of stock ownership is concentrated, by virtue of their market capitalization, among the top biotech companies — Amgen, Biogen Idec, etc. But, they were both startups once."

Interest in newer companies is largely concentrated in the ones that have compounds in later stages of clinical development — Phases 2 or 3 — or are about to launch. "There is a lot less interest today and money flowing to companies that may be doing very exciting science but are still in the preclinical stage."

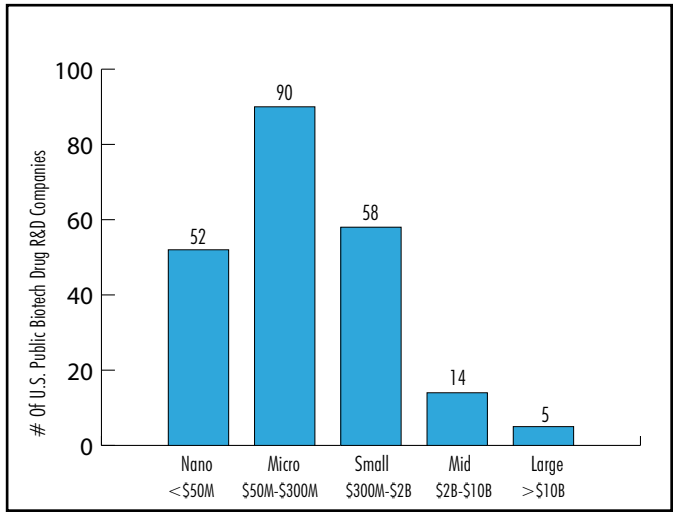
Papadopoulos sees this investment climate change — this "bifurcation of funding," as he puts it — as a fundamental problem for both biotech and pharmaceutical companies because biotechs need VC funds to develop their products, and pharmaceutical companies need products to sell.

NONPROFITS, GOVERNMENT STEP INTO THE VOID

As the flow of venture capital into early-stage biotechs has ebbed, savvy nonprofit disease foundations, state governments, and the federal government have devised ways to support them.

Nonprofit disease foundation investment in biotechs is often referred to as "venture philanthropy." The investments are relatively small, but, in addition to money, foundations can offer deep expertise in a particular disease, and some may be able to offer help with patient recruitment, protocol design, and other CRO-like services. Venture philanthropists can get a biotech's compound over the "Valley of Death" — the preclinical stage of development that venture capitalists tend to avoid now — to the proof-of-concept stage, a point when VCs feel more comfortable investing, especially if companies have already been able to attract knowledgeable, well-respected foundation investors.

In addition, top-ranked states in terms of biotech, such as



Source: BIOtechNOW

Massachusetts, California, and North Carolina, have financed initiatives to invest in biotechs in their respective states. And on a federal level, the NIH created a new institute in December 2011 — The National Center for Advancing Translational Sciences (NCATS), which could have a lot to offer biotechs. In fact, Papadopoulos served on the advisory group to the Director of NIH with regard to the formation of NCATS. The central role of NCATS will be to provide integrated, systematic approaches to link basic discovery research with therapeutic development and clinical care. In addition, NIH launched a program in October 2011 to benefit startups. (To read more about this program and about NCATS, see "NIH, Industry, and the Translational Science Revolution" in the December 2011 issue of *Life Science Leader*.)

Mitigating Risk In Biological Frozen Transportation

The advances made in the last decade in healthcare technologies have contributed significantly to global improvements in health and economic growth. The World Health Organization recognizes the importance of biological medicines such as vaccines, blood products, and biotherapeutics for the prevention and treatment of disease. However, biological products, unlike more traditional chemical drugs, are more complex and less stable. These newer, biologically based products have resulted in manufacturers and regulatory authorities being challenged with an increasingly difficult task of insuring stability, quality, and efficacy in a globally connected marketplace.

Stringent temperature control in the clinical trials and research supply chains is increasingly important. As long ago as 2009, a *Business Insight* report noted that failures in the cold chain that result in adverse temperature changes during the storage, handling, or distribution of biological products can result in serious problems for the patient and the manufacturer:

- Patients could be administered an unsafe product because of variations in biological response to temperature fluctuations in transit
- Temperature excursions caused during shipping can lead to inconsistency of patient or trial results between and within batches
- Costly delays can occur in treatment of patients or the progress of trials if shipments cause product quality issues.

For those working with these biologics, the risk of sample or cell degradation is a significant problem. And while advances have been made in recent years in thermal packaging, the majority of today's global frozen shipping still relies on the use of dry ice — a material that is both hazardous in its dry form and emits a greenhouse gas when sublimated. This poses a risk for viability after transportation as dry ice is fairly unstable and sublimates quickly. The sample or product can experience temperature excursions during transit, particularly for longer overseas flights and processing through importation and customs inspections. Adding more dry ice to the packing becomes a guessing game of how much is enough to maintain stable temperature but doesn't exceed carrier restrictions or increase packaging weight and cost prohibitively. Although liquid nitrogen as a refrigerant has long been known to provide longer holding times and a more stable temperature profile, it was not convenient and is considered a "specialty" solution, not for everyday use in cold chain logistics. Now, due to a recent technology breakthrough and an end-to-end shipping solution, liquid nitrogen dry-vapor shipping is now becoming a more viable alternative, especially for international logistics.

"Now, due to a recent technology breakthrough and an end-to-end shipping solution, liquid nitrogen dry-vapor shipping is now becoming a more viable alternative, especially for international logistics."

At Cryoport, our customers are telling us that they have two major concerns, mitigating risk in sample or cell degradation and managing the increasing complex cold chain. They've shared that regulators are spending more time and attention during audits reviewing standard operating procedures for shipping and logistics. Such scrutiny creates an opportunity for service providers to bring solutions that address the changing regulatory and quality landscape. Product and service solutions must address customer needs of convenience and cost while delivering unquestionably safe and reliable solutions. Validated packaging can provide a good starting point, but we may find the need or emergence of certain standards to be measured against. Additionally, it is likely that the use of technologies like temperature-monitoring devices, RFIDs, and other tracking technologies will become increasingly important in creating audit trails. Cold chain partners must consider the entire chain of custody and chain of condition and whether such data meet electronic records security and integrity requirements like those in FDA Code of Federal Regulation (e.g. 21 CFR Part 11).

Cryoport is committed to a constant reanalysis of regulations, and believes it is crucial for all manufacturers to do so, if we are to meet the growing and changing needs of an industry transporting important life-saving and life giving products.

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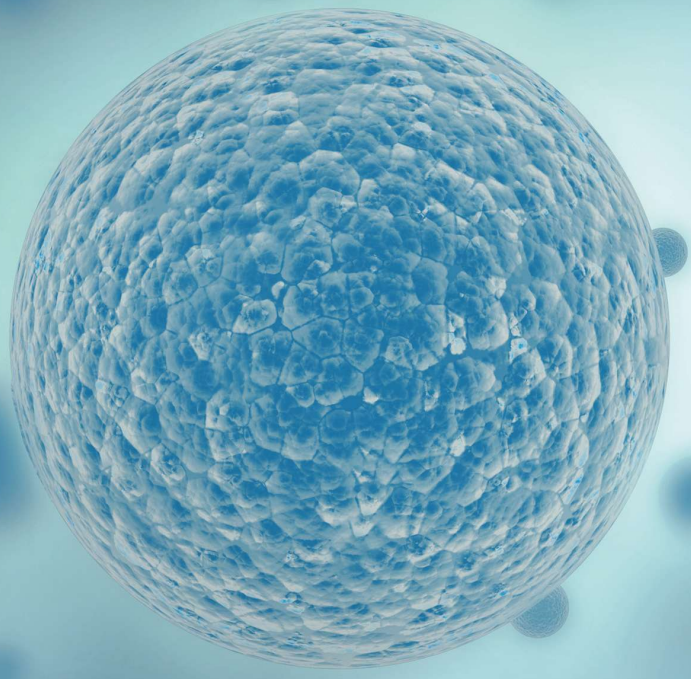

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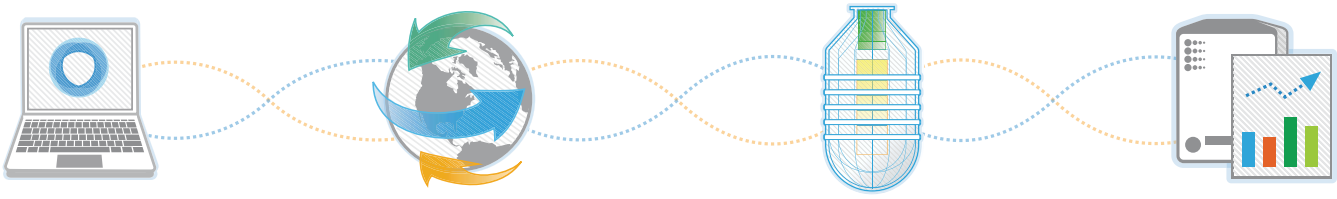

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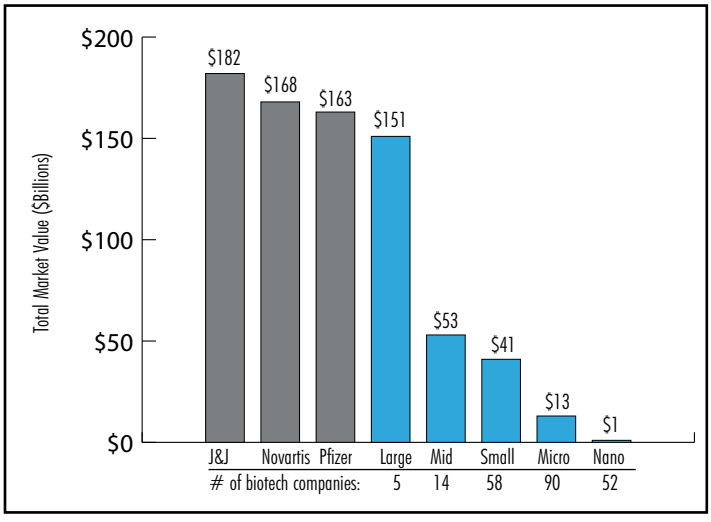
CROSSING THE DIVIDE

Despite the funds available from government and foundations, there are simply fewer financing options available to privately owned early-stage companies — even though they may be doing cutting-edge science. Papadopoulos maintains that there is "no clever solution" to private biotechs' financing issues. He said, "I think the most important point is to manage to cross the divide from being a privately owned company to being a publicly traded one."

Going public is not an option for all privately owned biotechs by any means. Papadopoulos cautions that becoming public has a hefty price tag attached. Compliance with Sarbanes-Oxley and other Securities and Exchange Commission-related requirements can cost a company a few million dollars per year. "For a company with about 100 employees that may spend $25 million per year in R&D, there needs to be an outlay of $3 or $4 million on regulatory compliance. That's a lot of money. On the other hand, in a publicly traded company — even though you may suffer from neglect or be penalized by bad results that make the stock price low — there is a lot more flexibility in how you can raise money. There is a lot of customized financing being done for the smaller companies once they're public," Papadopoulos said.

There is not as much creative financing even for publicly traded companies as there once was, however. In the 1990s, Papadopoulos was known for his creativity in the area of financing biotechs. "I started my career in physics, which I believe is the ultimate science in terms of reason, logic, and analysis. I looked at the financial challenges of biotech companies as scientific problems, and I tried to come up with an appropriate solution, then cast it in financial terms and worked from there." He invented a number of ways to finance them that had never been tried or even thought of previously. "In the early 1990s, as Wall St. leaders and company executives, we created and promoted a variety of ways to raise money for companies that turned out to be quite useful in helping create sustainable enterprises. We're a lot less creative now.



Source: BIOtechNOW

It's not because we're lazy or stupid, but it's because the regulatory environment has made it that much more difficult."

It is also difficult to be an above-average investor in the stock market. As someone who has viewed the biotech industry from several different vantage points — analyst, investment banker, investor/company cofounder — Papadopoulos knows that success relies on a very simple formula, which, paradoxically, is very difficult to execute. "When it comes to investing in public stocks, you need to have a point of view of the company that is different from the consensus and be convinced you are right and that within 6 to 12 months the consensus will come around to your point of view. You also need to understand why the market is making a mistake. That's really the whole of investing. It's that simple — in theory. In fact, it's very hard. The reason is that, by and large, the market is efficient," he said. "It takes a lot of experience, and that's why most fund managers perform about average in the end."

> "I'm suggesting a way by which we can reintroduce into the life cycle of biotech funding an interest in investing in preclinical-stage companies with exciting science and take them public."
>
> Stelios Papadopoulos, Ph.D.

BIG PHARMA NEEDS NEW APPROACH TO BIOTECH INVESTMENT FOR FUTURE SURVIVAL

In the 1980s and 1990s, venture capitalists typically made their money from selling stock in companies after they went public. In the last few years, they have done some of that, but a very large proportion comes out of direct sales of private companies to pharmaceutical companies. "The venture capital business has redefined itself," Papadopoulos said. "We have a lot of pharmaceutical companies that have reached a mature growth rate in terms of how much more they can sell every year. There isn't a single Big Pharma that hasn't bought a dozen or more biotech companies over the years."

In fact, according to Biotechnology Industry Organization (BIO), the top 10 Big Pharma in terms of cash position have enough cash to buy more than 90% of all publicly traded, drug-focused R&D biotechs. There are 300 publicly traded U.S. biotechs, and nearly

¾ of them develop drugs.

"Nowadays, venture capitalists will either fund a specific project or two at a biotech with a skeleton crew on a virtual model basis, or they'll start a company on the assumption that by the time it matures a few years later in terms of its technology, Pharma will want to own such a company. That's a pretty difficult thing to guess," Papadopoulos said. However, he has made such guesses and been proven right, so it is not impossible. "You have to have an understanding of how the pharmaceutical industry evolves and what its discovery challenges are. I've spent 30 years thinking day in and day out about how one goes about discovering drugs."

Big Pharma needs to take a different approach to investing in biotech, according to Papadopoulos. Up until this point, they have created joint ventures and strategic alliances and set up their own captive venture funds, but none of these types of investments gets to the heart of biotechs' funding problems. Big Pharma's current investment strategies may work for them in the short run, but Papadopoulos warns that without investment in the IPOs of preclinical-stage companies pursuing novel biological ideas, pipelines will run dry.

Papadopoulos and some of his colleagues have proposed a mechanism by which Big Pharma can invest in biotech in a meaningful way — one that could restore the balance in the funding life cycle. As biotechs' innovations will comprise a significant percentage of Pharma's drug therapies in the future, it is in Pharma's best interest to help achieve this balance.

Papadopoulos and his colleagues envision a commitment of a few hundred million dollars from each pharma company for between five and seven years to fund management companies that would invest only in life sciences companies — either in IPOs or follow-on financings — no later than five years after IPO, excluding companies with valuations of more than $500 million. Papadopoulos believes a commitment by pharma companies of $1 billion per year in the aggregate for five to seven years would meet the financing needs of early-stage biotechs and that Pharma's commitment would attract co-investment of public funds.

Papadopoulos and his colleagues have proposed one such family of funds to help achieve these ambitious goals, though it remains to be seen whether this proposal will get any traction in the marketplace. He said, "I'm suggesting a way by which we can reintroduce into the life cycle of biotech funding an interest in investing in preclinical-stage companies with exciting science and take them public. If we do that, we'll reinfuse innovation and creativity into the space."

The Top 10 Partnering Pitfalls And How To Avoid Them

Part One

By Wayne Koberstein, contributing editor

The following is a list of "pitfalls" — actions, distractions, and missteps that can ruin a company's chances for a successful partnership — plus some expert advice for avoiding them. This month, part one contains the first 5 of the top 10 list; the final 5 pitfalls will appear next month in part two. Generally, the viewpoint of the article is of small, entrepreneurial life sciences companies, from the early stages of searching for large-company partners through partnership selection, deal negotiation, and operational implementation. But, the list should be equally valuable as insights for the large companies that, most often, are on the other, more dominant side of the deal. Some of the "best practices" offered may seem obvious but are often overlooked in practice. Experts with a range of small- and large-company experience, as well as supporting backgrounds in partnering, contributed suggestions, observations, and advice.

1. POOR TIMING — SEEKING A DEAL AT THE WRONG STAGE OF COMPANY/ASSET DEVELOPMENT

Big companies are spreading their external investments to the earliest and latest stages of drug development, leaving a large gap in between. Small companies should plan the timing of any major deal accordingly, but open a partnership dialog with large companies well in advance of the planned deal time.

Timing is all-important. Large partners will want to take on Phase 3 development at a time that is advantageous to them. Start-ups often lack the infrastructure necessary to implement early-stage deals.

Yet some innovator companies prefer to wait even longer. Jane Hollingsworth, CEO of NuPathe, says her company already has decided to complete Phase 3 trials and gain approval for its antimigraine patch before signing with any partner. "In a perfect world, you have an approved product, and then you're really getting a lot more competition among prospective partners to obtain it. So, our Plan A is to wait until we get approval and partner at that point, because that's when we'll get the best deal," Hollingsworth explains.

2. THE BLEEDING EDGE — FAILING TO ADJUST WHEN WHAT YOU'VE GOT IS JUST NOT HOT

Some experts frankly observe that, if the technology offered is not the "flavor of the month" (i.e. using a mechanism or target currently of wide interest to Big Pharma), it may not matter how good it is, how much it will help patients, or how much money it could make for the partner.

"The industry is like a well-aligned flock of birds, all heading off in the same direction, despite any logic to the contrary," says Llew Keltner, CEO of AgonOx, a developer of OX40 agonists in cancer in partnership with MedImmune/AstraZeneca. "In some cases, no amount of hard work will get a deal done, so you should consider repositioning, adding to the offering to make it 'hot,' or pulling back until the area gets hot."

Historical examples include anti-angiogenesis, championed for many years by a lone researcher, before it was finally developed into an actual therapeutic drug, Avastin. Once that happened, but not before, the large companies rushed to obtain every anti-angiogenesis compound or platform in sight. Significantly, it was a large entrepreneur-founded company with many other assets that had successfully positioned and developed the breakthrough product.

"With a new scientific rationale, first it's really important for pharmas to decide whether they want to be in the space," Sudhir Agrawal, chairman of Idera Pharmaceuticals, says. Idera began developing compounds targeting toll-like receptors (TLRs) long before they held wider interest. "Once they make a positive decision and look at what technologies are available in the space, we are ahead of the game, so the dialogue can start. But some of the companies might wait to mitigate the risk by having more data in hand, and that's helpful to us in making our own choice of potential partners."

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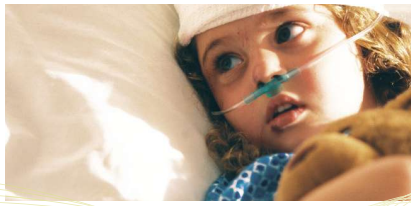

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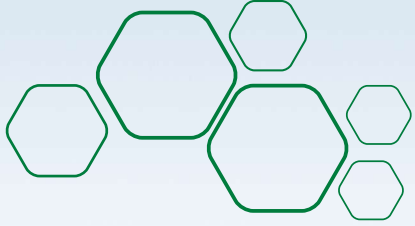

3. NAÏVE NEGOTIATING — PAYING TOO LITTLE ATTENTION TO THE DETAILS OF DEAL-MAKING AND DEAL TERMS

Small life sciences companies may let enthusiasm for their native science and technology blind them to business factors critical to finding the right partner and negotiating favorable deal terms. "It's imperative to set and stick with agreed milestones. The drug development business is a high-risk, high-return business, and the investment-relationship philosophy should reflect this by incorporating the same discipline as if one were investing in stocks with varied volatility and return profiles," says Paul Coggin, principal at the consulting firm Wipro.

"Relying on generalizations and assumptions to form the basis of a relationship can establish artificial barriers early in the process that are difficult to eliminate later," adds Mary Lynne Hedley, Ph.D., president, chief scientific officer and cofounder of Tesaro, a biopharma company that is developing licensed-in oncology drugs. "A small innovative company may bring to the table the belief that large organizations are incapable or unwilling to move quickly or unconventionally to advance drug development. A larger organization may have a preconceived belief that an innovative company is incapable of managing a development program that meets the requirements of regulatory agencies. In reality, the best relationships are those that encompass a whiteboard of ideas, equality in rendering those ideas, and a focus on progressing in the fastest, smartest way to reach a common goal."

Keltner takes a tactical view for small companies: "Partnerships are the result of sales — an innovator selling itself, the company and its assets, typically to large potential partners. The potential partner is a customer and must be treated like any customer: Know their corporate and personal needs, fill those needs, create trust at all cost, send flowers to the executive assistants and secretaries, and so on. Sales 101."

At the same time, remember that a good salesperson is well prepared. Always have a deal ready to go before approaching the target. Companies fixate on "term sheets," but those are just tools for generating and speeding up negotiations; trying to fashion them into stand-alone legal documents can waste months. Go right to agreement drafting and negotiation if both parties are serious. Don't make up values — get average values for the best comparisons, and derive the deal terms from these. It is much easier to arrive at a reasonable deal when using industry standards as a base rather than having to defend created valuations.

For similar efficiency on the compensation side, avoid confusing cash and equity. With most big pharmas or big biotechs, partnering/licensing and equity investment decisions are made in much different functions of the company, in much different ways, and the equity process tends to cost a lot of effort for little reward. If equity investment has no particular value, say, as a hefty stake in likely future sales, don't ask for it. Just go for the cash.

For nonfinancial terms (e.g. how IP will be pursued, who will do pharmacovigilance, how meetings will be held, how communications will be done, how financial/sales data will be shared, etc.), never agree to provisions in a legal agreement, due to time or cash or other pressure, that are literally impossible to execute. If the potential partner is serious, they don't want that either. Do the slogging in negotiations and get the terms to the point where they can be carried out.

"Relying on generalizations and assumptions to form the basis of a relationship can establish artificial barriers early in the process that are difficult to eliminate later."

Mary Lynne Hedley, Ph.D., president, chief scientific officer, cofounder, Tesaro.

4. FLAWED EXECUTION — NEGLECTING TO RECOGNIZE AND FULFILL BUSINESS OBLIGATIONS

Once the deal is signed, don't let the euphoria distract you from what the deal terms and operating as a company obligate you to do. Virtually every partnership is complex, and the agreements are usually full of both obvious and arcane requirements. Manage the details of compliance using the best methods of project management.

Erin Brubaker, VP, worldwide business development alliance management (AM) and head of the AM Centre of Excellence, GlaxoSmithKline, says, "Alliance Management plays a pivotal role in enabling the flawless execution of a collaborative partnership, by proactively identifying opportunities to execute more effectively, enabling efficient decision making, removing barriers that impede the collaboration, and fostering a culture of collaboration."

Brubaker's large-company perspective is reflected by a small-company executive, Jason Rhodes, chief business officer of Epizyme, which is developing a platform of small-molecule histone methyltransferase (HMT) inhibitors and screening technology — with GSK as one of its partners. "In 2011, we put in place a robust alliance- and project-management function that enhances our partnering ability. Given the scope of what we're doing, the number of programs combined with the fact that we have two corporate partners and two foundation partners, it really became necessary to have more structure and planning

around those activities."

Founders of start-ups — especially those with science-only backgrounds — tend to see income from the partnership as pure research funding, forgetting other obligations such as debts and taxes. You must be sure to pay all suppliers, if possible, at the optimum time in the tax cycle, as well as regular federal and state government income taxes on up-fronts and milestones.

Before getting too far down the road on deal terms, get very concrete advice from an expert tax counsel on how the deal should be structured so that payments either offset losses or can be treated as long-term capital gains. If that means changing your corporate structure or amending existing license/IP agreements, do it. The tax differences can be huge.

Keltner offers another expert tip: "Do not allow transaction attorneys to operate without constant supervision. They may be very good; they may provide invaluable advice; but they don't know the business as well as the principals, and it is not their business or financial risk. Stay fully engaged. Do the work. Sit in on the meetings. Help argue the points. Read the documents. Understand the documents and their ramifications."

5. VALUE CONFLATION — CONFUSING MILESTONE AND OTHER CONDITIONAL PAYMENTS WITH REAL MONEY

Headlines typically announce new deals with a total value, which will only manifest if the innovator partner meets very strict conditions. The words "up to" are usually missing from the copy. Some companies now deliberately keep financial terms confidential to avoid misperceptions of its deal values.

Whether or not releasing financials misleads the headline readers, small-company partners may also mislead themselves into seeing total deal dollars as ready cash. Arguably, such a mentality could have consequences such as creating a false sense of security in the company and possibly causing it to take its eye off the ball. The effect may be subtle, because both partners should be well aware of the financial terms, but it is nonetheless a hazard.

Planning For Serialization

By Gail Dutton, contributing editor

The mandates to serialize all pharmaceutical products are as challenging for pharmaceutical manufacturers as the Y2K situation was to computer software engineers in 1999. Unlike the computer situation, however, the pharmaceutical industry has no defined protocols or solutions.

Instead, it is stressed to interpret regulations while working with partners throughout the supply chain to devise interoperable data management solutions that accurately record, track, and manage data as it moves from manufacturer to distributor to dispensing point. The opportunity for error is great.

Serializing individual items, cases, and cartons isn't as simple as adding a bar code to a label. Often the label must be redesigned to accommodate the bar code, and regulators must approve the new label. The packaging line must be revalidated as equipment is added to generate each bar code, link each bar code to product data, apply the bar code to packages, and track that code throughout the supply chain. That data also must be managed, transforming it from data to actionable information. Employees must be trained to use the new equipment. And, sometimes, the package itself must be changed. "For example, small round bottles aren't read as easily as small square bottles, because the equipment has to read the bar code straight on," says Greg Cathcart, CEO, Excellis Health.

Learning details like that now, before the implementation deadline, is the goal of the many serialization pilot projects under way at pharmaceutical manufacturing facilities throughout the United States. Big Pharma is leading the way. "Small companies, in contrast, often have done little to prepare for serialization because they need to serialize only a few packaging lines. Their efforts will be minimal compared with Big Pharma, which sometimes has more than 50 lines," Cathcart says. Rather than prepare, many in industry are working to delay the implementation date or change the current regulations. "An industry consortium is appealing to both state and federal regulators for a single, national standard," Cathcart adds.

Regardless of the outcome of such lobbying, companies should prepare now for serialization implementation. "Start now. Companies can't wait until they are close to the implementation date to begin," advises Peggy Staver, director of product integrity, Pfizer. "There is so much to learn and do, and it all needs to be tested extensively with all of the trading partners."

STRATEGY DEVELOPMENT

Pfizer has been planning for serialization for much of the past decade. The first objective was to develop a strategy. Despite the many serialization regulations throughout the world, Pfizer has succeeded in developing a single, standards-based strategy that can be applied locally, with any necessary variations.

Regardless where, geographically, serialization is being applied, or whether it is at the pallet, case, or individual item level, the planning and implementation process is virtually the same. The key is to form a global serialization strategy team. It provides internal governance and insights into global serialization regulations, relying on the expertise of internal and external resources to implement standards-based solutions.

In devising Pfizer's strategy, the global serialization strategy team considers local drivers. "Although the approach to serialization may be the same, local implementations may vary, based upon local business needs," Staver says. For example, the California requirement focuses on track-and-trace methodology to thwart counterfeiting. In Europe, the business drivers include provider reimbursement, so a point-of-dispense authentication model is used. "We can use the same coding in both regions, but the business process implications are very different.

"It's also important to consider the way product is distributed," Staver continues. In regions where the original manufacturer's packaging reaches the patient — Nigeria, for example — a process relying upon consumers to authenticate a serial number via cell phone text-messaging may make sense. Using a similar process in the United States is not very practical because, in many instances, the original manufac-

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"The biggest issue in defining a global strategy is the need for clarity," Staver says. "Globally, there are many emerging requirements. As soon as we hear of them, we immediately mobilize our global serialization strategy team to get as much information as possible." Oftentimes the timelines for implementation are quite short — sometimes only a few months from passage of the law — and the requirements may be unrealistic. Therefore, pharma engages with regulatory authorities globally to understand their requirements and, sometimes, to educate them about the constraints of the pharmaceutical industry.

"Defining the implementation team and resources is a dedicated effort," emphasizes Natalie Lotier, VP of strategic supply chain operations and planning, Bristol-Myers Squibb (BMS). The planning also must consider vendors who are or may become partners in the future, so the implementation plan should include critical questions and milestones that will be important as implementation is expanded.

SERIALIZATION REQUIRES PACKAGING LINE CHANGES

In designing a serialization plan, Lotier advises manufacturers to consider starting with their desired outcomes and design the process backward. For manufacturers, introducing serialization involves changes to the packaging lines and the distribution systems that cascade throughout the organization. Making those changes requires input from product managers as well as specialists from engineering, packaging, finance, commercial operations, government relations, supply chain, logistics, and master data departments.

To effectively plan the changeover, companies also must determine their business priorities and consider upcoming launch plans, Lotier says. "That can be a very challenging process for industry. It's a balance of line capacity, line criticality, inventory, and regulatory requirements. You must be well-prepared for everything to go well." Although companies usually aren't changing the boxes or cartons, they are changing the labeling. Nonetheless, manufacturers still must install new hardware, as well as the business technology to manage the serial numbers that are provisioned to the packaging line and the data that is transmitted to customers. "Business process changes are required to enable data capture and exchange, and the new processes must be tested and validated," Staver says.

Big pharmas, including BMS and Pfizer, are piloting changes to their own lines now and are working with their CMOs to identify changes to the lines they have outsourced. Pfizer, for example, expects to change approximately 60 lines internally for its U.S. operations and is working with its CMOs to change over some 60 additional lines. Manufacturers must expect to also change their international packaging lines because of the growing body of global serialization requirements.

Companies say changing over their packaging lines to accommodate the new bar codes takes four to eight weeks. For a company with 120 lines, that's between 480 and 960 weeks of cumulative downtime. To minimize downtime, savvy companies are modeling the changeover offline to minimize unforeseen issues. Then, they coordinate the upgrades with other work that is required for the line to minimize overall downtime.

"Some products have a very short shelf life, which further complicates the issue," Cathcart points out. "Building a stockpile for the interim could reduce the effective shelf life of some

products by 20%." Therefore, companies must work even more closely with their sales representatives to help their customers plan ahead.

DATA EXCHANGE IS BIG CHALLENGE

As BMS and Pfizer gain experience with serialization, they each stress the importance of integrated, interoperable IT systems. BMS created a new position — the director of enterprise data operations — specifically to deal with this business need. "Data exchange is the most difficult of the serialization challenges facing pharma companies. It's costly and complex," Staver emphasizes. Throughout the entire supply chain, from manufacturer to pharmacy, items must be identified using standard data carriers and identifiers and exchanged in a standard way so products may be tracked accurately and efficiently. Establishing and enforcing that system and then installing the proper hardware and software to enable track-and-trace and data mining are only part of the solution, however. The IT systems used by each link in the supply chain also must be interoperable. The individual systems must pass information seamlessly, despite the use of potentially different platforms, applications, and configurations.

To ensure interoperability and seamless, error-free data transmission, Pfizer has conducted multiple pilot projects with its distributors and pharmacies during the past several years. Recently, the company scaled up those smaller pilot projects to include some of its larger distributors and a high-volume product to identify any additional data exchange challenges.

NOW IS THE TIME TO START

"Serialization projects need a strong commitment from the top down. Management must be invested in the outcome and must designate leaders for the business and IT aspects of the projects," Lotier insists. Making the necessary commitment is difficult for companies because serialization requires a significant financial outlay of finite resources in a globally constrained economic environment.

Half-hearted commitments to serialization will inevitably fail. "Jumping in with fully integrated teams makes sure everyone is aware of each of the issues. Diversity of opinion is vital to move forward holistically," says Terry Young, director of enterprise data operations, BMS. "This is an evolving space, and as with any new technology or process, you must account for variability and manage expectations."

It may take as long as one year from the time planning begins to the time products are shipped, in Pfizer's experience. Although the process becomes more efficient over time, unforeseen issues — often involving legacy equipment and applications — can easily slow serialization programs. "Few implementations are identical, and each is a learning experience," Staver observes.

As pharmaceutical manufacturers gain experience, their insights are being shared informally, as well as through serialization working groups. GS1, for example, is compiling the learnings of its committee members into what will become serialization best practices. But some things are evident now — serialization is an expensive, time-consuming process.

When pharmaceutical manufacturers began their pilot programs, most knew only a fraction of what was necessary to fully implement a serialization program. And, they still are learning. The message is clear. If you aren't already planning for serialization, start now.

Editor's Note: This is the second of a four-part series examining serialization strategies in the United States.

Insights Into Your Capital Structure

By Christopher Geier

Access to appropriately and affordably priced capital is often the lifeblood of any company. The search for that capital — whether through bank loans, private funding, research grants, equity investment, or other sources — while a daunting exercise, is a must for growing companies.

The good news for life sciences companies is that this industry is considered a healthy, growing sector, and there are numerous capital options — both in terms of equity and debt — available for companies that demonstrate sound business fundamentals. The trick is in understanding what potential capital resources you are looking for in order to improve your chances of securing appropriate capital with optimum terms and in the time frame you want or need.

Fundamental to any quest for capital is your ability as a company owner or leader to guide your company to achieve and maintain an optimum capital structure — that ideal combination of equity and debt. That combination will be different for every organization, but it always means balancing your desire for financial returns with your stakeholders' appetite for risk.

THE BASICS

In the simplest form, an organization's capital structure is its combination of debt and equity. This combination is clearly reflected on the balance sheet, one of the very first things a capital provider will want to see. Depending on the company, if it is in need of raising any type of capital, either equity or debt, investors and lenders alike prefer, and often require, a strong balance sheet complete with an appropriate composition of equity and debt. The reason? A strong balance sheet reflecting a healthy equity/debt ratio is an indication of a company with good fundamentals.

EQUITY

In general, a company's equity consists of:

- common stock
- preferred stock
- retained earnings.

A healthy amount of existing equity capital is a strong indication of a company's financial fitness. Investors and lenders are both biased toward a meaningful level of equity relative to debt. You can build equity in your company by retaining additional earnings rather than deploying them or by additional paid-in-capital.

EQUITY FUNDING OPTIONS

The life-stage and existing financial health of your organization will largely dictate the options you have in attracting equity capital. Start-ups, early-stage companies, and those in need of growth capital are almost always forced to approach equity investors. Equity investors, such as venture capital or private equity firms, will supply an infusion of capital in return for a partial ownership interest in the company. The cost of the investment is directly related to the expected return on that equity, adjusted for risk. In other words, the higher the risk, the higher the need for return to those investors; ergo the "risk-reward proposition." And, because early-stage and start-up companies are inherently more risky propositions, equity will likely be quite expensive. By expensive, I mean the investor will require a larger ownership interest.

One of the more common examples of equity investing is securing partial ownership in a company through the purchase of common stock or, more often, preferred stock. Preferred stock typically bears a coupon, or interest rate, and is convertible into common stock at the holder's discretion. Although common and preferred stock are technically unsecured capital, they are theoretically and practically the most valuable capital in a company's capital structure because they represent the company's ownership.

So what exactly do equity investors look for in making investments? That is an excellent question, and the answer is surprisingly consistent around the world. Equity investing is about finding those companies that either have high-growth potential or demonstrate healthy business fundamentals:

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Remember, an equity investor generally does not want to run a company, but rather invest in one that will return a multiple on the investment. So, the more you can demonstrate sound business practices and show demonstrable results — generally through a well-thought-out business plan and execution — the more options you will have.

DEBIT AND CREDIT LINES — THE DEBIT SIDE OF THE EQUATION

In exploring the lending environment for your capital needs, there are three essential questions:

- Can you borrow the money that you need?
- How much will you pay for that funding?
- When should you borrow or explore refinancing options?

There are numerous traditional debt structures, which include:

- senior term loans — in which a company's assets serve as the collateral for a loan
- revolving lines of credit — credit which fluctuates up and down as it is used
- subdebt or mezzanine debt — often a hybrid of debt and equity financing.

There are alternative structures that are interesting options for businesses that aren't quite a fit for a traditional structure. An example might be a company that has good cash flow but has little in the way of assets. Alternative structures include:

- unitranche (debt that combines both senior and subordinated debt into one debt instrument with one interest rate, which is a blended rate between senior rates and subordinated rates)
- second-lien term debt
- club-term sub debt
- rate-only sub debt
- high-yield private debt.

What drives the differences in these structures? The answer can be found in your company's balance sheet and cash flows. There are many things bankers look at as they evaluate the creditworthiness of your company, but chief among them are:

- assets — your assets are the collateral for the debt. Assets are generally physical things such as your brick-and-mortar, equipment, or inventory.
- cash flow — The cash flow is what will be required in order to make the debt payments or "service the debt."

How does that translate into how much you can borrow? Banks like to look at something called total leverage, which is defined as total debt to your earnings before interest, taxes, depreciation, and amortization (EBITDA).

Part of this total leverage concept is most certainly senior debt, that which is fully secured by assets of the company, and quite possibly a piece of mezzanine or subordinated debt. Currently, senior debt to EBITDA is approximately 2.3x for middle market companies, and subordinated debt to EBITDA is approximately 1.0x, for a total debt to EBITDA ratio of approximately 3.3x. Simply put, if your company is doing $10 million in EBITDA, assuming you had sufficient collateral, you could likely borrow approximately $33 million.

What drives the need for a more alternative structure? Lack of collateral and cash flow — the challenge of many early-stage or start-up entities. Those two things alone will drive not only the amount of money your company is capable of borrowing, but your cost of borrowing. In the relationship between risk and reward, lenders will require a higher reward as the amount of risk they are taking increases. There are significant differences in cost to be sure. How significant? Typically secured debt is priced at 150 to 400 basis points over LIBOR (London Interbank Offered Rate), unsecured debt at 14% to 19%.

If you are wondering how banks charge you the rates they do, let me shed some light. Macroeconomic variables drive changes in the short-term interest rate, which in turn also affect longer-term rates. For instance, when the Federal Reserve raises the federal funds rate in response to high inflation, expectations of future inflation, and/or improved economic activity, longer-term rates will adjust upward accordingly. Why? Because investors, capable of receiving greater rates of return with capital invested in short-term maturities, will now require an even greater return for investments in longer-term maturities, risk-adjusted for time.

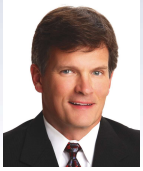
If that seems complicated to you, you're not alone. Everyone, including policymakers, economists, and businesspeople would like to better understand how a change in short-term rates will affect longer-term rates, largely because the latter rate determines borrowing costs for businesses and consumers alike, which in turn helps to determine aggregate demand in the economy.

The takeaway? Typically lower interest rates mean lower borrowing costs. The right time to refinance existing debt is when you can secure lower rates and associated fees than what you currently have. In addition, lower rates also may provide you with the flexibility to recapitalize your balance sheet or, more simply, to borrow money at a lower rate to change your company's capital structure in some way.

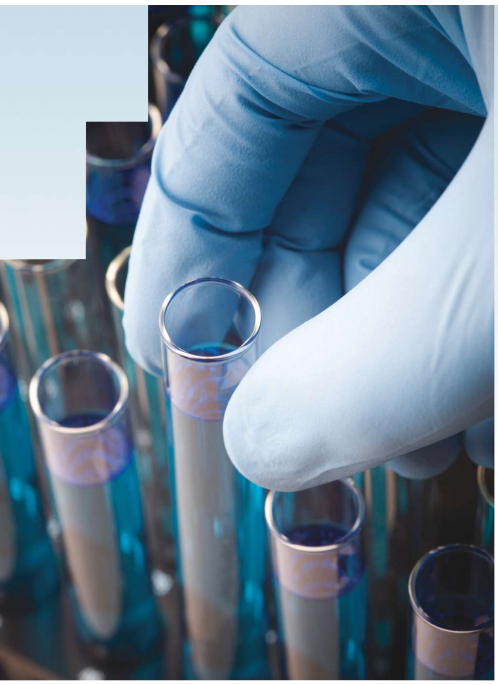
As an example, which we've also seen in the life sciences industry, one of our recent clients found itself in a situation where the owners were required to pay back their early-stage equity investors with principal plus interest. More frequently than you might think, companies in this situation are often forced to sell their companies to pay back those early equity holders. In essence, the price or cost of the equity needed to start and grow a company may very well require the sale of the company. In our client's case, this happened at a time when debt was affordable, which allowed the company's principals to borrow the capital needed to pay off their investors at a very reasonable interest rate.

So at this point you may be wondering: Is there an optimal capital structure; the perfect mix of equity and debt? The simple answer is no. For those sagacious management teams, the use of leverage increases the amount of financial resources they have available to them. The notion that management is good enough at deploying capital to create greater returns on that borrowed capital than the cost of those funds is well accepted and generally practiced. Oh, but there is a problem with too much debt or being what is affectionately referred to as "overlevered," a condition we don't have near enough time to talk about here. Simply put, smart money usually always favors higher levels of equity and lower levels of debt.

About the Author



Chris Geier, a 20-year veteran in the capital investment and investment banking field, is CEO of Sikich Corporate Finance LLC. Over the course of his career, Geier has provided financial advisory and mergers and acquisitions services to public and private companies across disparate industries.



Preformulation Reduces The Risk Of Drug Failure

By Cindy Dubin, contributing editor

When Millennium Pharmaceuticals wanted to find a formulation that would alter the biodistribution of an oncology agent, it turned to Particle Sciences, Inc. (PSI), a CRO, to perform the development. But, if not for the preformulation work that Millennium performed up front on its own, augmented by PSI's preformulation, finding the right formulation would have been a more time- and cost-consuming process. "Preformulation enabled us to find the right dosage form that would overcome the toxicity issue we were having," says Michael Kaufman, Ph.D., VP of pharmaceutical sciences at Millennium: The Takeda Oncology Company. Kaufman was a panelist at the Drug Delivery Partnerships (DDP) conference this year, discussing how preformulation is the new formulation.

Preformulation is an important development step used to understand the challenges that a particular compound may pose. The panel describes this step as a bridge between discovery and development, where the physical and chemical characteristics of a new molecular entity (NME) are determined through solubility, dissolution, and physiochemical studies in an effort to better understand the molecule. Initial compatibility studies with excipients also can be performed during preformulation.

PREFORMULATION OVERCOMES COMPOUND CHALLENGES

"Getting this data earlier in the development process enables formulators to make more informed dosage form decisions," says Robert Lee, Ph.D., VP of pharmaceutical development and quality at PSI and a member of the DDP panel. Preformulation is not a new stage of development, but can be defined differently by different companies. The panelists agree that preformulation brings formulation teams into the development process earlier. At Eisai Pharmaceuticals, for example, the formulation group gets involved when issues arise with difficult-to-deliver compounds. "Recently, we have worked with our discovery teams on low-solubility compounds to enable dosing in animal models at the pre-candidate selection stage," explains Geoffrey Hird, Ph.D., principal scientist, formulation and drug delivery technologies at Eisai, and a member of the discussion group. "Our involvement has allowed the discovery teams to rapidly screen promising compounds and develop preclinical formulations that overcome compound challenges."

At Millennium, the challenge was related to toxicity. It was found during early preformulation that upon delivery in animal studies, the oncology agent was localizing in the liver more than in the tumor. Kaufman believed it was critical to bring the PSI formulation team into the fold to help overcome this obstacle.

Millennium provided PSI with the drug and physiochemical information obtained during the preformulation work to help PSI scientists determine which of many formulation approaches would enable the active pharmaceutical ingredient (API) to bypass the liver and target the tumor. Kaufman says that eventually two formulation approaches presented the most favorable delivery options and were tested. Ultimately, it was PSI's nanoparticle approach that had the most pronounced results in mice for delivering the drug to the tumor and sparing the liver. "Our up-front preformulation work helped to quickly narrow the formulation search and weed out the formulations that wouldn't work for intravenous drug delivery," says Kaufman.

While Millennium is still contemplating its next step in relation to the PSI formulation, Kaufman says that combining the preformulation data with PSI's formulation produced the correct measured amount of drug to avoid organ toxicity. This knowledge can be applied to develop a final dosage form (i.e. tablet, capsule, parenteral) that meets the needs of patients and caregivers.

While preformulation data may support a compound moving forward to formulation development, in other cases, it may become apparent from the data that it may be difficult to develop a suitable final dosage form (i.e. due to low permeability and high required dose). At that point, the team may choose to synthesize a new molecule, or other formulation technologies may be required.

"If you don't understand the compound, it's hard to design appropriate dosage forms for the best chance of success," says Lee. "You might get lucky if you happen upon your dosage approach by chance, but the best approach is through methodical, systematic preformulation."

PREFORMULATION CAN SAVE $500,000

By having formulators interact with discovery organizations at an earlier stage, the benefits of formulation and drug delivery technologies are being realized earlier for compounds going through the discovery

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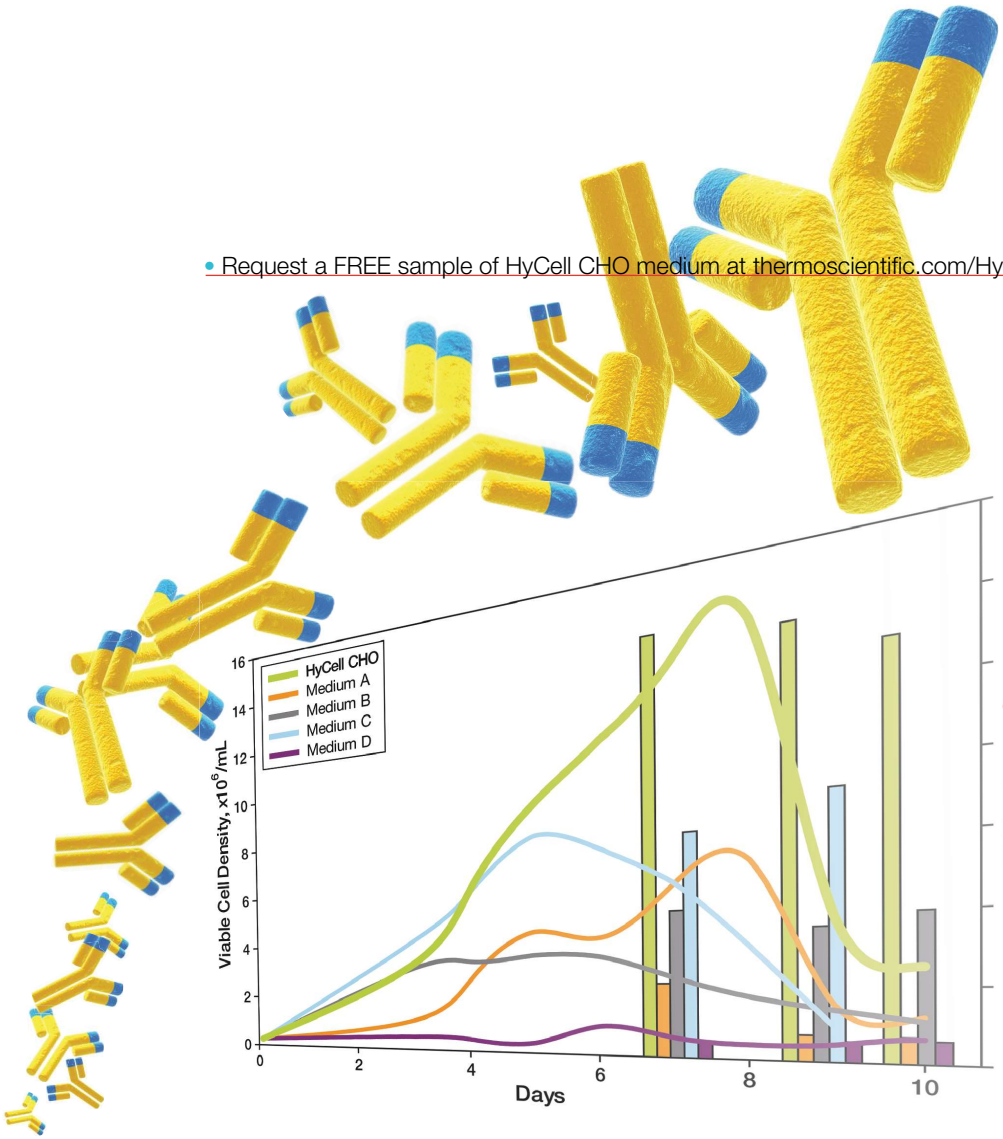

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process. Hird says some of these benefits of early formulation interaction with the discovery organization are:

- applying drug delivery technologies, such as solubilization technologies, to *in vivo* compound activity screening studies
- increasing administered doses to support toxicology studies
- improving the transition between the discovery and development organizations
- incorporating pharmaceutics and drug delivery technology input into candidate selection.

"Earlier interactions between the discovery, preformulation, and formulation teams can help to speed development timelines and clinical trial entry by applying formulation and drug delivery technologies to challenges faced during the development process," says Hird. "If, during preformulation, a decision is made to use enabling formulation technologies, the earlier the technologies are implemented and used in discovery and toxicology studies, the sooner the drug can enter the clinic."

The panel agrees that most drugs do go on to clinical testing if preformulation is performed. The panel also agrees that companies that do not perform preformulation run the risk of drug failure.

According to Hird, companies have to do some sort of preformulation in order to understand the molecule enough to formulate it. "I think that having good interaction between preformulation and formulation at an earlier stage in development helps to increase a chance of a drug making it to the clinic."

For those companies that prefer not to take the risk and perform preformulation, they can expect to add a couple of months to the development time line at the outset, but time is saved in the long run because the number of false starts (formulation development studies that result in a drug product that is unstable, poorly dissolving, or otherwise does not meet requirements) is reduced. For instance, says Kaufman, if preformulation studies show that a new drug is unstable at high humidity, then the formulation group can quickly select moisture-resistant packaging without having to perform extensive stability studies.

Preformulation can also save a significant amount of money. According to Kaufman, each time a formulation is tested, a portion of the API is used. If preformulation is performed, and there is a good understanding of the compound, this helps sift through a myriad of formulation options. Thus, less API will have to be used.

"Let me put it in numerical figures. Using just one kilogram of an API can cost $100,000 at the early stage of development," explains Kaufman. "Through preformulation, we can theoretically save 5 kilograms of API. Saving time and money. What more is there?"

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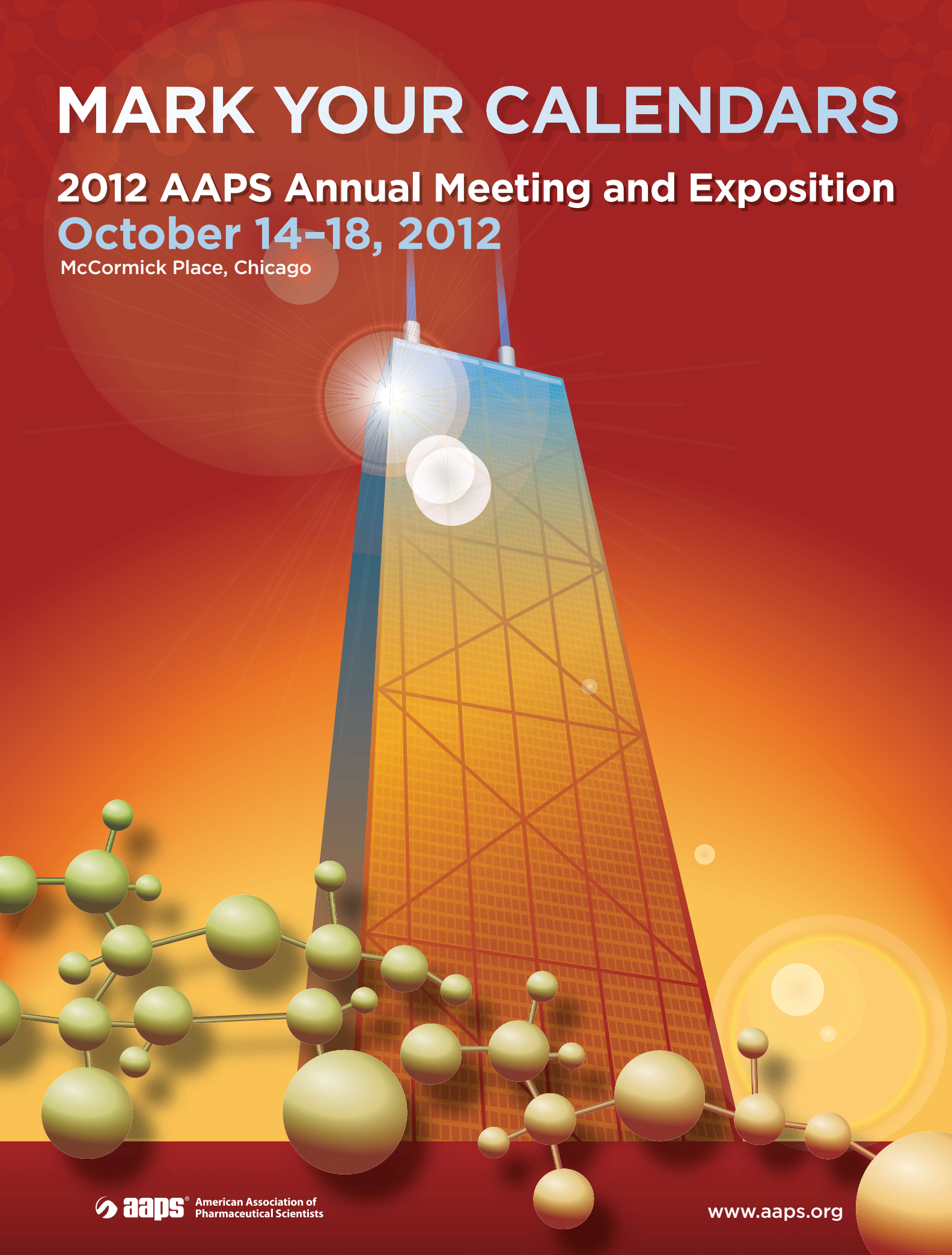

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Fostering Asian Pharma Innovation

By Gail Dutton, contributing editor


Steve Yang, Ph.D., VP, head of R&D for Asia and emerging markets, AstraZeneca

"China represents a tremendous opportunity for AstraZeneca and other pharmaceutical companies to pilot new ways of conducting R&D," says Steve Yang, Ph.D., VP, head of R&D for Asia and emerging markets for AstraZeneca. That opportunity extends throughout much of Asia, he says, where the lack of entrenched drug development bureaucracy provides a relatively clean slate for innovation. "Asia is very important for AstraZeneca for commercialization and for R&D," Yang notes. "It's been one of the fastest growing markets for the past five years."

AstraZeneca recognized Asia's potential several years ago, not just by locating facilities in China and India, but by developing local research collaborations with academic institutions and companies throughout the region at a time when many in the West considered that risky. Many of those collaborations, nurtured for 10 and 20 years, are developing into increasingly innovative partnerships.

Those relationships include long- and short-term collaborations and licensing deals with biotech companies, CROs, hospitals, and academia, as well as with individual researchers and entrepreneurs. AstraZeneca seeks out scientific opportunity wherever it is found, he says. "In December 2011," for example, "we in-licensed a Phase 1 oncology compound from a Chinese biotech company, Hutchison MediPharma Ltd. This is the first time a major pharmaceutical company licensed a clinical-stage compound in Asia. Hutchison is leading the development in China, while AstraZeneca leads development for the rest of the world." The compound, called Volitinib (HMPL-504), is a highly selective inhibitor of the c-Met receptor tyrosine kinase for the treatment of cancer.

TRENDS FOR PHARMA IN ASIA

"I see three major trends affecting life sciences companies operating in Asia," Yang says. "Long-term relationships are resulting in collaborations, collaborative research is evolving to product delivery, and collaborations are becoming regional, multinational endeavors."

Since entering China in 1993, AZ has consciously worked to forge relationships that are key to productive collaborations. Because of that early commitment, the company now is benefiting from major collaborations including those with Peking University for cardiovascular disease and metabolic disease and with the Shanghai Institute of Material Medica on a preclinical safety alliance.

As AZ develops its Asian track record, its collaborations become deeper. Hutchison Medi Pharma, for example, initially worked with AstraZeneca in collaborative research, but now is beginning to deliver projects. "We've moved from functional to wholistic collaboration in a range of areas, building deeper relationships with institutions rather than just at the level of the laboratory," Yang adds.

These collaborations are transcending national boundaries. With its strong, well-established research network throughout Asia, "We are linking collaborations to increase the benefit for science, discovery, and research portfolio development," he says. By building relationships with clinicians and key opinion leaders — particularly in oncology — AstraZeneca has fostered collaborations among researchers in Korea, Japan, China, and Singapore.

According to Yang, the interest in broad collaboration stems partially from the huge unmet medical need in Asia, particularly around gastric, liver, and lung cancer. Statistically, Asia accounts for 75% of all new cases of liver cancer in men and 66% in women. More than 70% of the world's new esophageal cancers and 50% of the world's new cases of stomach cancer occur in Asia. By working closely with researchers in Asia on these particular cancers, researchers gain an important, perhaps unique, perspective on the disease. "Data from such collaborations helps explain the varying population genetics of cancer and justify developing therapies targeting those variances," he explains. Consequently, "AstraZeneca is one of the first pharmaceutical companies to develop targeted therapies for specific populations."

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One of the keys to success, Yang says, is to develop meaningful collaborations. There's no specific checklist, but "Crafting a meaningful relationship involves developing mutual value and complementary approaches so both parties bring something to the table. The Hutchison Medi Pharma collaboration is a good example," he adds. "Hutchison has a relationship with a Chinese player and unique insights into targets. We have experts in developing products around the world."

AstraZeneca doesn't always take the lead in its collaborations. The leadership role fluctuates based upon what makes sense at the time. For example, Yang says it makes sense for the multinational to lead when global expertise brings value and for local partners to lead in areas where local insights make a difference. As an example of that difference, AZ is pursuing a new strategy of branded generics for emerging markets, giving physicians and patients an alternative to either branded drugs or generics. "We bring branded generics—off-patent drugs sold under their branded names—to complement innovative drugs, based on local needs, capacities, and operating environments." That approach capitalizes on China's need for lower-cost drugs as well as the population's preference for high-quality, Western-branded medicine.

The company is building out its branded generic capacity quickly, through the acquisition of a Chinese-branded generic company, privately owned Guangdong BeiKang Pharmaceutical Company Ltd. To support longer-term growth, AZ announced plans last autumn to build a $200 million manufacturing plant in China. Located in China Medical City (CMC), Taizhou, Jiangsu province, the facility represents the largest single investment in a manufacturing facility that AZ has ever made. Scheduled for completion in late 2013, it will produce intravenous and oral solid medicines for the Chinese market.

ANTICIPATE REGULATORY CHALLENGES

In developing an Asian strategy — or any international strategy — understanding the differences among regulatory guidelines is a key hurdle. The regulatory environment is highly country-specific, so no single approach works for all of Asia. Even within China itself, the regulatory environment differentiates between products for Chinese use and those for export. "The regulatory environment in China is quite different from other nations; therefore tailored products are being developed for China," Yang says. As China's market matures, the "In China for China, and In China for Global" policies are converging, speeding the day when one policy may apply to Chinese pharmaceuticals, regardless of their intended market.

Throughout Asia, "Regulatory environments and policies are dynamic and are evolving rapidly, especially in emerging markets where innovation is becoming very important," Yang says. "Regulatory policies are becoming more open and supportive of innovative drugs. That's a long-term trend, but that road has its ups and downs. For example, the Chinese government has shown a willingness to invest in healthcare, and demand for high-quality medicines is growing exponentially. However, the government is subject to cost-constraint themes similar to what we see in other markets." Those cost constraints temper its enthusiasm for investment.

Regulatory experience is one of the advantages large multinationals bring to partnerships in emerging regions. For example, AZ has colleagues with regulatory expertise and regulatory relationships in each country. The company leverages those relationships and expertise to help its global team tailor drugs for development.

INNOVATION CENTERS FUEL REGIONAL STRATEGY

China is very important to AZ's Asian strategy, but is only a part of that strategy. Japan and India also play important roles. "Our overall strategy is to produce products better and faster for the Asia Pacific region and to help the West access Asian innovation. One of the ways that's accomplished is by building innovation centers to tap into Asian expertise," he says.

AstraZeneca's Center for Excellence in Bangalore, developed in collaboration with two Indian companies, and the translational research center dubbed AstraZeneca Innovation Centre China (ICC) are helping fuel the company's innovation engine. The ICC, which opened in 2007, has become a robust discovery center delivering drug candidates and medicines. "Within the next three to five years, I expect a steady stream of clinical candidates coming out of the ICC," he says.

THERAPEUTIC FOCUS

To continue to foster innovation in Asia, the company has developed a three-pronged approach based around broadening the scope of therapeutic interests, building a clinical operations center, and strengthening internal capabilities. Oncology was AZ's primary focus, but now the company is beginning to look at other diseases that are prevalent in Asia. For example, two years ago AZ collaborated on a chronic obstructive pulmonary disease (COPD) study with a Chinese hospital. That work focused on assessing the presence of biomarkers associated with COPD for comparison with Western patients, adding to the body of knowledge. Ultimately, the information may shed light on the disease mechanisms to increase survival of COPD patients.

To leverage that and other research work, AZ opened its global Clinical Operational Hub in Shanghai one year ago to collect data and exchange information among researchers. "This is one of five in the world and the only one AstraZeneca has in Asia," Dr. Yang notes. He sees the centers as a hub for global regulatory studies in all therapeutic areas.

The company plans to continue to strengthen its capability for innovation by increasing the number and quality of its Asian collaborations with academia, biotech, and other organizations. The knowledge gained from those relationships will support internal innovation as well as collaborative projects.

"AstraZeneca's approach in Asia is not an isolated effort, but an integral part of a global strategy. China and all of Asia represent a tremendous opportunity for our company."

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Managing Partnerships To Achieve Complex Production Objectives

Building an effective, long-term CMO relationship poses significant challenges. In addition to an open, collaborative spirit, a strong partnership requires a successful technology transfer, a clear understanding by both partners of the key objectives at each project life cycle stage, and effective management of unexpected events.

FACTORS FOR SUCCESSFUL PARTNERSHIPS

A successful program with a CMO requires a detailed plan, a flexible approach, and open, transparent communications. Two fundamental tools that set the tone of the partnership are (1) the manufacturing service agreement (MSA), the road map for launching the project and how to manage when things don't quite go according to plan, and (2) the quality agreement, which provides greater detail on the operational rules of engagement. Once a program is launched, effective project management and regular face-to-face team meetings are essential for sustaining a strong partnership. Finally, both partners should establish and adhere to positive behavioral norms for team interactions. Managers must clarify these norms, correcting ineffective behaviors early, while building team competencies. These elements help build a high-performing team that engenders the most critical factor for success: a spirit of trust and collaboration.

CASE STUDY 1

As a CMO service provider, Abbott partnered with a sponsor for a recombinant product. Key project objectives included transfer of development activities to Abbott's Worcester, MA, facility, conversion from a perfusion-based to a fed-batch cell culture process, and implementation of downstream unit operations. Abbott also had to validate a viable process and gain commercial manufacturing approval.

Working cooperatively between the two laboratories, the team efficiently completed process transfer, characterization, and validation. Following commercial approval and demonstration of process performance with numerous batches manufactured, a sudden change in process performance challenged the team's ability to deliver standard batch yield. Leveraging their strong partnership, the joint technical team was able to troubleshoot the problem and recover the process, delivering 10% more than was previously thought possible.

CASE STUDY 2

As a sponsor, Abbott sought to enhance its security of supply for an approved product by contracting with a CMO for additional capacity. The commercial product had been previously launched at the 6,000L scale and transferred to a second facility at the 12,000L scale. Project objectives included adapting the process to fit the capabilities of the CMO, transferring the project to both a European facility at the 10,000L scale and a new Singapore facility at the 20,000L scale, and gaining regulatory approval at both sites.

SUCCESS FACTORS

Both parties must own the project. The sponsor must set clear performance expectations, and the CMO must demonstrate a successful fit. When starting a process in a new facility, both must jointly navigate the nuances accompanying each unit operation.

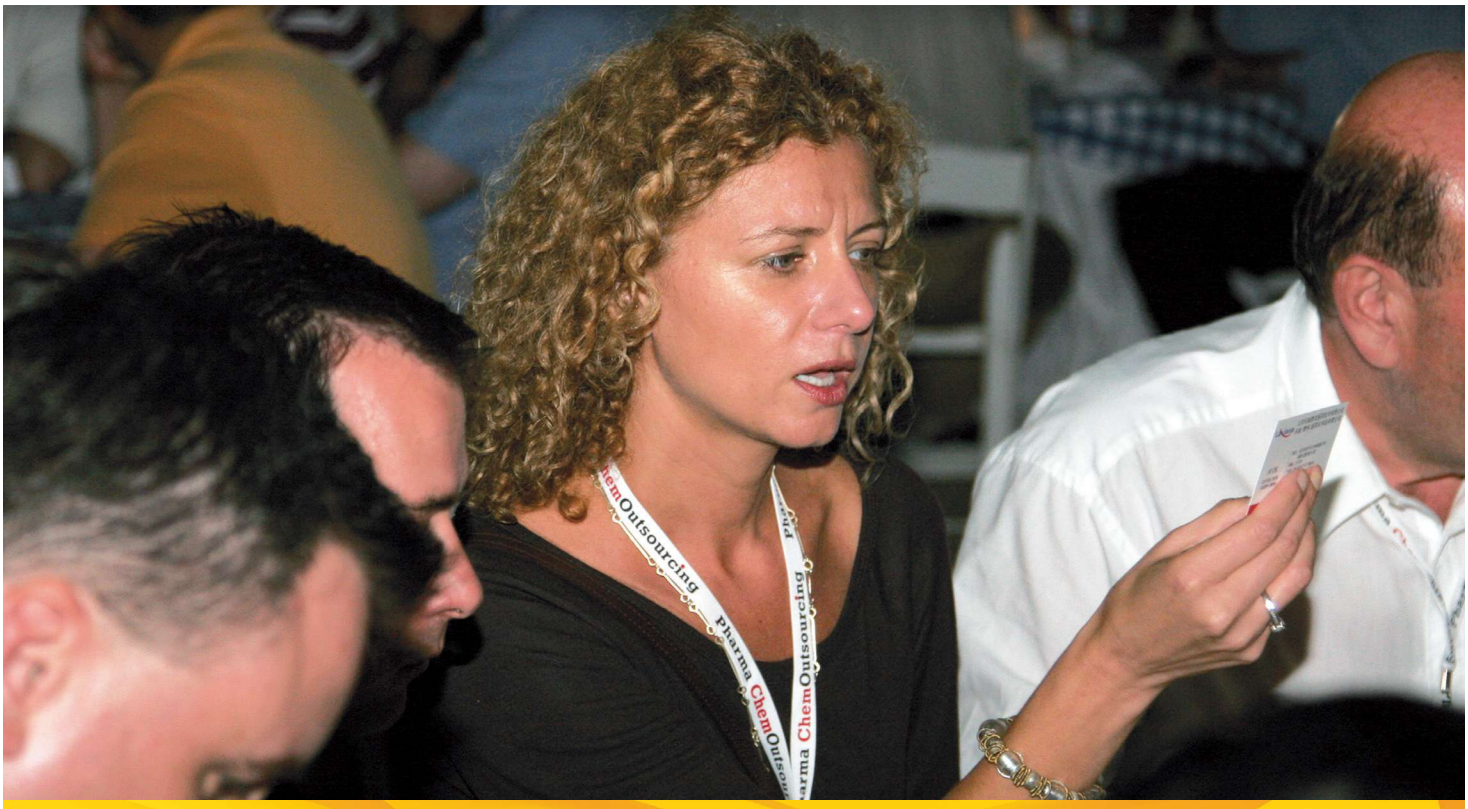
Gaining approval requires careful planning and execution. Together, the team defines the process validation master plan, performs a careful process risk assessment, and plans sufficient manufacturing runs to establish confidence in the process and facility performance.

Sustaining optimal performance of the commercial process requires diligence from both sides. Working together as one team, the sponsor, with its detailed product and process knowledge, and the CMO, with its extensive operational experience, must react quickly to problems before they evolve into significant issues.

A central dashboard that captures key performance indicators (e.g. in-process controls, specifications, nonconformances, out of trends, CAPAs [corrective and preventive actions]) at all sites is critical to avoid even minor variations in product quality and ensure interchangeability within the supply chain. When manufacturing in multiple sites, one central team should collate data and tune the process to deliver consistent product quality and eliminate process variability. Coordination of these activities requires a highly organized, dedicated program manager.

Ralph Lambalot, Ph.D.

Lambalot is the DVP of Abbott's biologics development & manufacturing launch. He has 16 years of experience in numerous roles spanning the continuum of drug discovery, development, and commercial manufacture for both small molecules and biologics.



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Scientific Leadership: What They Never Taught You In Grad School

Ken Stuart, Ph.D.

Ken Stuart, Ph.D., is president emeritus and founder of Seattle BioMed. A world-recognized pioneer in infectious disease research, he founded Seattle Biomedical Research Institute (Seattle BioMed) in 1976.

As I was building Seattle BioMed from a handful of researchers in a strip mall in a Seattle suburb to a world-class facility filled with 400 of the brightest and most compassionate people in the world, I learned a few things — concepts about scientific leadership that I was never taught in grad school.

Typically, in scientific careers, you anticipate there will be a progression through the ranks that requires the combination of knowledge and technology to make new discoveries. However, one quickly finds that some of the most important factors are practical, and that leading a scientific organization requires facing very basic challenges. These obstacles include the acquisition of resources as well as making decisions on what you are actually going to do (and, importantly, what you should do) and converting these into systematic plans. Then, there's the need to address the basics of developing and sustaining a complex infrastructure and operations.

As organizations grow and develop, many of the sought-after discoveries are not so much scientific but rather discoveries of issues, problems, and challenges that are standing in the way of those research breakthroughs. These issues, ranging from matters of personnel to space to funding, need to be solved daily. They cannot be ignored lest they fester; rather, it is best to be systematic and proactive because it is much more efficient than putting out fires.

A key to scientific success is bringing together the best in the field and giving them the opportunity to work together under one roof with the best tools and technologies. Through the years, the collaborative nature of science has become more prominent and more expected. No longer is science a singular exercise of one person in one lab, but an interconnected activity that reaches across lab benches and even across organizations, bringing together scientists from around the world.

However, true success in any scientific organization is based not just on the caliber of the researchers, but on the support system that is built around them. It is just as important to have a keen administrative team — including operations, facilities, information technology, human resources, external affairs, and finance — as it is to have world-class scientists. And, making sure that you identify, hire, and retain those with the right skill sets, as well as the right fit for your organization's unique culture, is equally important.

In scientific research, the management of science is often less to put constraints on these activities than to create opportunities, enable activities, and, most importantly, regularly question the directions that are chosen. Leadership runs through an organization from top to bottom, and providing opportunities and responsibilities for growth within an organization is very healthy. Growth will help people in the organization develop and stretch while creating an environment of success for both individuals and the organization.

LEADERSHIP SKILLS

Perhaps most important is the growth of leadership skills. Everyone in an organization should be in transition to some degree. In a dynamic and healthy-functioning organization, as people gain experience, their skill sets should be applied in different ways. Our organization thrives on healthy transitions. For example, the project manager for our BioQuest Academy, Seattle BioMed's hands-on summer immersion program for high school juniors, is a Ph.D. who was formerly one of our malaria vaccine researchers. By giving her room to grow and stretch, she's found a new way to apply her expertise, leadership skills, and passion.

Typically, in career progression for a scientist, the scope of opportunities is narrow but broadens over time. Scientists should be encouraged to reach out beyond their comfort zones to try something new. Developing skills in public speaking or advocacy, for example, can be enriching.

In the 35 years I've led Seattle BioMed, I find there are three critical areas for success: financial management, communication, and transparency. You may think these three areas wouldn't necessarily be the strong suit for most scientists, and I'd likely agree with you. A key is surrounding yourself with people who have expertise in these fields and learning from them. And use the expertise on your board. Seattle BioMed wouldn't be where it is today without the leadership and support of our board, particularly during critical times of growth and expansion. From those experiences, I learned a great deal, including skills that I now use daily.

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Selecting A CRO For Ocular Drug Development

The market for ophthalmology drug products presents significant growth potential for life sciences companies. In particular, the market for drugs developed for major ocular diseases is expected to grow from approximately $10 billion in 2011 to nearly $20 billion in 2014.

As the population ages, there will be an increase of people suffering from diseases such as age-related macular degeneration (AMD) and diabetic retinopathy that may be accompanied by macular edema and dry eye. In an era of declining revenue, fierce competition, and the need to quickly launch innovative products on limited budgets, pharmaceutical and biotechnology companies developing products for ocular diseases are seeking ways to improve research efficiency.

To reduce research time and costs, many life sciences companies are relying on highly experienced CROs for their ocular drug development studies. Partnering with leading CROs offers significant advantages, such as established ocular-disease animal models, expertise in developing new customized models and cutting-edge technology to thoroughly document and measure pathology in the eye. Integrated access to analytical services and toxicological expertise for drug and device safety assessments following compound selection and proof-of-concept studies using *in vivo* models shortens time along the development pathway. That leads to faster market entry and considerable cost savings.

OCULAR DISEASE MODELS

A variety of *in vivo* ocular disease models are available to screen for compound efficacy or establish proof-of-concept for treatment of or protection against diseases caused by metabolic disorders, unregulated inflammation, or neurodegenerative conditions such as wet or dry AMD. The rodent blue-light-damage model is characterized by photoreceptor and RPE (retinal pigment epithelium) cell death and shares many pathological features exhibited by patients with the photoreceptor loss of geographic atrophy associated with dry AMD. The light-exposed rat retina displays increased oxidative stress and deposition of inflammatory components at the retinal-RPE interface that is similar to the human AMD condition. The light-damaged retinas in these animals are characterized by both structural damage and functional impairment that can be assessed using noninvasive technologies applied at multiple intervals over the study duration.

State-of-the-art ophthalmic technologies to support ocular studies using animal models of retinal degenerative disease include the Heidelberg Spectralis platform for imaging ocular structures and the Espion E^2 electroretinography (ERG) platform to assess retinal function. The photoreceptor cell death characterizing the light-damaged rodent retina results in changes in retinal layer thickness due to cell loss that can be quantified using spectral-domain optical coherence tomography (SD-OCT). OCT provides for 1 to 3 μm resolution retinal layer measurements similar to histology, but without the requirement to harvest tissues. Analysis of retinal function by ERG demonstrates up to a 70% reduction in ERG amplitudes within days after completion of the blue light exposure. Fundus photography and retinal angiography using fluorescein and indocyanine green are additional retinal imaging techniques that allow visualization of the retinal tissue and determination of vascular health in various disease models for wet AMD, diabetic retinopathy, glaucoma, and other conditions.

Thomas Vihtelic, DVM, Ph.D.

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THE CRITERIA TO LOOK FOR

Life sciences companies looking to partner with a CRO for ocular drug development services should identify those with considerable experience and scientific expertise in conducting ocular studies. The CRO should provide both standard ocular assessments and specialized and customized services. Multiple ocular dosing routes, such as intravitreal, subtenon, and subconjunctival injections, in addition to the standard topical and systemic routes, should be offered. Expertise to perform detailed ocular tissue dissections to determine the ocular pharmacokinetics and pharmacodynamics of selected compounds will provide accurate dose selection and frequency of administration information for subsequent studies. Comprehensive clinical evaluations, including indirect ophthalmoscopy and slit-lamp biomicroscopy, should be available. Capabilities provided by bioanalytical and analytical services and thorough quality assurance allow the early discovery work using animal disease models to be efficiently followed by GLPs (good laboratory practices) safety assessments for IND (investigational new drug)-enabling and market entry of the product.

Adding Value To The Development Process:

Beyond Just Engaging a CRO

One of the greatest challenges facing life sciences companies today is the growing move to evidence-based medicine with a need to generate health outcomes data throughout the full drug or device development process. The so-called "value proposition" is increasingly important in guiding everything from the creation of protocols for registration for clinical trials to providing a clear indication of the value and benefit of medicines, vaccines, and devices, which affects pricing and uptake. This is a fundamental change from the way drugs historically have been developed. The change is being influenced by external and internal factors. The drive to limit ever-escalating healthcare costs is leading to a growing move to value-based pricing. Meanwhile, life sciences companies are struggling to cut the high costs of successfully developing and delivering new medicines and devices.

The current environment places a new, compelling need for life sciences companies to obtain, analyze, and demonstrate real-world evidence of the value of their products from discovery through clinical development and then on throughout commercialization. If done properly, starting early, this evolution in product development and commercialization can help ensure that life sciences companies realize the full value of their products throughout the full life cycle.

MISSING THE BIG PICTURE

Unfortunately, many life sciences companies of all sizes are missing the big picture by not taking a broad, comprehensive, global view of their regulatory and development (R&D) strategies, to focus on the needs of multiple stakeholders — regulators, practitioners, consumers, and payers. Too many companies continue to look at the R&D process in segments and not as a unified path to success. Many companies continue to engage CROs to help them execute the strategy, however fail to take advantage of the broader perspective that they might gain from working with an external partner that is able to bridge the strategic divide between drug development and commercialization/market access. A true strategic partner can bring more to the table, and can act as an advisor in both the design and execution of research that meets the needs of multiple stakeholders. There is a growing need for companies to have a comprehensive strategy in place that bridges the regulatory, development, and commercial marketing functions, to serve as a key driver for product development and decision support in all stages.

For companies looking for outside support from CROs, there is a danger in focusing on clinical trial design, and in the process, overlooking the market access objectives that they ultimately need to achieve. A true partner needs to be able to provide both input into the strategy and the ability to execute upon the strategy. Today, as life sciences companies are under mounting pressure to deliver and succeed in an ever-changing and increasingly competitive global economic and regulatory landscape, many, if not most, are likely to benefit from a more comprehensive approach to engaging and gaining from expertise that spans the full product development and commercialization time line.

It is important that companies start early on gathering the evidence to address the tough questions, including:

- How will a potential new entry differentiate itself from currently available therapies?
- What will drive its adoption by most patients, providers, and payers?
- What value does a drug bring to marketplaces?
- Will the development package be sufficient in and of itself to demonstrate value, or will there be a need for additional data and trials?
- What are the benefits related to current health policy, and what are the implications economically, as well as therapeutically?

Preapproval stage research is vital and sets the stage for late-phase, patient-focused outcome studies to further reinforce the values and benefits of treatment in evidence-based settings. Today, more than ever before, the life sciences development process does not end with regulatory approval and a marketing plan. While the three traditional hurdles to new product approval — safety, efficacy, and quality — remain in place, companies now face increased pressure to deliver post-marketing surveillance, earlier recognition of safety signals, and a rapid response to potential problems.

William Crown, Ph.D.

Dr. Crown is group president of health economics and outcomes research and late phase research for OptumInsight's life sciences group.

Three Tips On How To Be A Better Mentor

Rebecca Shambaugh

Being a mentor should not be taken lightly. In my experience, the best mentors gain as much from the process as those they seek to help. When mentoring your staff, it's important to help them look at what they might be doing, or not doing, to hold themselves back. There are a number of self-limiting beliefs, assumptions, and behaviors that hold people back from tapping their full potential.

Push People Outside Of Their Comfort Zones

People often stay in one role too long, based on the assumption that if they just continue to do a good job, people will see and recognize their great contributions. To avoid this, take an active mentoring strategy to push people outside of their comfort zone by doing the following:

- Lay the groundwork for future moves by helping to network your understudy and make their work/accomplishments, skills, and interests known to others.
- Continually check their marketability. Are they in line with others that are within the same level of responsibility and experience?
- Teach them to see risks as opportunities, so when one comes along that might be a stretch, they understand it in the context of *what is the worst thing that could happen*?

Embracing Good Enough: Perfectionism Versus Excellence

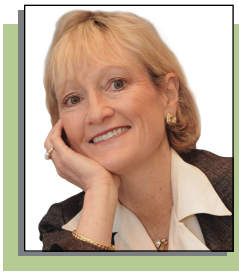
Perfectionism is always placing the same high standard for performance on everything you or your team does. We can lose sight of the priorities, as well as the important expectations of your company's future leaders — driving them to burnout. Strategies to avoid this while in a mentoring role include:

- Teach what the most critical tasks are and have the understudy put energy there. Most importantly, teach the concept of when to know a job has been done "good enough" — and move on.
- Seek and give feedback. Use it to calibrate your own performance standards as a mentor. Knowing the difference will allow you to manage your work better.
- Let go — delegate to your understudy the more detailed tasks and allow them to operate under the "good enough" standard of performance.

Making Your Words Count

Your credibility and power as a leader and mentor depend greatly on how others perceive you. Much of this is determined by how well you communicate. Making your words count is not only about what you say, but how you say it. Guidelines for making your words count as a mentor include:

- Be a person of few words. Provide a clear, concise message and then own that message.
- Know your audience. Do your homework before talking with someone and adapt your style to how they want to be spoken to.
- Speak up. If you have something valuable to say — speak up! Act confident, balance emotion with logic, present relevant facts and information, time your contribution, and have good information at your fingertips to back up your perspective.



A nationally-known leadership strategist, Rebecca Shambaugh has more than 20 years of experience helping organizations and executives respond to critical leadership challenges and opportunities in today's business environment. She is president and CEO of SHAMBAUGH, where she founded Women In Leadership and Learning (WILL), an organization dedicated to the research, advancement, and retention of women leaders and executives. Shambaugh is the author of *It's Not A Glass Ceiling, It's A Sticky Floor*. www. shambaughleadership.com.

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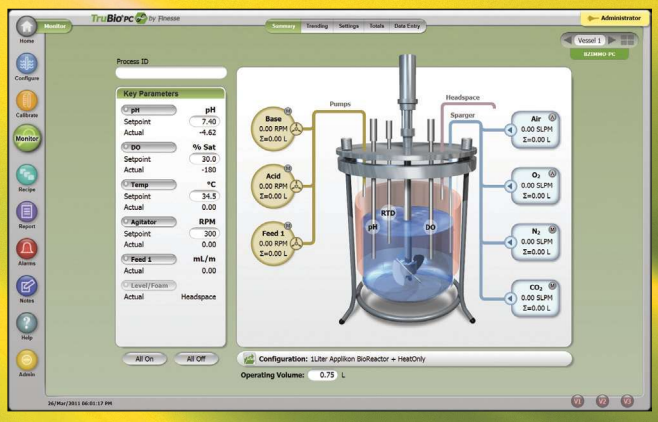

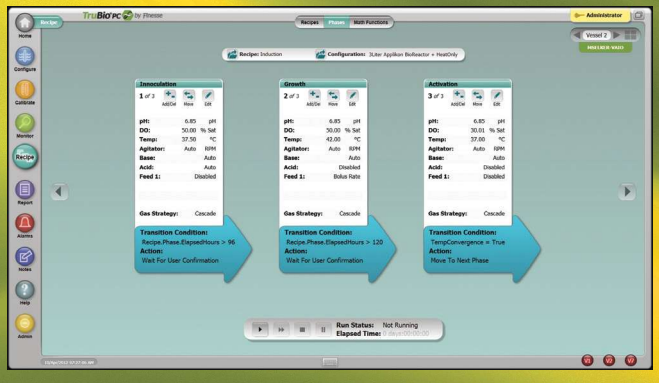

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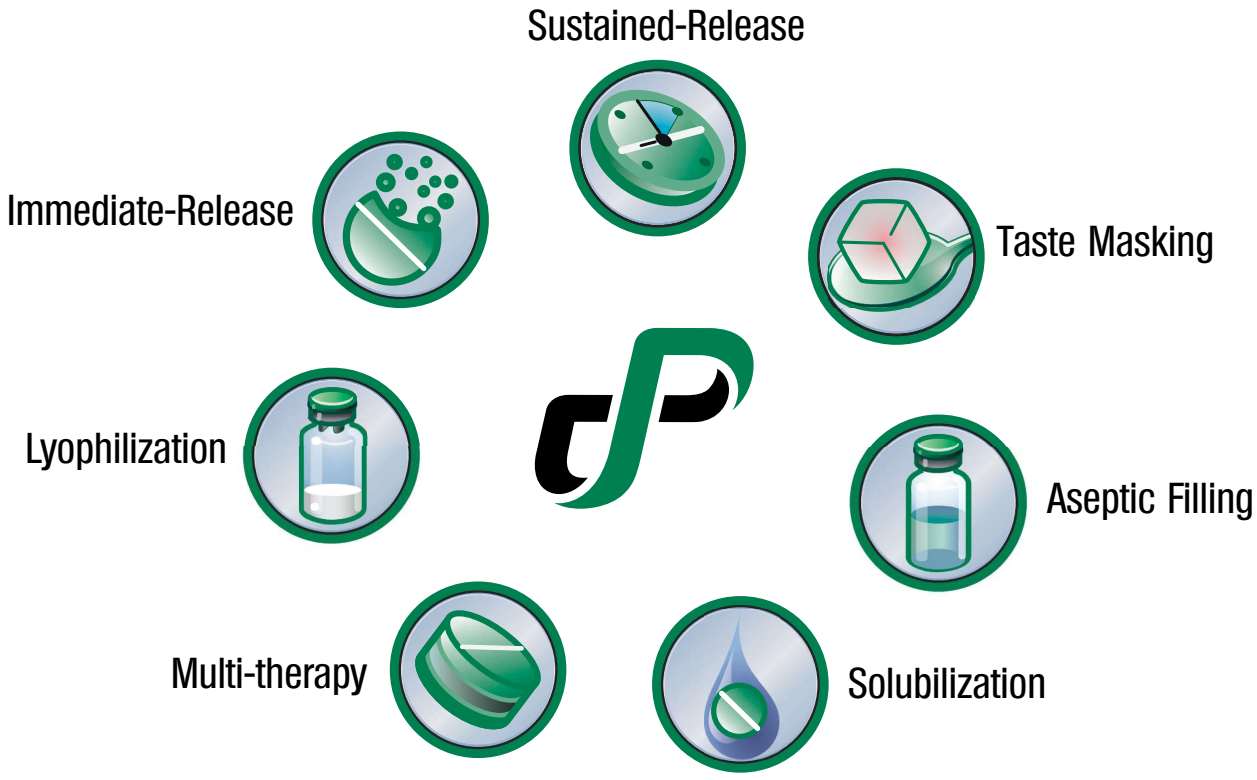

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