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FEBRUARY 2012
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How To Persevere Through Today's Funding Challenges

A conversation with G. Steven Burrill, CEO, Burrill & Company

"Without my capital, your ideas aren't worth a lot, and without your ideas, my capital isn't worth a lot." p. 16

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16 FEATURE: G. STEVEN BURRILL

"There is plenty of money in the world today to finance the companies that should be financed, and the challenge is that it's highly inefficient to get it."

February 2012

Life Science Leader

DEPARTMENTS

Correction: In the January issue on page 21 it should have stated that Komen raised nearly $400 million last year.

Welcome to *Life Science Leader*

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EDITOR'S NOTE

More Conferences, Old Acquaintances

After a short hiatus from traveling during the end of 2011, I got "back in the saddle" in January, attending two different conferences. The theme of both events revolved around getting drugs to market quicker — a consistent theme this past year and one that is sure to continue through 2012. The first conference focused on finding the fastest path to funding and regulatory approval, while the second elaborated on new drug delivery technologies, formulation strategies, and partnerships. One of the nice things about attending these shows is hearing a variety of perspectives on how to solve this longstanding problem.

Another thing I enjoy about attending these shows is the networking opportunities they provide for both new and old acquaintances. Speaking of old acquaintances, two of the folks featured in this month's issue I had met at past shows. When I first met Coreen Oei, Ph.D, she was working for GSK. Now she is serving as the SVP of clinical operation and project management with BeiGene, a China-based biotech start-up. I had the chance to sit down with her and Peter Ho, M.D., Ph.D, BeiGene's founder and president. I was curious to find out why Ho and Oei, both U.S. citizens and former Big Pharma execs, decided to step outside of their comfort zone to start a new company located halfway around the world in Beijing. Starting a new company is tough enough, but add to that the prospect of moving to a new country, where you aren't fluent in the language, and it makes for a very interesting and inspiring story (p. 24).

The other old acquaintance is G. Steven Burrill, whom Wayne Koberstein wrote about on page 16. Burrill has been with us since our early years, having graced the cover of *Life Science Leader's* June 2009 issue. When we asked if he would be willing to serve on our editorial advisory board, he graciously accepted. I recall having a discussion with someone at a show recently who doubtfully asked, "How really involved are your editorial advisory board members in providing industry insight?" In response, I opened the issue I had in my hand and pointed to "Ask the Board" — which has since become one of our most popular monthly features (p. 8). Throughout the year we receive a variety of industry questions from readers. I don't consider myself to be an expert in these matters, so rather than try to come up with a response, we decided to sort through them, pick out the best, and send them to the most appropriate board member for a response. We then publish the question and answer. In this month's issue we have responses from Burrill as well as Sequella's CEO Carol Nacy and former rocker now converted scientist, Jerry Martin, chairman, Bio-Process Systems Alliance (BPSA). Personally, I have found the section to be very informative, and I believe the board members would agree. But, I couldn't do it without you — our readers. So keep sending your questions to atb@lifescienceconnect.com and remember — the only stupid question is that which is not asked.

Rob Wright
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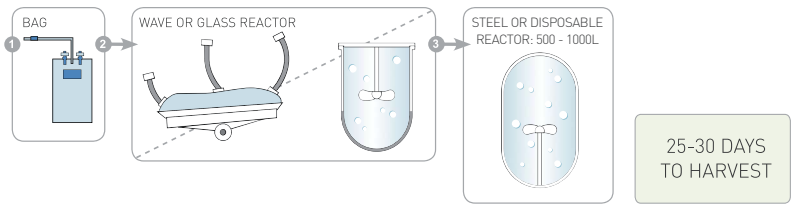

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CHIEF EDITOR'S BLOG

Our Chief Editor, Rob Wright, has been pondering naming his blog. How about "Rob's Rants" or "Wright Writes?" Or, maybe you have a good idea for a name. If so, send him an email at rob.wright @lifescienceconnect.com. He writes about a variety of issues such as recent shows attended, conversations with industry experts, and irritating business buzzwords. And don't forget about your opportunity to pick the brains of our editorial board. Send your questions for our monthly "Ask the Board" section to atb@lifescienceconnect.com.

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ASK THE BOARD

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

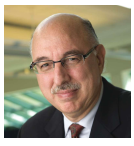
Q: How do you create and sustain an innovative environment?

Innovation is driven by vision, opportunity, opportuneness, passion, risk, and reward. To create an innovative environment one must encourage visioning — you must see what others don't — a view of the future and of the underlying market needs. And, one must foster an environment where taking a chance is encouraged as part of the innovation cycle. You must require opportuneness — the willingness to seize on opportunities that might be real. And, you need to create an environment where, while risk is always there, failure is not penalized and rewards are real, often thru equity. Incentives work, and to have successful innovation, economic participation in the rewards are critical. Finally, innovation is driven by passion — passion to create things not previously created, passion to take a chance, passion to work 24/7 to make something happen, passion to excel, and passion for life.

G. Steven Burrill
Burrill founded Burrill & Company as an extension of his 40-year involvement in the growth and prosperity of the biotechnology industry. He has been an active advisor and catalyst in some of the industry's most notable companies and transactions.

Q: Is it advantageous first to develop a Six Sigma Green Belt/ Black Belt team to diagnose and tackle areas of opportunity, or is it best to focus holistically on continuous improvement and transform the culture?

I have a gut preference for the latter, as I believe it is difficult for even Six Sigma Green/Black Belts to be unbiased, tending to focus on their areas of familiarity or interests of the team leader over other areas where problems should be addressed. Plus, if they are not a permanent function, once they achieve whatever goals are set, problems are allowed to rise to a level that demands their reinstatement. In contrast, a culture where participants have a common language for continuous improvement, have basic problem-solving skills, and are empowered to apply them, can yield significant, ongoing results.



Jerold Martin
Martin is senior VP, global scientific affairs for Pall Life Sciences and chairman of the Bio-Process Systems Alliance (BPSA) single-use biomanufacturing trade association. He has more than 32 years experience in the biotech and pharmaceutical industry.

Q: How do you measure innovation in your organization?

We look for new ways to do routine tasks that improve a regulated process, so the definition of innovation is in the eye of the beholder. Since drug development is such a tightly regulated industry, there are times when innovation is totally inappropriate. However, I encourage my scientists and developers to think strategically about what we want to accomplish and then plot a course that gets us there with the least time and cost and the most assurance we will achieve our goal. Inevitably, the discussions around time, cost, and goal result in new and novel actions that we might not have thought about had we just followed the paths others forged in our business. But, innovation MUST be underpinned by excellent conceptualization and strong science to make an effective case for doing something different. Otherwise, the innovation will be rejected by the various regulatory groups that provide oversight of our development activities, and rightly so.

Carol Nacy, Ph.D.
Dr. Nacy is CEO of Sequella, Inc., a private company that develops new antiinfective drugs. She was formerly CSO at Anergen and EVP/CSO at EntreMed. Prior to her business experience, Dr. Nacy directed research in tropical infectious diseases at Walter Reed Army Institute of Research, Washington, D.C.

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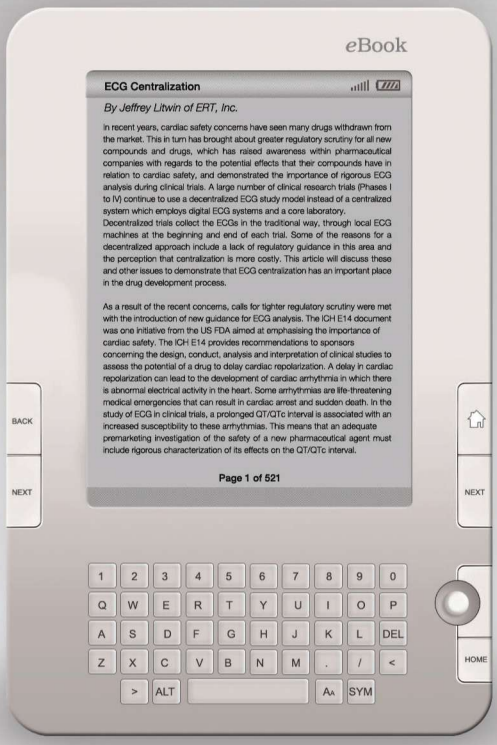

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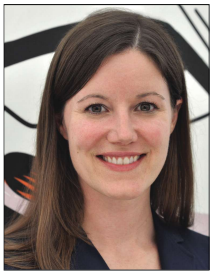

OUTSOURCING INSIGHTS

Key Drivers For Outsourcing Partner Selection

By Kate Hammeke, research manager, Nice Insight

Each business has its own approach to outsourcing, from functional to full service, and often that approach is dependent on the requirements of a specific project. While needs change and outsourcing practices evolve, there are several fundamental traits that have shown their relevance when selecting a partner. Preliminary research through in-depth interviews with industry professionals helped Nice Insight generate a list of attributes that drive outsourcing decisions and uncover how and why these attributes impact partner selection. Each quarter, Nice Insight surveys the pharmaceutical and biotechnology industry and asks that respondents rank these traits in order of importance.

The six most influential attributes driving partner selection in 2011 were: quality, reliability, affordability, regulatory track record, productivity, and accessibility.

QUALITY AND RELIABILITY

Quality and reliability held the number one and two positions respectively throughout the year, showing the importance of delivering to the standards established by the sponsor of the project as well as meeting the agreed project milestones and timelines. Contract businesses fared well within these measures, establishing a benchmark rating for CMOs and CROs at 70% for quality and 69% for reliability. When selecting a full-service partner, look for businesses that score at or above the industry average/benchmark on these attributes.

AFFORDABILITY

Affordability, or how competitively and accurately a contract organization prices a project compared to other bids within the market, ranked fourth in Q1. However, affordability was ranked as the third most influential driver during the Q2, Q3, and Q4 surveys. As such, affordability ranked third overall for 2011. Again, CMO and CRO benchmark scores were similar, in that the average affordability rating for CMOs was 68% and 69% for CROs.

REGULATORY TRACK RECORD

The contract organization's regulatory track record ranked third in the Q1 survey, but dropped behind affordability and productivity to fifth in Q2 and Q3. Perhaps related to several high-profile contract manufacturers receiving 483s in the latter part of the year, regulatory compliance moved up in rank to fourth place in Q4. The aggregate ranking across all four quarters for regulatory positioned this driver in fourth place for 2011. Across each of the outsourcing drivers, CROs and CMOs scored the highest in regulatory, each averaging at 73% to set the benchmark.

PRODUCTIVITY

Productivity links closely to innovation, as CMOs or CROs that score well in this category have demonstrated the ability to allow the sponsor to focus on core competencies while trusting that the agreed technical objectives for the project are being fulfilled. Interestingly, productivity was ranked fifth in both the Q1 and Q4 surveys and fourth in the Q2 and Q3 surveys. The benchmark for productivity was 71% for both CMOs and CROs. Productivity received the second highest benchmark score out of the six outsourcing drivers.

ACCESSIBILITY

The final driver in facilitating collaborations speaks to the communication challenges iterated by pharmaceutical and biotechnology sponsors. Accessibility, or knowing that personnel will be available when needed, ranked in sixth place across all four quarters. While accessibility may have ranked last among these six attributes, it is still an absolute essential for a strong (and long-lasting) outsourcing relationship. Especially considering that a "lack of support" and "waiting to inform [the sponsor] of a potential problem" are frequently cited as reasons to discontinue a contract relationship. Fortunately, the CROs and CMOs rated in the Q4 survey have established a strong score for the accessibility benchmark, both at 70%.

Whether it is time to review the CROs and CMOs on the preferred vendor list, or there are plans to enter into a relationship with a new contractor in the coming year, benchmarks can help provide context on how the industry performs — and offer assurance that the contractor selected has been meeting or exceeding the industry standard. When considering a full-service partner, it is essential to evaluate how the business scores on each of the outsourcing drivers as a whole. Knowing how satisfied industry peers have been with their outsourcing partners can help serve as a guide.

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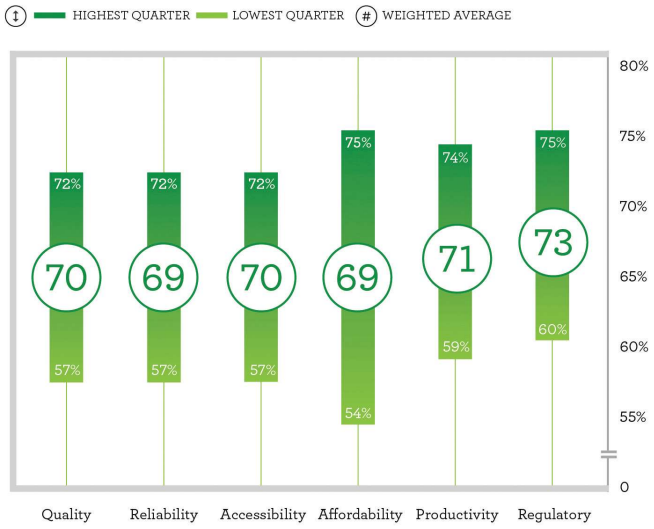
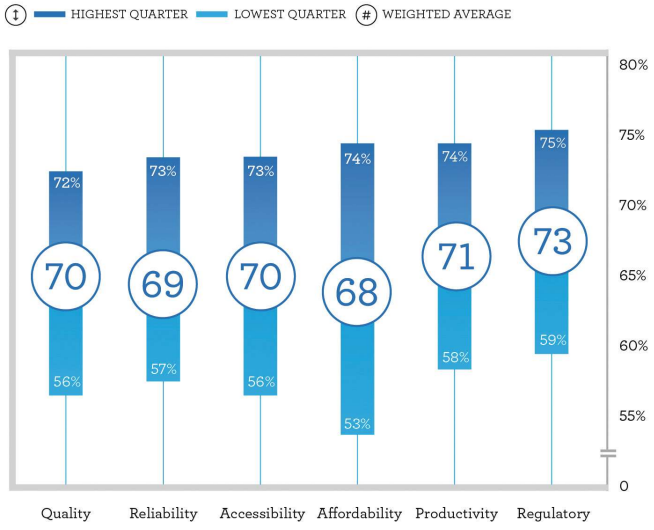
NI 2011 CRO Driver Benchmarks



NI 2011 CMO Driver Benchmarks



Survey Methodology: The Nice Insight Pharmaceutical and Biotechnology Survey is deployed to 40,000 outsourcing-facing pharmaceutical and biotechnology executives on a quarterly basis/four times per year [Q3 2011 sample size 3,021]. The survey is composed of 1,200+ questions and randomly presents ~30 questions to each respondent in order to collect baseline information with respect to customer awareness and customer perceptions on 406 companies that service the drug development cycle. Over 1,600 marketing communications, including branding, websites, print advertisements, corporate literature, and trade show booths, are reviewed by our panel of respondents. Five levels of awareness from "I've never heard of them" to "I've worked with them" factor into the overall customer awareness score. The customer perception score is based on six drivers in outsourcing: Quality, Accessibility, Regulatory Compliance, Pricing, Productivity, and Reliability, which are ranked by our respondents to determine the weight 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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BIO DATA POINTS

Biopharma Manufacturers Look For Product Innovation

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

Biopharma manufacturers are increasingly vocal about the new product development (NPD) areas they need to increase productivity and improve quality. The top three areas of NPD interest among biomanufacturers and CMOs this year were related to single-use solutions. This was led by "disposable product: purification," cited by almost two in five respondents, according to our 8th *Annual Report and Survey of Biopharmaceutical Manufacturers*. Within this area, slightly more CMOs are demanding new products. Of the 21 new product areas we measured, the next hottest, with more than 1/3 of the 350 qualified respondents, were improved disposable products: bags, connects, etc., and disposable product: probes, sensors, etc.

But, single-use devices are not the only hot items. Also on the list of nearly two dozen opportunities, and showing up in fourth position, was "analytical assays." This is partly due to increased interest in monitoring process improvements, but also as a means to develop biosimilars and demonstrate biologic comparability at different facilities. Disposable bioprocessing equipment is in high demand partly because innovation in these products has been slow in coming. For example, 29.2% also noted a desire for improvements in bioreactors. By comparison, only 6% sought innovations in fixed stainless steel bioprocessing equipment.

Looking at trends in demands for new products from vendors, we found some significant shifts from last year. Interest in better innovation in disposable, single-use devices for measuring and monitoring (probes, sensors, etc) grew from 29.3% of respondents to 37% over the past year. Further, interest in assays increased from 24.5% of respondents to 31.1%.

Areas that declined in interest included: chromatography products (36.7% down to 29.7%) and process development services, both downstream and upstream (down by as much as 10 percentage points). Cell culture media also dropped roughly 5 percentage points.

BIOPHARMA VENDORS DOING THEIR PART

The annual survey also separately evaluates spending and new technology development among hundreds of biopharma suppliers. When we match up where vendors are investing their R&D efforts in 2012, we find, from preliminary survey data, that most vendors' budgets are growing significantly and are aimed at the very areas that biomanufacturers demand. This year, of the 38 new product areas that vendors are developing, the top areas are included in figure 2.

We note that the 2012 data is preliminary and may change with additional data collection. It is clear that, although the overall percentage of vendors working on specific new product areas has declined slightly, the overall efforts remain substantial. The top groupings continue to align with the industry's explicit demands, including areas associated with downstream processing, chromatography, and single-use downstream devices.

BIOPHARMA'S BUDGET TRENDS

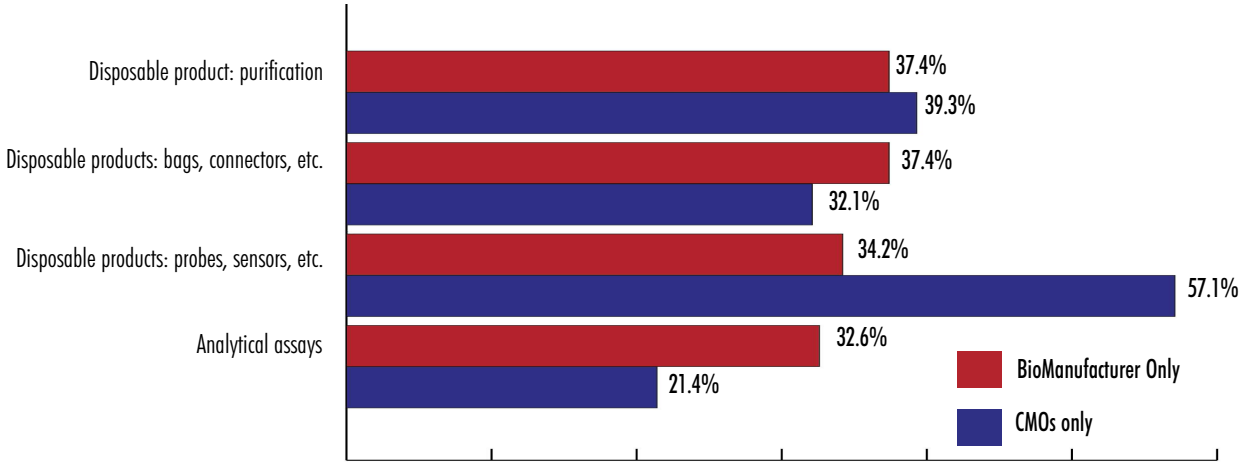
Budgets are a good indicator of industry strength. And budget estimates for 2012 are, once again, up strongly for acquisition of new technologies, capital equipment, and training. In fact, early returns from respondents to BioPlan's 9th *Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production* are projecting increases in all 12 areas measured in 2012, except for outsourcing. This budget bump clearly indicates a healthy continuation of investment and spending trends seen over the previous three to four years. Spending this year, in particular, is occurring in:

- new technology
- capital equipment
- process development and optimization
- personnel training and development.

Across all departments, both budget trends and R&D/NPD efforts are leading indicators of economic constraints loosening. This is especially evident in areas of expenditures that improve process performance. Our annual survey documents and analyzes how the rebounding and maturing biopharmaceutical industry is moving forward despite recent global economic challenges.

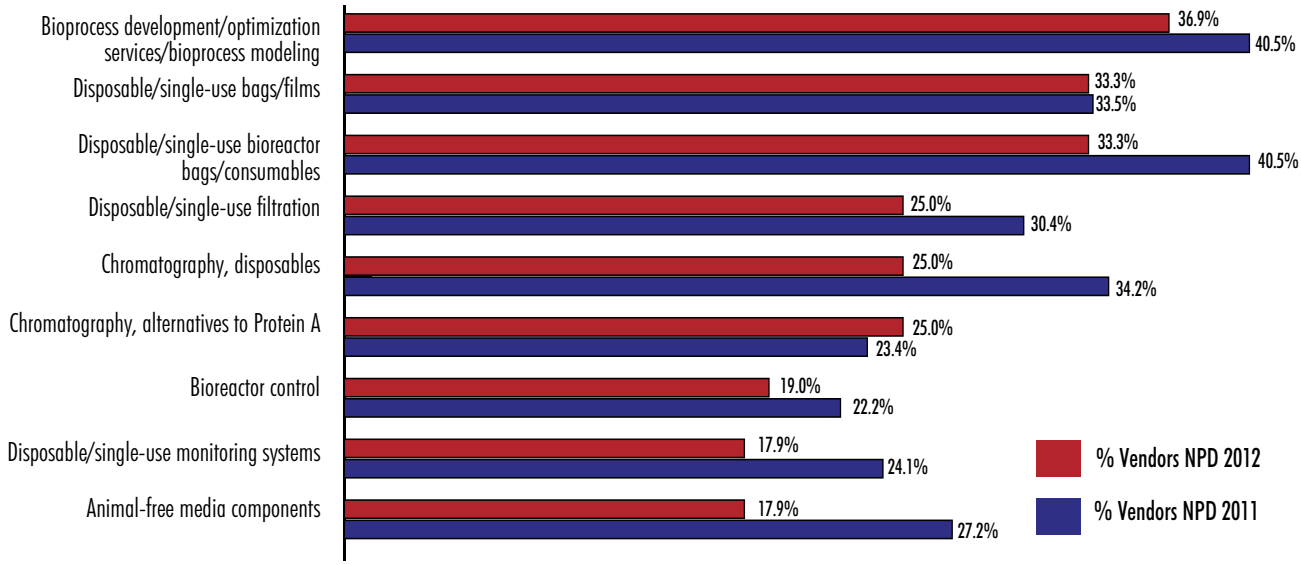
New Product Development (NPD) Areas Of Interest

Biotherapeutic Developers vs. CMOs



Source: 8th Annual Report and Survey of Biopharmaceutical Manufacturing, April 2011, BioPlan Associates, Inc. www.bioplanassociates.com

Selected New Vendor Technology Innovations And NPD



Source: 9th Annual Report and Survey of Biopharmaceutical Manufacturing, Preliminary Data, Release Date April, 2012, BioPlan Associates, Inc. www.bioplanassociates.com

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

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

"Partnering is different now; the big companies can get it cheap, and you can do some risk-sharing with them."

Photos by Daniel S. Levine

Life Sciences Funding:

Thriving Through The Storm

An Exclusive Interview with G. Steven Burrill

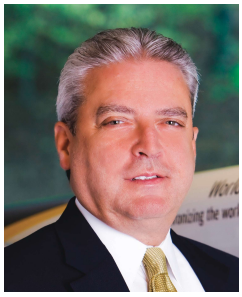
by Wayne Koberstein,
contributing editor

TO EVERY CHALLENGE NOW FACING BIOTECH THESE DAYS — EVERY TALL WAVE IN AN IMPERFECT STORM OF INVESTMENT AND PARTNERING ADVERSITIES FOR SMALL COMPANIES — STEVEN BURRILL HAS AN OVERARCHING RESPONSE: GET CREATIVE. It is quite the opposite of a pat answer; it is a call for companies to persevere in seeking individual solutions, despite the risk-averse and buyers-market conditions they now face among venture capital and Big Pharma investors.

Burrill's boosterism runs counter to current industry headlines, including some in his own Burrill Report, bemoaning the flight of VC capital and tough-minded partnering practices of pharmaceutical companies. But he insists his point is not to deny that adversity exists, but to believe the same entrepreneurial spirit that gave life to the life sciences industry will save it — and may in fact leave it stronger. Such an evolutionary approach to biotech's survival is inherently chaotic, imperfect, and, in Burrill's word, "inefficient." But in biotech as in biology, evolution is the only way forward.

Grand visions notwithstanding, Burrill's views and solutions match the times, an extended period of unfavorable economics that makes investors jumpy even as it gives them a leg up in deal-making. Everyone in the game seems acutely aware of dysfunctions in the current system of managing risks and funding innovation. But a discussion of broad reforms, aimed at improving the system for everyone's benefit, may seem like an unaffordable luxury.

Burrill does not dispute that small companies remain at a distinct disadvantage in securing investment and partnering deals, especially to fund late-stage development. And with looming cuts to government funding, basic research



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.

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seems threatened as well. His view: Harm is inevitable given an already inefficient system, and — pragmatically assuming that VCs and pharma companies will achieve no greater wisdom any time soon — the small companies must find inventive ways around the harm to the benefits beyond. Not only can companies survive the storm, he asserts; they can thrive in it by putting their faces to the wind.

"The big companies can no longer pump money into their internal labs and generate blockbusters, so they will continue to shop through the biotechs as a more efficient vehicle."

WITH START-UPS AND SMALLER LIFE SCIENCE COMPANIES CAUGHT IN A TOUGHER PARTNERING AND INVESTMENT ENVIRONMENT, IS BIOTECH IN AN UNPRECEDENTED CRISIS, AND IF SO, HOW SERIOUS IS IT?

First, I don't think we're in the middle of an unprecedented crisis. There is plenty of money in the world today to finance the companies that should be financed, and the challenge is that it's highly inefficient to get it. I'm not trying to be naïve. No question, there is complexity in applying for early-stage capital, in going through the capital rounds, in taking companies public, and in the already public companies. But that doesn't mean you can't find capital or be creative in the use of capital. It doesn't mean that the R&D engine is dead or that we are defeated by the global economy and the extent of our public debt. There are still so many diseases that are poorly treated and extraordinary opportunity to take technology and solve many of the unsolved problems. A confluence of technology is changing the nature of some solutions; I can put my iPhone on my chest, and through my shirt, I can get my EKG. There are many possible answers to how healthcare will evolve, how we will diagnose and treat, and how we will move from a dysfunctional sickness-care system to an increasingly effective wellness-care system.

IF I'M STARTING UP OR RUNNING A SMALL COMPANY, WHAT ARE SOME OF THE REALITIES I MUST EXPECT TO DEAL WITH IN LOOKING FOR INVESTMENT CAPITAL?

We see 100 or more deals a month, and we say no to 99 out of 100. So if you are a small-company executive, you must know this is a business for the tenacious. Of course, I hope I see and fund the right deals. But I don't see every deal in the world or always have the absolutely perfect deal come to me at the perfect time and price. So efficiency is a big issue, but the lesson is to be tenacious as hell. Capital is clearly more expensive than it's been, but not too expensive to make deals. You need my capital, and I need your company. Without my capital, your ideas aren't worth a lot, and without your ideas, my capital isn't worth a lot. So, the two of us ought to be able to come to terms acceptable to both of us, so that you can start or build a company. Yes, there are intrinsic gaps in the system; it's a lot easier to get money if you've proven efficacy or have proof-of-concept (PoC).

WHAT WOULD BE SOME BETTER VEHICLES FOR FUNDING SMALL OR START-UP LIFE SCIENCES COMPANIES IN THE NEW ENVIRONMENT?

I've been doing this for 45 years, and we have always found new vehicles that create pools of capital to meet these gaps when they occur. I've looked at each of those challenges as a great opportunity, not a gigantic, unsolvable problem. Now we may go to more consortiums for precompetitive research, we may see the NIH partnering with the private sector to replace the lost support from the public sector, or there may be more tax-based incentives. There are plenty of places around the world that are trying to use their capital to recruit companies to build their economies and create jobs. The big companies are looking increasingly to the academic world to replace NIH funding with corporate funding. Maybe short term we will see more funding of applied research than basic research in the United States, while the Chinese do more basic research. There are still a lot of people who lost Aunt Martha to breast cancer and want to invest in breast cancer research. So we may find the angels, celebrities, and patient advocacy organizations spending a lot more of their money on research for the disease they care about. There are new structures and new capital sources available every day.

BUT ARE THOSE SOURCES SUFFICIENT TO FUND THE MOST PROBLEMATIC PART OF THE BUSINESS — CLINICAL DEVELOPMENT?

Let's not just assume that we will always be going through a lengthy development process. We're going to change the way

clinical development happens and how we gain access to markets. Maybe we don't go the FDA route first; we go to the market in Brazil or China or Timbuktu, we get our product revenue from that business, and then we come to the U.S. market after we get more clinical experience. There are lots of ways that we will build companies differently from how we did it 40 years ago, when you could go through the rounds, get PoC, and go public. That is not a model that works today. It doesn't mean you can't develop technology. Funding development is more challenging, it puts a reward on the creative, but the game is not over.

IN PUSHING FOR TOUGHER DEAL TERMS, HAVE BIG PHARMA COMPANIES CREATED AN ASYMMETRIC SITUATION THAT PUTS SMALL COMPANIES AT A DISADVANTAGE?

Partnering is different now; the big companies can get it cheap, and you can do some risk-sharing with them. Big Pharma is bifurcating its partnering between early-stage and late-stage opportunities. It is looking for new vehicles for value creation. The big companies can no longer pump money into their internal labs and generate blockbusters, so they will continue to shop through the biotechs as a more efficient vehicle, and that's good for us. About 10,000 companies out there have announced plans to go public or do a big partnering deal — not all 10,000 companies achieve those goals, but that doesn't mean that all will fail. Many of the companies will change their business models, and scientists from some of them will win the Nobel prize, and some will discover the cure for cancer, and some may fall through the bottom. But over time, the biotech universe has gotten bigger, not smaller. We have more biotech or life sciences companies today than ever before. To some extent, the power in the value equation is still shifting from the big companies to the small companies.

WHAT ARE SOME NEW BUSINESS MODELS THAT SMALL COMPANIES MIGHT EMPLOY TO DEAL WITH THE TOUGHER FINANCING ENVIRONMENT?

One, companies have to compete more globally. Let's say you spin your rights to a Brazilian investor who will take those rights and

accelerate your commercialization in Brazil but provide you with nondiluted capital to do what you want to do in this country. Two, you can use a model such as an accelerator (i.e. non-VC investors offering a combination of guidance and money in exchange for a small interest in a company) to help determine whether you form the company on day one or after you get past PoC. Maybe there's a better thing to do than form the company; maybe you sell the program to a big company at that point and monetize your investment in the research. Three, your company should have a balanced team of people with varied backgrounds bringing more micro-creativity into solving each problem. Real innovation and problem-solving tends to happen more in smaller companies, which can rely on the sweat equity of their people because they have some skin in the game. Four, use virtual resources. There may not be enough available capital these days to start with a big office and a bunch of people, so maybe you start with an idea, identify the white-hot risks that you need to eliminate, and find some capital to eliminate the risks — then it's easier to fund your company because you have created some real value.

Capital is clearly more expensive than it's been, but not too expensive to make deals.

AMGEN AND WATSON RECENTLY STRUCK A $400M CANCER BIOSIMILARS PACT. DO SUCH DEALS MEAN THAT, IF BIOTECH CAN'T LICK BIOSIMILARS, IT'S READY TO JOIN THEM?

There is a lot of technology going off patent, and there will be biosimilars. The secret sauce is in how we make them, not necessarily what they do, and we need a clear clinical pathway for getting biosimilars to the marketplace. But I don't think the big pharma companies or big biotechs will just hand it over to a new industry; they will be creative in hanging onto the products. Even if it leads to unusual alliances, they will find a way to provide biosimilars that meet the market needs, not just wait for some company to charge in and take the market share away. We were just bankers for Samsung on a big deal in biosimilars with Biogen Idec. It would be difficult to imagine that one of the biggest electronics companies in the world could even spell biosimilars, nonetheless be willing to spend $300 million to be in that space. But lots of people outside of the traditional world see the problems and opportunities differently from people in the industry.

CONGRESS IS CUTTING THE NIH AND OTHER FEDERAL HEALTH RESEARCH BUDGETS. IS THERE A DANGER THAT THE UNITED STATES COULD LOSE ITS LEAD IN BIOTECH RESEARCH AND INNOVATION?

It is true that spending on R&D is going up in China and going down in this country. But out of all that turmoil still comes good opportunity, as well as capital to chase that opportunity. We are still going to create great companies with great opportunities. There is no question that this country has benefited from federal spending on health-related research. The "D" that represents innovation in this country has been a function of the "R" that has been funded with public-sector support. A lot of the support flows down to the academic world and local communities, and into technology for building the companies of tomorrow — though I don't think that people in general correlate their tax dollars with such benefits. We have to invest in our future in order to have a future, and I don't believe the game is over because the NIH budgets may be cut. Still, in all of the healthcare-reform dialogue, very little of it is correlated to research spending. The way we can solve our healthcare problems is by investing more in research, not less.

ARE YOU HAPPY WITH THE DIRECTION THE FDA IS MOVING UNDER ITS PRESENT LEADERSHIP WITH COMMISSIONER HAMBURG?

Peggy is doing a wonderful job, though she has a dramatically underfunded agency relative to her needs. She has been dealt a tough deck, given what the FDA is expected to do — keep the food supply safe and get all of the right drugs and medical devices onto the market. And of course, there are the big issues such as how to build inside the agency the kind of science it needs to stay in touch with scientific advances on the outside, what role does the FDA play in mobile health and the new generation of diagnosis and diagnostics, and how it can help put personalized medicine into practice. With pharmacoeconomics, we're not just trying to evaluate safety and efficacy but treatment efficiency, to increase value, reduce cost, and improve outcomes. That's going to make the regulatory role even more challenging.

WHAT IS YOUR APPRAISAL OF THE NEW INITIATIVE BY NIH DIRECTOR FRANCIS COLLINS TO "MOVE BASIC DISCOVERIES INTO THE CLINIC?"

Francis is trying to do some interesting things. He has a lot of bureaucracy around him without a lot of flexibility, and there are those who think he's doing something that the private sector can do more effectively. But he is trying to find a way to do translational medicine, so I'm not uncomfortable with the experiment to see if he can make some progress in that area.

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Building A Biotech In China

BY ROB WRIGHT

The BeiGene staff with Peter Ho (center with gray turtleneck and arms crossed), M.D., Ph.D., founder and president, and Coreen Oei (maroon jacket to the right of Dr. Ho), Ph.D., SVP of clinical operations and project management

Pharmaceutical and biotech companies are looking to emerging markets as the next frontier for drug development, discovery, and perhaps, the next breakthrough. The emerging markets are hot, and the BRIC countries — Brazil, Russia, India, and China — even hotter when it comes to drug development. Though all are important, when you consider the size of China, ranking fourth in geographical size, first in population, and second with regard to gross domestic product (GDP), it is easy to see why pharmaceutical and biotech companies are tripping over themselves to establish a presence there.

Of the top 50 pharmaceutical/biotech companies in the world, not one can claim to having been started in China — yet. Previous models of entering China's pharmaceutical industry have focused on bringing Western ideas to the East. One company, BeiGene, is taking a slightly different approach — a combination of the best of both worlds and starting from scratch by being founded in China, Beijing to be specific. All of its four founders have worked, lived, or had extensive training in the United States. Two members of the BeiGene management team, Peter Ho, M.D., Ph.D., founder and president, and Coreen Oei, Ph.D., SVP of clinical operations and project management, took time out to explain why they see China as the place to be for launching a new biotech company.

FROM EAST TO WEST AND BACK AGAIN

Ho was born in Taiwan and moved to the United States at the age of 4. He completed his college, graduate, and medical education at Johns Hopkins, Yale, and Harvard. Oei, on the other hand, was born in Singapore and moved to the United States upon completing her Ph.D. at the Institute of Molecular & Cell Biology. Their combined resumes are impressive and include stints with the FDA, the National Cancer Institute (NCI), Howard Hughes Medical Institute, Duke University Medical Center, Dana-Farber Cancer Institute, Novartis, GSK, and J&J. Oei has lived in the States for nearly 20 years. Both are U.S. citizens, which makes you wonder — why would two highly successful former Big Pharma executives jump at the opportunity to start a biotech company halfway around the world, and in a communist country no less? For Ho, the decision to build BeiGene in China was not about the money, but the need.

WHY CHINA — WHY NOW?

It is evident that China has been growing economically. However, many people might not be as aware of other areas in which China has seen dramatic growth. For example, in the past 30 years, China's cancer death rate has risen by more than 80% and is expected to continue to rise as a result of the high rates of tobacco usage, dietary changes, environmental conditions, and an aging population whose life expectancy has nearly doubled to 71.1 since 1949. According to Ho, many prevalent cancers in China are not as common in the United States or Western Europe, and as such, don't get the same attention. Ho has held an interest in oncology drug discovery his entire career, having completed a fellowship at the Dana-Farber Cancer Institute, as well as having served as a senior investigator at the National Cancer Institute. But his interest in treating cancer is personal. "One of the reasons I went into the whole area of drug discovery/drug development was when I was in medical school, my mom was diagnosed with breast cancer. So, I witnessed what a loved one goes through when they are getting chemotherapy treatments," he states. Later, Ho's mother developed a second cancer, nasopharyngeal carcinoma, which is fairly common in southeast China and very uncommon in the United States. It was difficult to find experienced physicians to treat her. "It spurred me to try to do something about it," says Ho.

In addition to the unmet medical need in China, both Ho and Oei are driven by the excitement of the multiple challenges inherent in building a start-up organization. There is the challenge of creating a small, nimble organization that, by virtue of not having all of the resources of a Big Pharma, must quickly and efficiently conduct the critical experiments, both in the lab and in the clinic, to determine which drug candidates have the greatest potential. There is the challenge of raising the external funding, hence external validation, to support their vision. And finally, there is the challenge of discovering and developing new drugs for China's rising cancer patient population. Ho sees China as being much more fertile for putting these elements together for building a biotech versus going someplace else where the landscape is not as mature, or in the case of the United States, overly mature.

SOME DIFFERENCES IN WORKING/LIVING IN CHINA

What was the biggest surprise about working in China?

Oei: Beijing is a city with 20 million people and 5 million cars. This means that traffic congestion is very challenging at most times of the day and not just during the rush hour as we know it in the United States. I have also been very surprised by the prevalence of stores that carry luxury branded goods in many of the malls in Beijing.

Ho: No question that traffic in Beijing has to be experienced to be believed. It is far worse than any in the world that I have ever experienced. New York and Los Angeles cannot hold a candle to traffic in Beijing. Also, though not a surprise, it remains a sobering reminder that the pace of modernization in China is unlike any elsewhere. This affects all aspects of everyday life including architecture, urban infrastructure, diet, fashion, technology, jobs, and recreation.

What hobbies do you have that have been altered by living in China?

Ho: My primary recreation is running. While I enjoy running outdoors in the United States, the traffic, urban environment, and air quality in Beijing are not the most hospitable for long-distance running. So, I have learned to run 10 and even 12 miles on the treadmill while watching repeated episodes on CNN or Discovery Channel.

Oei: I love to bike and walk outdoors in North Carolina where there are plenty of outdoor spaces and parks close to where I live. In Beijing, it has been difficult to be outdoors a lot, but we are very fortunate to live in an apartment complex with a well-equipped gym. So I am able to adjust my workout by using the treadmill and exercise bike.

For Oei, there was yet another reason for her to leave her senior position at GSK — the need to be reenergized. Prior to joining BeiGene, she experienced feelings of "corporate grief" — where she saw many of her colleagues who were previously excited about their jobs in Big Pharma just going through the motions at work due to the upheaval and changes in the pharmaceutical industry. Even though her team had recently delivered a successful proof-of-concept study for a compound that has since transitioned to late-stage development, something still seemed to be missing. "When Peter asked me to be part of starting an oncology biotech company in China, I was excited at the opportunity to work with him again," explains Oei. (Having previously worked with Ho at GSK, she had a great deal of trust and respect for him as both a friend and colleague.)

IF YOU WANT TO BE IN THE GAME, GO WHERE THE ACTION IS

There is another reason why it makes sense to build a biotech in China. Watching a sporting event on television is very different from seeing it live, and neither can compare to the athlete's experience of being down on the field competing. If you want to truly be in the game, you need to be where the action is. Technology cannot replace the importance of being on-site when conducting a clinical trial. Ho explains, "If I'm sitting in the United States and managing global development, what goes on in China or Asia represents a small fraction of my daily demands." Ho feels it is difficult for anyone to give a clinical trial the same level of attention when directing it from a distance as compared with being in the country where the trial is taking place. By being in country, Ho believes BeiGene can do a better job conducting clinical trials in China. "Being there, physically, on the ground with our staff, brings us closer to the investigators who are actually running the trial," he clarifies. This benefits the team by bringing them closer to the data, which improves communication between members of the project team and clinical persons, allowing for better and faster interpretation of the data and enhancing the team's ability to operationalize the results. Another benefit of having the company truly operational in the country where the trial is being conducted is greater clinical trial participation. "One measure of success is sample collection," explains Ho. "In the short time we have been in existence in China, we have already collected more than 100 samples from patients through hospital collaborations. That's a lot more than I was able to do in prior settings while sitting in the United States," he states matter-of-factly.

LANGUAGE SKILLS MATTER BUT NOT A DEAL-BREAKER

Many of the employees who are working at BeiGene, such as Oei, were handpicked by Ho or other members of the leadership team, based on having previously worked with them. Ho advises that if you are going to ask people to join your team and make great sacrifices, such as moving halfway around the world, be sure to put procedures in place to help them through the transition process.

At BeiGene most of the employees are "returnees," while around 15% could be considered expatriates from other countries. By keeping the percentage of employees who lack native language and cultural experiences fairly low (20% to 25%), there are plenty of folks who can help on both a personal and professional level (e.g. how to set up a bank account, how to get a credit card in China). "The business of the company internally, high-level meetings, and so forth, is conducted in English," explains Ho. "But, a lot of the day-to-day conversations, especially at the bench scientist level, and certainly when we go out to work with government agencies or with academic investigators, is conducted in Chinese. It is essential for someone to have strong language abilities." Ho also has found the language skills key to collaborating with the government, local medical institutions, and funding and regulatory agencies, such as the SFDA — China's equivalent of the FDA. "However, if we can get someone who has really unique capabilities and is very strong in an area, but doesn't have the language skills, then we'll try to work around that," he confides.

> "In the short time we have been in existence in China we have already collected more than 100 samples from patients through hospital collaborations."
>
> Peter Ho, M.D., Ph.D., founder and president

A GROWING, TALENTED STAFF

By taking the bold initiative to create a biotech based in China, combining Eastern culture with Western training, BeiGene looks to break new ground in Chinese drug discovery. The company already has been successful in the talent acquisition department, growing to more than 140 employees who have worked for many of the top Big Pharma companies, including Bayer, Pfizer, BMS, GSK, J&J, Lilly, Merck, and Novartis. Being based in China has demonstrated BeiGene's commitment to quality drug discovery. "As a sponsor in China, we have a big stake in the game to make sure the product that is prepared for our use and the clinical trial material is up to standard," Ho concludes.

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"The process of getting funded is a game of getting in front of people. It's meeting them in person, not over the phone," says Laura Shawver, CEO, Cleave Biosciences.

Cleave Biosciences: From Concept To Biotech Start-up

By Fred Olds, contributing editor

"You have to be comfortable with chaos when your company's bank account goes from $0 to $44 million overnight," says Laura Shawver, CEO of Cleave Biosciences, which received series A funding in Sept. 2011.

Shawver recently guided the fledgling biotech start-up through the first three months of operation after she and the founders convinced investors to fund their company. Cleave is a rare survivor in the tortuous passage from concept to operation. To get here, Shawver says, you simply need good science, a good plan, and a good team. Of course, that's not a simple thing to do. Organizing, funding, and opening shop is an exceedingly difficult process that requires persistence and a network of contacts who will provide sober analysis and direction.

"Most funding proposals are denied because they should be," says Larry Lasky, a business-savvy scientist at U.S. Venture Partners and an investor and board member of Cleave. Lasky was a pioneer in biotech and has seen more than his share of hopeful projects. He says there is a naiveté among suitors about what's needed to get support. So, most proposals lack both depth of science and a credible business plan. Cleave cofounder and biology professor at Cal Tech Ray Deshaies puts it this way, "Researchers face a threat in their optimism. Sometimes you believe elegant science will lead to a final product, but it's much more. You've got to be able to trace a line from basic science to the market and do that with as few question marks as possible."

The good science at Cleave began with Deshaies' basic research in protein degradation. While the precise nature of the research is a secret, it does relate to ubiquitins, naturally occurring markers that identify proteins for destruction. Deshaies collaborated with Francesco Parlati, senior director of biology, Cleave Biosciences; and Seth Cohen, chemistry and biochemistry professor, UC San Diego, to further develop the science and understand the biology of the targets. Once they had lead compounds that could affect tumor growth and survival, they felt they had enough to pursue translational science and possible commercialization.

INSTILL CONFIDENCE FOR INVESTORS WITH EXPERIENCE

Gaining financial support for a drug discovery company is an esoteric process that most often meets with denial, frustration, and failure. So Deshaies took the research to Lasky to get an opinion on the viability of Cleave's science and business possibilities. Lasky saw promise in the enterprise and encouraged Deshaies to proceed. Deshaies then sought the assistance of Peter Thompson, an associate who had years of experience in biotech and venture capital, to develop a business plan and put together a team.

Deshaies says, "You want to show up with as many boots on the ground as possible when you present your plan to investors." Those boots need to be filled by experienced professionals with demonstrated success in science and business. It's about credibility. Deshaies says if you think there's a question about a potential team member, ask an investor if they would back the candidate you were considering for a position like CEO or CSO (chief science officer).

Lasky says that with Deshaies and Parlati, Cleave had premier scientists from a world-class institution who had started and sold Proteolix to Onyx Pharmaceuticals. Mark Rolfe would join the team as chief scientific officer. Rolfe's previous work at Millenium gave him a depth of knowledge in Cleave's operating space — small molecule inhibitors of the ubiquitin system. For a CEO they got Shawver, a bench researcher who became president at Sugen and CEO at Phenomix.

THE COINCIDENCE OF SCIENCE AND LIFE

Shawver was entrepreneur in residence at 5AM Ventures when Deshaies contacted her. She says she was immediately taken by the science. It was novel chemistry and novel targets, which she describes as an "interesting warhead" that had both potency and selectivity. With a career in molecular and genetic cancer research, she recognized the scope its impact could have on difficult-to-treat cancers.

The science drew her on a personal level, as well. In 2006 Shawver was diagnosed with ovarian cancer, a cancer with a poor prognosis and a high recurrence rate. Professionally, she knew what the state of the science was when she received the diagnosis, and she set out to map her tumor and select the appropriate therapy. "What I found was a completely different experience as a patient. The standard of care outside the big four (lung, breast, prostate, colon) was 40 years behind current science."

"I was lucky," she says, "that standard care worked for me, but I began to understand how difficult it is for people with recurrent and refractory cancer when standard care fails." She founded the Clearity Foundation to help women with ovarian cancer in getting tumor mapping and access to appropriate nonstandard therapies. Shawver says, "You can imagine how jazzed I was when the opportunity at Cleave came along. I couldn't think of a better marriage of all my personal experiences and professional skill set."

DEVELOP A COMPELLING RATIONALE, AND GET IN FRONT OF INVESTORS

When seeking support, the team has to have a rationale that investors understand and see the value in. A company needs to show that the compound will meet an unmet need, can be moved through the regulatory approval system, and gain support from payors. Shawver, Deshaies, Parlati, and Thompson developed hypotheses for how they would develop their lead compounds, what the patient subsets would look like, and what companion diagnostics they would need to identify those subsets. Shawver says, "In this day and age we need to identify the subsets of patients who will benefit from drugs. It makes no sense to deliver toxicity without benefit." Working toward greater specificity in patient selection stacks the cards in the patient's favor and provides greater clarity for regulatory and payor approvals.

Shawver says, "The process of getting funded is a game of getting in front of people. It's meeting them in person, not over the phone." She says sending proposals in an email, cold calls, or asking for a lunch meeting with a phone call are generally time better spent networking. "You have to identify whom you need to meet and find someone who can introduce you to them."

Deshaies advises, "Get used to hearing 'no,' and don't take it personally." Persistence is a necessary virtue. Believe in what you're doing, and focus on that. Shawver advises one to learn from the negative replies. Come away from any meeting with an understanding of why you were turned down. That knowledge can help you improve your plan, presentation, timing, or target.

"Don't let your first meeting with venture capital be the time you ask for money. What I like to do," says Shawver, "is talk to people who might want to invest in this or a future venture, and say here's what we're doing. Would you be interested? A lot of times you get turned down. Sometimes you get 'maybe.' When you have data, you go back to the ones who said maybe and say, 'Here's what we said we were going to do, and here's the evidence. We're looking for X amount of money to take us to A, B, or C.'"

And don't forget to always maintain contact. She says over time you develop relationships not only with those that fund you, but with those that don't. She already had a long-standing relationship with 5AM Ventures; it had funded Phenomix when she was CEO there. That relationship helped Cleave get in to make a presentation and led to 5AM agreeing to fund the new company. The investors who didn't invest in Phenomix knew her as well and were willing to listen to the Cleave proposal. In the end, Lasky says that once 5AM agreed to fund Cleave, the syndicate coalesced with the addition of U.S. Venture Partners, Clarus Ventures, OrbiMed Advisors, Astellas Venture Management, and Osage University Partners.

With syndicates of this size in a high-risk business, it's critical to get good legal counsel. There are many lawyers familiar with these types of transactions. The ticklish part, Shawver says, is finding one willing to work ex ante facto for ex post facto payment. The process for the Cleave venture lasted more than nine months, and arrangements for that amount of work on a promise may pose problems.

DON'T OVERLOOK MANAGING THE OPERATION

"One thing that comes with $44 million is expectations," says Shawver. "The board and investors expect to see immediate progress on the business plan." The other thing that comes is acceleration. Usually a company starts with seed money and has time to ease into operation. Cleave's business plan had timelines for research, but none for setting up shop. Nonetheless, that had to happen simultaneously — and appear somewhat magically, Shawver adds.

Operational issues are background noise to the mission, but can become a frantic test of ingenuity that can dominate your time. Cleave had no lab space, equipment, bank accounts, or Internet. "You have to be resourceful, dive in, and get your hands dirty." You also have to look for ways to solve problems, not just patch things for later.

The funding closed on Sept. 9, 2011, and the company borrowed space from Clarus for the first month. "We found suitable space and moved in Oct. 3. While T1 lines were being installed, we used MiFi (My Wi-Fi) and worked in the conference room while office and lab space were being finished, and we were able to find good used equipment to save money."

Probably one of the more annoying situations was to have $42 million in the bank and no credit. Shawver says they couldn't set up accounts with vendors and ended up paying by check or putting purchases on personal credit cards. She cited an incident with a pipette vendor who said his company wouldn't set up an account because they couldn't verify credit through the bank. She suggested the vendor have their company "Google" the Cleave press release. An account was set up the next week.

IT'S NOT FOR EVERYBODY

Today, most of the operational issues have been solved, and the company is focusing on proof-of-concept — classic drug discovery research. Shawver explains, "We have to recapitulate with a small molecule what others have shown against the same targets using genetic strategies." Optimistically, she says they may be able to do that with one of Cleave's three lead compounds in the next six months, but she adds, "It will probably take longer than that."

There's no doubt that developing and running a start-up is challenging. "This sort of work is living on the edge. It's not for everybody," says Shawver. "In the end, I hope we do something here that helps cancer patients where there are no options or poor options." Getting this far was the result of good science, a good plan, and a good team.

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Efficient Contracting Processes For Clinical Trials ... From The Legal Perspective

By Sara Gambrill, contributing editor

On Dec. 1, 2011 in Cambridge, MA, law firm Pepper Hamilton's Timothy Atkins, partner, life sciences, and Jason Reiser, associate, life sciences, gave a presentation as part of the firm's Life Sciences Speaker Series. "Clinical Trial Contracting: Lessons Learned" is the second in the series.

Throughout their talk, Atkins and Reiser shared best practices for how the biopharma industry could be most effective in contracting clinical trials, from the legal perspective — with a particular focus on multinational Phase 3 clinical trials. The two main takeaways for sponsors were: Think ahead, and involve your counsel early on. They also emphasized the need to select a good CRO to help run very large clinical trials.

Though many different constituencies contribute to the successful conduct of a clinical trial, the presenters focused mainly on the contracting process with investigative sites. "Contracting with clinical sites is probably the biggest rate-limiting step that sponsors have in operationalizing trials," Atkins said.

IDENTIFY THE TEAM

For a Phase 3 clinical trial to run efficiently, Reiser described the need to start on the right foot. He believes it essential to have a kickoff meeting to meet the internal team working on the trial, including the chief medical officer, some of the scientists, perhaps members of the regulatory team, and others, as well as the external team — the CROs — if not in person, then over the telephone during this meeting.

As legal counsel, Reiser wants to learn: What is the drug supposed to do? What are the anticipated outcomes? What are some of the possible downfalls? How many CROs are involved? In which countries is the study being conducted?

"I want to sit down for a couple of hours and get a good sense of things, so when the first contract comes in, I already have a great knowledge base to help run the trial," Reiser said. Meeting face-to-face is important for building rapport before the work begins so the first conversation between the company and its counsel isn't about a problem. The kickoff meeting is also a good time to point out potential issues to each other that neither side might have thought of. "The more comfort you have with your team — the more familiarity — the better it will speed the process along later on, especially when things get hairy," Reiser said.

Atkins stated that an all-one-team approach to doing the trial is critical, instead of approaching the trial as separate teams of clinical and legal. Having a client services team at the law firm dedicated to the trial is also important. "If you're dealing every day with the same people at the law firm who know what the trial is about, then they've gone through the issues, they know what needs to be negotiated and what your 'gives' are and what you're not willing to do. That familiarity is critically important from a legal perspective. Your team should certainly have contracting experience and also regulatory and international experience," Atkins said.

Roles and responsibilities should also be clearly delineated and assigned. There can be overlapping areas, so it's important that the legal team know what each party is supposed to be doing and that everyone is well-coordinated, working together, and interacting regularly.

IDENTIFY AND PREPARE ALL LEGAL DOCUMENTS TO BE REGULARLY USED IN CLINICAL TRIALS

Atkins and Reiser recommend identifying the necessary legal documents for a trial and having them in place early on to have a smooth contracting process. These documents can include the non-

disclosure agreement (NDA), clinical trial agreement (CTA), letter of indemnity, and various vendor contracts.

NDAs are typically written up first. Though fairly straightforward, sponsors need to keep a few considerations in mind when having them made up. "NDAs are considered dime-a-dozen type agreements, but they're there for a reason — to protect proprietary confidential information. It's a good idea to tailor it to what you're trying to accomplish. One-size-fits-all isn't the best approach for suits or for NDAs. You need to think about what you're trying to protect, how long you need to protect it, and the things you'll give on," Reiser said.

Sometimes sites, notably academic institutions, have their own NDAs that they will hand back to the sponsor to use instead. Sponsors need to be prepared for this situation, deciding whether they will respectfully insist on their own form being used or, if the language is different but says the same thing, are prepared to give. It's also important to think of all the different vendors a sponsor will need contracts for and have them in place or know that the CRO will take care of some or all of them.

The CTA "comes in many flavors," depending on the scope of a clinical trial and how many countries the research is conducted in. A CTA can be a two-, three-, even four-party agreement. It's important for sponsors to anticipate some of the contract scenarios they might encounter outside the United States. For example, though a sponsor may have a CTA with an investigator who is going to conduct research for the trial at a hospital, the hospital may not be a signatory to the CTA. In this case, it may want the sponsor to sign a letter of indemnity so that if anything goes wrong, the sponsor will pay for the damages. Reiser believes that it's fine for sponsors to sign this letter of indemnity, but that they should ask for something in return, such as a signed consent from the hospital that the sponsor had permission to conduct the study there in the first place. "It's important to think about your paper trail. What are you going to point to if something goes wrong and somebody asks, 'Did you have permission to conduct the study at the hospital?' A couple of sentences should take care of it."

Sponsors in this situation might also want to get confidentiality agreements, as the PI (principal investigator) will be using staff at the

hospital. Atkins pointed out that one of the issues in this scenario is that the institution is not signing the contract, but the PI is, though the PI will be using the personnel of the institution. "There is a property issue here. You have to think about how you're going to get a release of claims from the institution as it relates to the use of their personnel for extracting data and putting them on a case report form and the like." Being ready with one's own documents to be signed when the institution asks for a letter of indemnity is key to saving time.

LEGAL REVIEW OF BOTH INFORMED CONSENT AND PROTOCOL

Atkins and Reiser recommend that sponsors have their law firms review the protocol — early on, before FDA approval — and the informed consent side by side to ensure consistency between the two documents and regulatory compliance. For example, safety reporting and medical care should be described clearly in both documents and in a consistent manner. "We don't think many sponsors actually have their legal departments look at the protocol and read it through, compare it to the informed consent, and ask, 'How are these things different?'" Atkins said.

Counsel can also advise on anticipated developments arising from recent lawsuits and regulatory action and guard against "failsafe trials," or trials set up to find a certain answer, by reviewing the protocol for risk avoidance. Atkins said, "It may not be at all what you're trying to do. We know how to read through a protocol and say, 'That's a risk. You should probably get another endpoint or something else in there to take away that risk.'"

Every informed consent document goes through a site's IRB (institutional review board), and the IRB may require changes to it. This presents legal risks when a sponsor must decide what to do from there. Reiser said, "It could be a material change, and, if you made it for one site but not all your other sites, you've just set yourself up for a real problem, in terms of litigation around informed consent."

"Contracting with clinical sites is probably the biggest rate-limiting step that sponsors have in operationalizing their trials."

Timothy Atkins, partner, life sciences, Pepper Hamilton

Sponsors also should provide counsel with a list of prospective sites. "We want to know who your sites are as early as possible so we can run it through our conflict-checking process, and we can then either start getting conflicts waived or we can tell you which ones are going to be a problem," Atkins said.

ESTABLISH TRACKING MECHANISM FOR CONTRACT REVIEW PROCESS

Figuring out what the sponsor's gives are, what language the sponsor will and won't work with, and what types of issues the sponsor does and doesn't need to go to legal for are important to establishing a tracking mechanism for the contract review process. "It's important for us to keep the trial moving. We all want to know where every contract with every site is. Who has the ball? How long has it been there?" Atkins said. CROs tend to run the process, but the law firm should be able to, and, either way, someone needs to be accountable for tracking the process and allowing everyone on the team to see on a weekly basis where all the contracts are.

If the process isn't thought through and led by someone, "a contract can circle the globe in three weeks, and you're back where you started," Reiser said. "Have a spreadsheet, have a process, and have team leaders who are in charge, so, if a contract's missing, you can track it. You don't want it sitting in limbo."

IDENTIFY THE GEOGRAPHIC FOOTPRINT OF THE TRIAL

Biopharm companies running a multinational, multiyear Phase 3 trial face complexities that revolve around the many different countries where the research will be conducted. Contracts drawn up for clinical research conducted in the United States have to be made appropriate for use in foreign jurisdictions, which will involve translation but also could require breaking the contract apart into several pieces.

Atkins advised, "You want to keep the contract as consistent as you can across jurisdictions. You must have the explicit intention when you break those contracts apart and make them appropriate for the foreign jurisdiction that you're not losing something in the translation, that you have consistency across your contracts and across your trial. It puts a premium on your organization's communication skills."

It may seem obvious that biopharma working internationally would need international counsels, but the form they might take is not as obvious. Big Pharma with offices and legal teams in all the countries where their research will be conducted has to make sure they get the legal input they need. Other companies may choose a big law firm with international offices or a U.S. law firm that has a network of firms — international affiliates — it works with. Reiser said, "Whatever you do, you need to know one thing: Regardless of how big, how broad, how well-known the counsel is, they have people on the ground in the countries where you're going to do clinical trials. When you're vetting law firms, know what capabilities they have and where."

Reiser says it's key to have one lead counsel to vet all the counsel, make sure the process is running efficiently, and that all the necessary calls are made. "Law firms need to have been through the process, know the players involved, get you through the Ministry of Health, know how many 'gold seals and red ribbons' you need on documents, and identify contract issues you simply hadn't thought of," he said. What is necessary for each document needs to be understood ahead and built into the process.

The same applies to a company's choice of insurance firm. Biopharma companies should work with insurers that have done work for international clinical trials before. "Ask them: 'Have you been in this country

before? Is this the first time you're going to be writing a policy for clinical trial coverage in this country?'" Atkins explained.

Before conducting clinical research in the EU, biopharma companies must have a legal representative, the sole purpose of which is to grant the EU jurisdiction over the company. It gives the EU authority to contact the company and communicate with it. CROs often offer this service to smaller companies.

CLINICAL TRIAL AGREEMENT TERMS

Atkins and Reiser ended their talk by discussing some of the areas of the CTA that sponsors should pay particular attention to. One of the major areas of consideration is compensation. They advised sponsors to make compensation attractive to sites so that their trials get attention throughout the trial but also ensure that start-up fees are recoverable under certain circumstances, such as when a site never enrolls a patient or hasn't enrolled one for six months. They also recommended that compensation be structured so that sites don't get fully paid until they fully perform.

They reviewed their recommendations to sponsors to think through what they wanted in terms of IP, confidentiality, and indemnity. They also stressed the importance of including the timing of publication in the CTA and to be consistent about it across contracts.

One of the issues that can come up in contracting work with foreign countries is the Foreign Corrupt Practices Act (FCPA). Atkins said, "The FCPA is a huge issue these days in terms of enforcement." Because many foreign health systems are government-run, sponsor companies are actually contracting with a foreign government when conducting clinical research in countries outside the United States. "Make sure you've done all your due diligence on compliance around FCPA and that you've done fair market value studies on your payments to clinical research personnel and your fees. Make sure when you're making an investigator payment that you're not handing out gifts and things like that."

Atkins pointed out that there's very little litigation around CTAs; their purpose is to lay out normative behavior. CTAs describe expectations and provide sponsors with the ability to withhold payment if expectations are not met. Ultimately, he recommended that sponsors send investigative sites a "middle-of-the-road" contract. "Send a contract that's easy for them to accept. You're going to be better off doing that than going through multiple versions of a contract."

Pharma R&D Productivity Drops 70%

Cindy Dubin, contributing editor

You have to spend money to make money. But, for the pharma industry, the return has been less than robust these last six years. According to a new study from consulting firm Oliver Wyman, the value generated by $1 invested in pharma R&D has fallen by more than 70%. Yet, it appears that pharma is not addressing what the study authors say is an urgent situation.

"We entered the analysis with the understanding that R&D productivity had declined," says Jeff Hewitt, a partner at Oliver Wyman's Health and Life Sciences Practice. "The R&D problem was stated as an accepted fact — one that we've certainly known about for years — and without much acknowledgement of the severity or the urgency to respond. When I compare the sense of urgency and willingness to make big changes, it's out of proportion with the seriousness of the situation. The environment has changed so dramatically that R&D has not been able to catch up. This is not to say that pharma isn't taking actions; the industry certainly is. It's just that the pace of change doesn't match the severity of the problem."

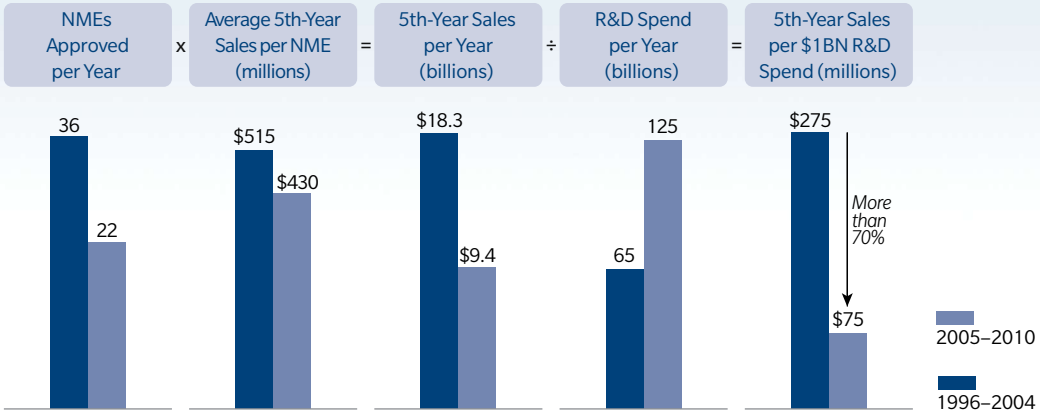
The purpose of the study was to better understand how and why R&D was changing and how life science leaders can use this information to improve their decision making in R&D. The study, "Beyond the Shadow of a Drought: The Need for a New Mindset in Pharma R&D," looked at the 450 new molecular entities (NMEs) approved by the FDA between 1996 and 2010. "Our hypothesis in quantitatively analyzing these drugs was that recent drug approvals were less valuable to society and not generating the same revenue as drugs approved in the earlier portion of the 15-year period," says Hewitt.

What the data bore out was that two eras occurred during those 15 years: "The Era of Abundance" (1996-2004) and the "Era of Scarcity" (2005-2010), which continues to exist. In the Era of Abundance, 36 NMEs were approved per year, compared with 22 in the Era of Scarcity, a 40% drop. "This is a different era of drug discovery for the pharmaceutical industry, requiring pharma to change its approach to developing drugs to fit into the current era and do so quickly," says Hewitt. The solution is a new R&D mindset, which will depend on drugs that bring value to the market while at the same time reducing overall cost in the healthcare system.

IS PHARMA A VICTIM OF ITS OWN SUCCESS?

While drug expenditures are up, the value of produced drugs is down. The cost of developing a single drug has a price tag these days of $1 billion. But, the economic value created by a drug has dropped. The study looked at each drug's fifth-year sales and found that a single drug in the Era of Abundance produced an average of $515 million in sales compared with $430 million in the Era of Scarcity, a 15% decrease. Thus, the impact of fewer drugs approved each year, and the lower sales per drug, resulted in an average fifth-year sales for the industry dropping almost in half, from $18.3 billion to $9.4 billion.

Despite these reductions, R&D expenditures actually doubled over the 14 years of the study period, from around $65 billion per year in the Era of Abundance to $125 billion per year in the Era of Scarcity. And, those dollars produced significantly less. In the abundant years, drug companies produced $275 million in fifth–year sales for every $1 billion spent on R&D. In the



Era of Scarcity, the figure was $75 million.

The irony is that for many pharma companies, they are their own competitors. According to the study, after decades of abundant discovery, many disease categories are well supplied with safe and effective therapies. And many are inexpensive: In the United States, overall penetration by generic drugs reached 78% of prescription volume last year, up from 63% in 2006.

So, developing a blockbuster is proving more difficult, with the number being developed dropping from 12 to 6 per year. Unfortunately, says Hewitt, the nonblockbuster drugs have not done much to bridge that gap in the drop-off — they only closed the gap by about 5% — because there just weren't enough of them being developed.

The bar on innovation is being raised, and pharma leaders could consider taking new approaches to drug delivery for already-approved drugs as one way to boost their pipelines. But, Hewitt warns that this can only be a successful strategy if the new drug delivery method has a valuable and meaningful impact to the patient and to the cost of the care. "If payers push the choice to patients, and it is less expensive to take the drug packaged in the less convenient delivery system, the patient will probably choose price over convenience," he says.

Additionally, the goal of development should be finding and targeting patients for whom the drug has the greatest benefit. This reverses the classic approach of targeting the mass population. Biomarkers and patient stratification can bolster the value proposition to the healthcare system. Hewitt says payers are likely to accept high prices for drugs that significantly improve the standard of care for a clearly identified set of target patients.

PARTNER WITH PAYERS AND OTHER PHARMA

There is still opportunity for medicine to change lives, but the companies focused on this goal should do so while reducing costs in the healthcare system, states the study. Payers are scrutinizing every category of expenditure, including drug spend, and they are aggressive about using their purchasing power to push back on prices.

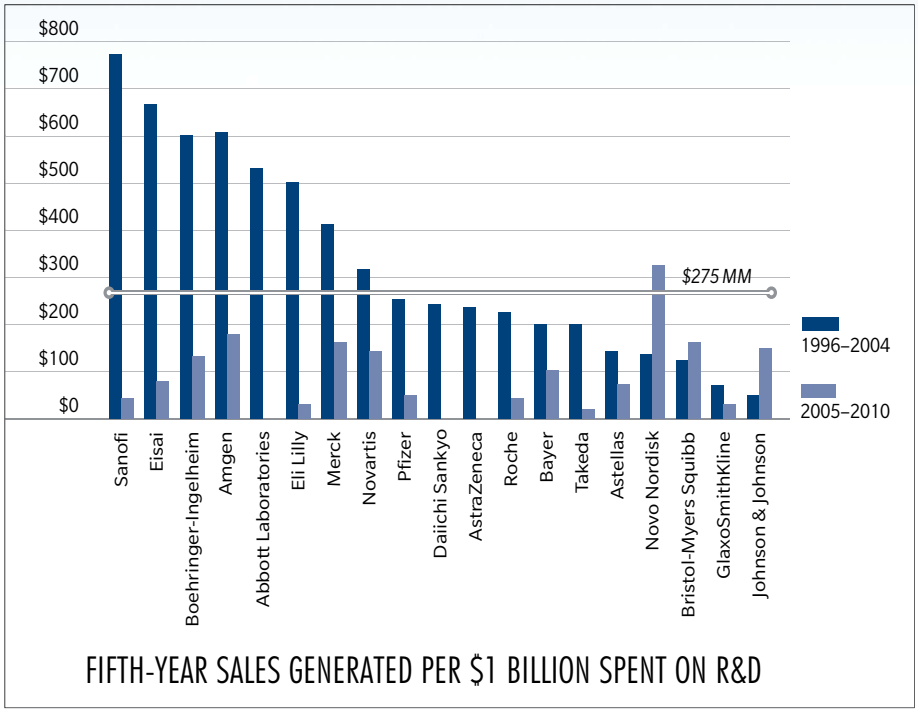
And while the Supreme Court has yet to hear the case on the constitutionality of the Affordable Care Act (ACA), often referred to as "Obamacare," Hewitt does expect healthcare reform to have a significant impact on pharma. If the ACA is implemented, enormous pressures will be placed on payer margins. The typical payer margin will decrease by at least 35% and possibly by more than 50%, states the study. "It will vary by disease area, and it won't happen right away, but providers and payers will look to take costs out of the healthcare system, whether ACA passes or not," says Hewitt.

The key is for pharma companies to shift from thinking of payers as customers and instead consider them partners and work together to provide continuity of quality care to patients. Hewitt says it is no stretch of the imagination for pharma, private payers, and government payers to collaborate and begin dialogue earlier in the drug development process. Savvy companies will actively consider risk and value to payers when setting a new drug's development system.

"There is opportunity for pharma to understand how payers view the cost challenges associated with treatment," he says. "This gives pharma a clearer picture of how to reduce costs in the healthcare system." This can result in fewer trips to the emergency room and expensive diagnostics. "An accelerated shift to reduce costs and still offer the best treatment means everyone wins, but it has to start with pharma."

A pharma company will need to prove the safety of the newly developed drug and prove that the drug is better than the current standard of care. And while payers will continue to voice their power to control costs, the complexity of the science being pursued by pharma will be greater than ever, says Hewitt.

In addition to partnering with payers, Hewitt recommends that in these times of financial constraint, life science leaders seek out partnerships with multiple pharma companies to



FIFTH-YEAR SALES GENERATED PER $1 BILLION SPENT ON R&D

expand access to new science. Companies can pool R&D efforts to decrease cost and risk of developing high-value products. Currently, only about 20% of pharma companies explore such partnerships.

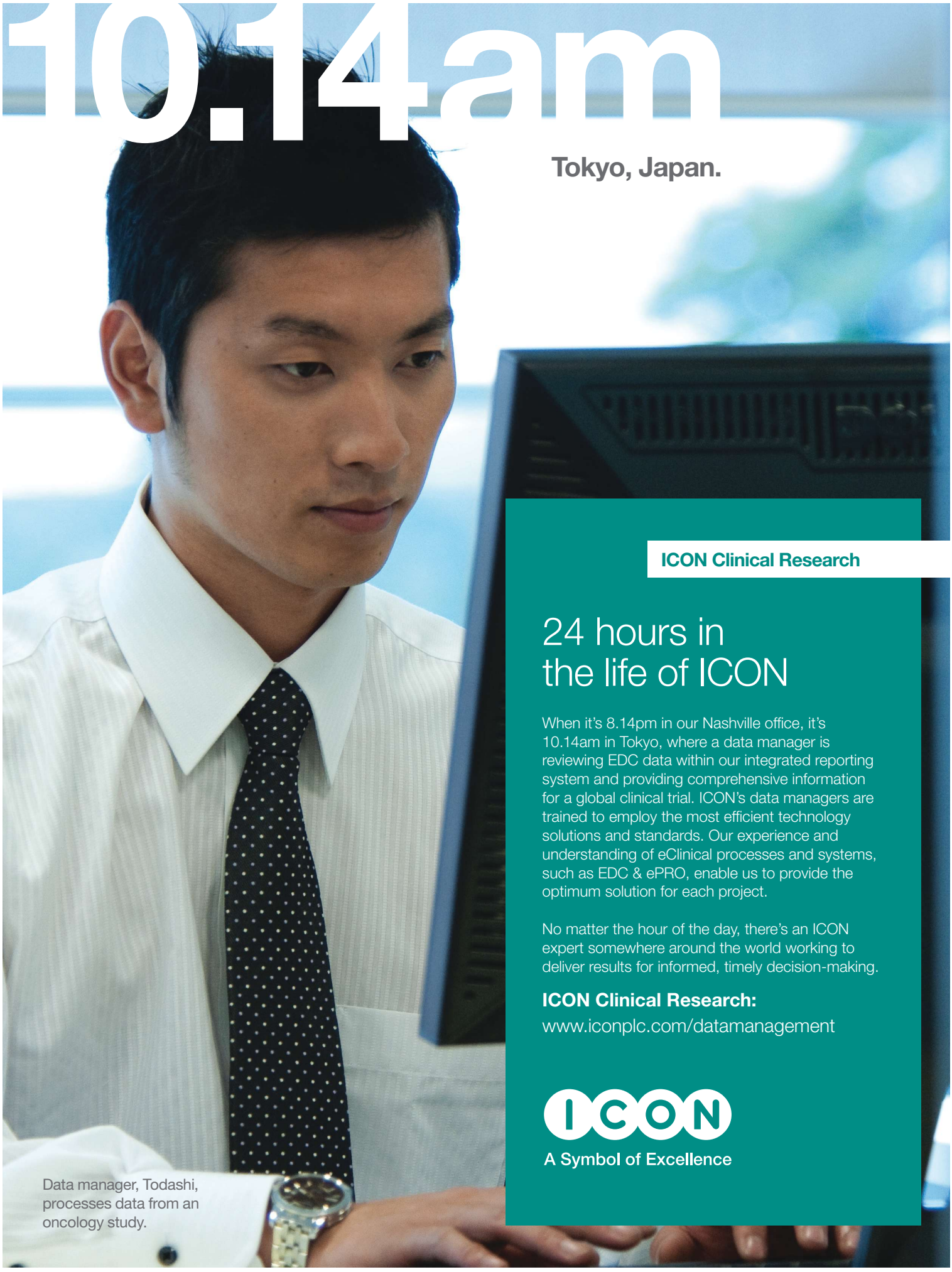
"We believe the industry will see more collaboration in R&D to build consortia to address disease states," says Hewitt. "Companies in the industry have operated as silos for too long."

2011 WAS A REALLY GOOD YEAR

Through partnerships and other business strategies, many drug companies have indeed maintained strong net income levels, and, as a whole, the industry has grown 6% per year for the last five years. Thus, 2011 was actually a great year for drug development. "NME numbers were better than they had been in the last six years," says Hewitt. And, 6 of the 25 new drugs approved by the FDA in 2011 have the potential to be blockbusters.

But don't get too excited. 2011 still falls into the Era of Scarcity, and Hewitt predicts another development drop-off is possible through 2014. Of the 180 NMEs projected to launch between 2012 and 2014, the authors found that when the expected output of these three years is combined with 2011 levels, the projected fifth-year sales is around $9 billion. And, the fact remains that only about half of all drugs entering Phase 3 trials will actually reach the market.

Hewitt and his colleagues remain optimistic, however, about the future of pharmaceutical R&D. The industry is merely going through a cycle, and the authors fully expect successful companies to emerge with a new mindset of developing new drugs that offer additional benefit, go beyond the current standard of care, and are attractive to payers. At the same time, the new compounds have to reduce costs out of the healthcare system. Hewitt says: "Despite the challenges, pharma can be successful in this new drug development era."



Data manager, Todashi, processes data from an oncology study.

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A Symbol of Excellence

So You Want To Be A Preclinical CRO Study Director?

By Chris Papagiannis

The scientist or toxicologist working as a study director (SD) in a preclinical CRO can find it to be a rewarding and also continually challenging career. The research for which you are responsible is critical in the development of new drugs for the treatment, cure, or management of many diseases or physical conditions.

You typically wear many hats and serve many publics. Beyond the title of scientist or toxicologist and the studies you run, you can be looked to as a scientific expert, leader, mentor, team builder, animal welfare point person, and sounding board among your colleagues/coworkers. You may serve on Lean Six Sigma teams and various internal business or scientific committees. Outside of your organization, you can be looked to by your sponsors (clients) as a go-to person, a consultant who makes scientific recommendations, an idea person for troubleshooting toxicology issues, and the one they are counting on to make things happen successfully. Other days you may be asked to put on your sales hat and work with your colleagues to close the deal on a package of studies, make a critical presentation as the face of your organization, or cross-sell other services your organization offers beyond your particular scientific discipline. It is thus essential that you be focused on two-way communication (including listening skills) and the quality of that communication — be it via phone, email, or in person.

BECOME THE SPONSOR'S ADVOCATE

You often need to become the sponsor's advocate within your CRO regarding price, potential start dates, and deliverables and to serve as an ongoing informational resource. In these instances, you are acting as a PR person. In the sponsor's eyes, you want to be seen as the go-to person, their personal advocate who can navigate and marshal the resources of your CRO for their benefit, thus fostering productive two-way communication and building long-term trust and ongoing fruitful relationships between your organizations. Sponsors have variable and specific requirements and preferences for their studies and how they want tasks done. It's your job to find a way to best meet, and preferably exceed, their needs .

You also have to be fully attuned to and respectful of subtle cultural differences in business protocol and ways of conducting business with various international sponsors. You would like them all to feel that you and your organization are an extension of their laboratory and/or scientific personnel, and when they visit your site, you want to come across as an ideal and knowledgeable host in showing them firsthand what your facility and its talent pool of professionals have to offer. Ideally, you'd like to be looked upon as a leader in the field by publishing articles, opinion pieces, or study results and attending and participating in scientific meetings and their related symposiums, roundtables, and continuing education courses.

THE ROLE OF THE STUDY DIRECTOR

The role of the SD is defined as the single point of control, as the good laboratory practices state (from FDA 21 CFR Part 58 Subpart B):

"The study director has overall responsibility for the technical conduct of the study, as well as for the interpretation, analysis, documentation and reporting of results, and represents the single point of study control."

Thus, you will be the one everyone looks to in all situations on a study, good or bad, both in terms of guidance and how you react. Hence, how you

To a courier, this is just another box.

To Marken, this is a fragile drug in your Phase III clinical trial.

When a study depends on the integrity of the drug being administered, any excursions can compromise the entire clinical trial. At Marken, we understand this better than anyone because Life Science is our business. Marken is led by experts from the pharma industry with deep knowledge of worldwide logistics and pharma regulations. Marken's global Pharmaceutical Service Network is purpose-built for the secure storage and distribution of your valuable IMPs and medical devices and our temperature-controlled depots offer a host of services, from pick-and-pack to return and destruction.

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communicate and respond during your handling of various situations is critical, both for that study and subsequent studies. The individuals and colleagues comprising the numerous departments that you work with on a daily basis are essentially the lifeblood of your studies and always deserve the professional and personal respect that accompanies such a critical role.

No one is perfect, and no CRO is error-free. When an error occurs, how it is handled is key, both internally and externally, and you are the point person who can make or break a relationship with a coworker or sponsor. Salient errors must be communicated to sponsors immediately so they are not blindsided after the fact. The communication must involve details of what happened, why it happened, what you are doing to fix it, and what new plans you are putting in place to ensure it does not happen again. In talking to a sponsor, there is no "they" did that or "he or she" did this; it is "we" who made the mistake, "we" who failed, with you taking personal responsibility as the single point of control, apologizing appropriately, and taking the corrective steps needed to make it right for the sponsor.

Such an event, if handled correctly in a sponsor's eyes, can turn a negative into a positive and further cement the relationship and trust factor. Similarly, internal investigations for such errors should be looked upon as learning tools; little is accomplished by placing blame or throwing someone under the proverbial bus. It is often a primary opportunity for teaching, mentoring, and moving forward, as in many cases the coworker involved is one who has demonstrated quality work on numerous other studies. You must relate to that individual in such a way as to bolster their confidence, rather than shatter it, as you can have a positive impact in that person's professional development while making sure the issue is corrected.

Thus, your role becomes a multipurpose mixture of scientist, toxicologist, animal welfare person, consultant, teacher, mentor, salesperson, public relations person, customer service person, host, psychologist, employee relations counselor, scientific results writer, published author, and ongoing student in the discipline. As the sophisticated man in the Dos Equis beer commercial might say … **the most interesting position in the world … stay ready my friends …** with a few key points to keep top of mind:

- Maintain a level of presence in laboratory areas (to interact with technical staff and see animals/functions firsthand). Frequency varies, depending on study duration/issues.

- Keep your alternate contact(s) informed about salient issues should they need to act in your stead.

- Conduct real-time review of data to spot early results trends or any unexpected issues. While the operations staff will let you know of major issues/findings, they should not be used to replace your eyes and ears on a study.

- Keep sponsors continually updated in real time so there are no surprises for them. Quickly inform them of mortality, important findings, and key deviations. Frequency of data updates depends not only on the sponsor's preference, but on the "busyness" of the study in terms of critical issues/findings.

- Conduct timely review and signing of study documents, and respond promptly to quality assurance observations. Issue all internal/external documents and protocol amendments in a timely manner.

- Take a prominent/positive role in formal investigations when they are needed. Assist in troubleshooting and providing possible solutions, while keeping the sponsor in the loop.

- If you've been informed of animal health issues from clinical observations or veterinary consultations, view the animals firsthand so you can speak from a personal view when updating the sponsor.

- Keep operations staff informed of any design changes that are being discussed with the sponsor during the study, even if a decision has not been made. The more lead time to digest and plan for possible changes, the better, and the more smoothly they can be enacted. Avoid lag time in capturing any price/cost revisions resulting from design changes.

- Make suggestions to the sponsor about study issues or errors and provide options; do not toss bad news at them, and let the ball sit in their court to come up with a plan of action. Be an extension of their laboratory, and engage them by presenting your ideas.

About the Author

Chris Papagiannis is a senior study director and general toxicology manager at MPI Research, a preclinical CRO headquartered in Mattawan, MI.

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A Biotech's Path To Acquisition

By Cathy Yarbrough, contributing editor

During the final days of 2011, Steve Worland, Ph.D., and his 26 colleagues at Anadys Pharmaceuticals transferred their work — and the company's assets in hepatitis C (HCV) drug development — to Roche Holding AG. Dr. Worland, CEO and president of the company since 2007, and his staff no doubt also spent some time updating their CVs, because in late November, the Swiss pharmaceutical company finalized its takeover of the San Diego company. When Roche first announced its plans to purchase Anadys (pronounced UH-nad-iss), its officials clearly communicated to the San Diego biotech's staff that it did not plan to use the acquisition to establish an R&D foothold in Southern California, said Worland.

Back in 2001, Worland and his team began research to develop drugs that would subdue HCV infection, the primary cause of liver failure. He had joined the company in March of that year as its chief scientific officer, after serving as VP, head of antiviral research at Agouron Pharmaceuticals, a Pfizer Company. Prior to Pfizer, he was a VP at Warner-Lambert. Six years after joining Anadys, the company's board of directors asked him to become the head of the company.

Even though the takeover meant he no longer would lead Anadys, Worland applauded the merger. "With Roche's considerable capabilities and experience in hepatitis C, we believe this acquisition provides the best chance of success for the new potential treatments to reach patients," he explained. "Roche has the resources to complete what we began."

5 YEARS OF UPS AND DOWNS

"Roller coaster" has been used to describe the past five years at Anadys. For example, the company began 2009 by announcing positive results from the first eight HCV patients enrolled in the company's Phase 1 clinical trial of ANA598 as the centerpiece of a drug cocktail that also included interferon and ribavirin. The cocktail eliminated 99% of the virus in the patients, who received the lowest dosage. The price of Anadys stock soared from $1.91 to $4.10 per share.

Several months later, Anadys again reported positive findings, this time from more HCV patients who were treated with higher dosages of ANA598. The combination of ANA598 with the two standard therapies increased antiviral activity without serious side effects or indications of drug resistance. However, despite these favorable results, Anadys' stock price plunged because healthy volunteers given the drug as part of the company's clinical studies developed skin rashes, a side effect that at that time had not been seen in the HCV patients treated with ANA598. "People thought the rash was more severe than it was," Worland recalled. "It was an extreme reaction."

For leaders of life sciences companies who are in a similar situation, Worland's advice is, "If you are confident in your compound, don't let the investment landscape overly influence your decisions. Perseverance is required in the biotech industry."

After the stock price dipped, Worland took steps to ensure Anadys would have the financial resources to continue its clinical trials of ANA598. He reduced the company's expenditures by terminating about 40% of the company's staff and setting aside its R&D program on ANA773, a toll-like receptor (TLR) agonist for the treatment of cancer and hepatitis C. To generate a cash influx, new shares and warrants were sold at reduced prices.

Also in 2009, Worland and his team

made two bold decisions that he now regards as "critical junctures" for the company, and in particular for ANA598. Their intent: to prove ANA598's long-term effectiveness and safety to the financial community as well as potential suitors in the life sciences industry.

TWO KEY BUSINESS/CLINICAL DECISIONS

First, with the FDA's blessing, Anadys adopted a rigorous 12-week protocol for the Phase 2a and 2b clinical trials of ANA598. "People asked, 'Can you really do that? Is the FDA going to allow you to do that?' The answer is yes. They encouraged it," Worland said.

This trial incorporated several features designed to further enhance the competitive position of ANA598, including 12 weeks of triple combination treatment and a randomized exploration of shortening the overall duration of HCV therapy in conjunction with ANA598 treatment. The viral levels of the 90 HCV patients who enrolled in the Phase 2a trial were measured at weeks 4 and 12. Patients with undetectable levels of virus at weeks 4 and 12 were randomly assigned to two groups, one of which stopped all treatment at week 24, while the second group ended treatment at week 48. Both the ANA598 and the control groups included patients who had not been previously treated for HCV.

The second part of the plan happened in 2010 when Anadys launched the Phase 2b trial, which involved about 300 patients, including prior nonresponders, individuals with HCV for whom previous therapies had been ineffective. In October 2011, just a few days before Roche announced that it would purchase the company, Anadys reported positive results from the Phase 2b clinical trial of setrobuvir as the centerpiece of a drug cocktail for treating HCV more effectively, faster, and with fewer side effects than the current standard HCV therapies — interferon and ribavirin. The drug cocktail eradicated HCV in 78% of the patients in the Phase 2b trial. In contrast, standard therapy alone eliminated the virus in 56% of the control group patients.

The most common side effect was a skin rash, occurring in 39% of the drug cocktail-treated patients and 22% of the control group. The incidence of rash in the setrobuvir group is consistent with prior reports of rash due to interferon and ribavirin through 19 weeks of treatment, said Worland.

If clinical studies continue to show a positive efficacy and safety profile for setrobuvir for first-round therapy of HCV, the FDA could approve the direct-acting antiviral drug in 2015, Worland predicted.

HCV THERAPY: AN ENORMOUS BUSINESS TARGET

Despite the availability of interferon and ribavirin, HCV therapy has a major unmet need: highly effective and safe drugs that patients will want to use. Only about 5% of HCV patients, which worldwide total an estimated 170 million people, now take advantage of the standard therapies because these medications are ineffective in the majority of people who are treated with them, and the treatment period can last as long as one year. In addition, interferon injections can be painful.

"Anadys' compounds provide additional modes of action that could lead to interferon-free treatment regimens without viral resistance," Jean-Jacques Garaud, M.D., global head of Roche Pharma Research and Early Development, said in the October 2011 announcement about the Swiss company's plans to acquire Anadys. "Our aim is to offer physicians and hepatitis patients a powerful combination of therapies that bring us closer to a cure, even without the use of interferon."

Setrobuvir expands Roche's HCV portfolio, which includes the blockbuster Pegasys (peginterferon alfa-2a) and an experimental protease inhibitor and an experimental nucleoside polymerase inhibitor. Setrobuvir is a small molecule nonnucleoside polymerase inhibitor of HCV RNA polymerase.

> "If you are confident in your compound, don't let the investment landscape overly influence your decisions."
>
> Steve Worland, Ph.D., former CEO, Anadys Pharmaceuticals

Roche is not the only life sciences company with HCV drug development programs. Hepatitis C is an enormous business target, according to Dan Veru, chief investment officer of Palisade Capital Management LLC. Market research firm Decision Resources has estimated that the global HCV market will reach $16 billion in 2015. It totaled $1.7 billion in 2010.

In 2011, the FDA approved two new medications against HCV: Merck's Victrelis and Vertex's Incivek, both of which were designed to be administered with interferon. In the closing months of the year, Gilead Sciences announced it would purchase Pharmasset, which, like Anadys, specializes in HCV.

Roche's purchase of Anadys for $230 million represented a 256% premium over the biotech company's closing price of $1.04 on Oct. 14, 2011, before the Swiss pharmaceutical company's announce-

ment three days later that it planned to acquire the San Diego company.

DEVELOPING A TRANSITION PLAN

Worland and his team celebrated the announcement, but not for long. The company quickly returned to business as usual. "We had a clinical trial and a research program to run," explained Worland, who also spent the last two months of the year developing a transition plan.

Because earlier in his career he had worked at a company that was subject to a takeover and whose senior leadership "told us very little up front," Worland realized that the Roche announcement would have a psychological impact on Anadys' staff. "Of course, people wondered about what's next." To minimize staff staring out of the window, lost in thought, Worland and other senior managers frequently and clearly communicated status reports to the team.

"Clarity is important," he said. "We acknowledged the uncertainty and communicated what we knew when we knew it and reminded people that we were all professionals."

Worland said he regrets that he'll not be at the finish line for setrobuvir. "I'm a finisher," he explained. "I'm driven to achieve a conclusion. My more dominant feeling is that I'll be very glad to see it get over the finish line if that happens, no matter where I am."

He also is driven by the opportunity to "make an impact every day on the organization so that it is successful," he explained. For Worland, a tight link exists between his work every day at a company and its success. "It's much harder to experience that in a big pharmaceutical company because the organization is so large," he said. Indeed, he joined Anadys because it enabled him to experience that tight link as well as the ability to make a real difference in people's lives.

"Personally, I feel a great responsibility to shepherd this asset, to not mess it up," he added. "People are waiting for these drugs."

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Greater Cold Chain Controls Through Enabling Technology

The term cold chain refers to the time-and-temperature-controlled transportation of temperature-sensitive products from the manufacturer to the end user. The goal of cold chain management is to provide patient safety, product integrity, regulatory compliance, process optimization, and cost optimization.

Emerging markets are increasing the requirements for quality control, highlighting the importance of proper documentation for the importation of temperature-sensitive products. Canada, Saudi Arabia, Singapore, Malaysia, Brazil, and Argentina are among the countries that have made the documentation of individual shipments of temperature-sensitive products a customs entry requirement. How will you and your organization react to these regulatory changes?

INTEGRATED COLD CHAIN DATA

Storage and transport needs have shifted as the proportion of biologics in new product pipelines and portfolios has grown. Integrated cold chain data corresponds to the integration of temperatures, storage conditions, logistics milestones, packaging performance, and quality data. This gives rise to an intelligent portal which provides analytical views of an organization's various needs in cold chain logistics.

It is commonly understood that transportation processes should be qualified rather than validated because processes are not possible to control in the real world, and all variables can impact the process. If the transportation process is not rigorously measured and continuously improved via systematic handling of relevant deviations and corrective actions based on integrated cold chain data, it will not be robust enough to succeed due to the endless intricacies and sheer complexity of the cold chain in global logistics. This can lead to the cold chain process being more susceptible to irregularities and negative outcomes (loss of product and/or product getting stuck in customs) from health authorities' audits or even import permit revocations. Undoubtedly, more than ever before, data management and integration has become critical to the success of the cold chain.

Data integration involves conversion of data into useful and meaningful interpretations and actions. The main question at hand is this: How can cold chain data be utilized to predict and determine when a problem will occur before it happens, with the goal of mitigating product issues and their resulting impact costs? The answer lies in technology that will enable cold chain data to be integrated and interpreted in an intelligent, meaningful, and useful manner. Simultaneously, technology will minimize risks and inversely provide practical applications for various uses of data and environments that are customer- and product-specific.

APPLICATIONS OF DATA FOR PATIENT SAFETY

Life science professionals in different areas and levels of supply chain, manufacturing, packaging, operations, quality, and compliance have one common goal in mind: patients. However, their needs to interpret and analyze cold chain data to make risk-based decisions on global cold chain networks can vary substantially. Nonetheless, it all comes down to "unknown unknowns" because there are things in the cold chain that we don't realize we don't know. As per the FDA: Adulterated Drug Products, FD & C Act Chapter V, sec. 501, "A drug or device shall be deemed adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and the purity characteristics, which it purports or is represented to possess." It takes a great amount of control to protect the integrity of temperature-sensitive medicinal products.

As temperature-sensitive products are shipped all over the world, ask yourself about your cold chain management goals for this year. Are data management capabilities a target for your organization? With the aptitude of data integration and management, life sciences organizations will be able to increase the speed for product release into the market, produce significant gains in productivity, maintain high levels of maximum regulatory compliance, and create cost optimization while conserving product integrity.

David Bang

David Bang is the CEO for LifeConEx, a DHL company dedicated to advanced cold chain management. Bang has held various positions in global contract acquisition, implementation, sales, finance, IT, and strategy within the life sciences industry.

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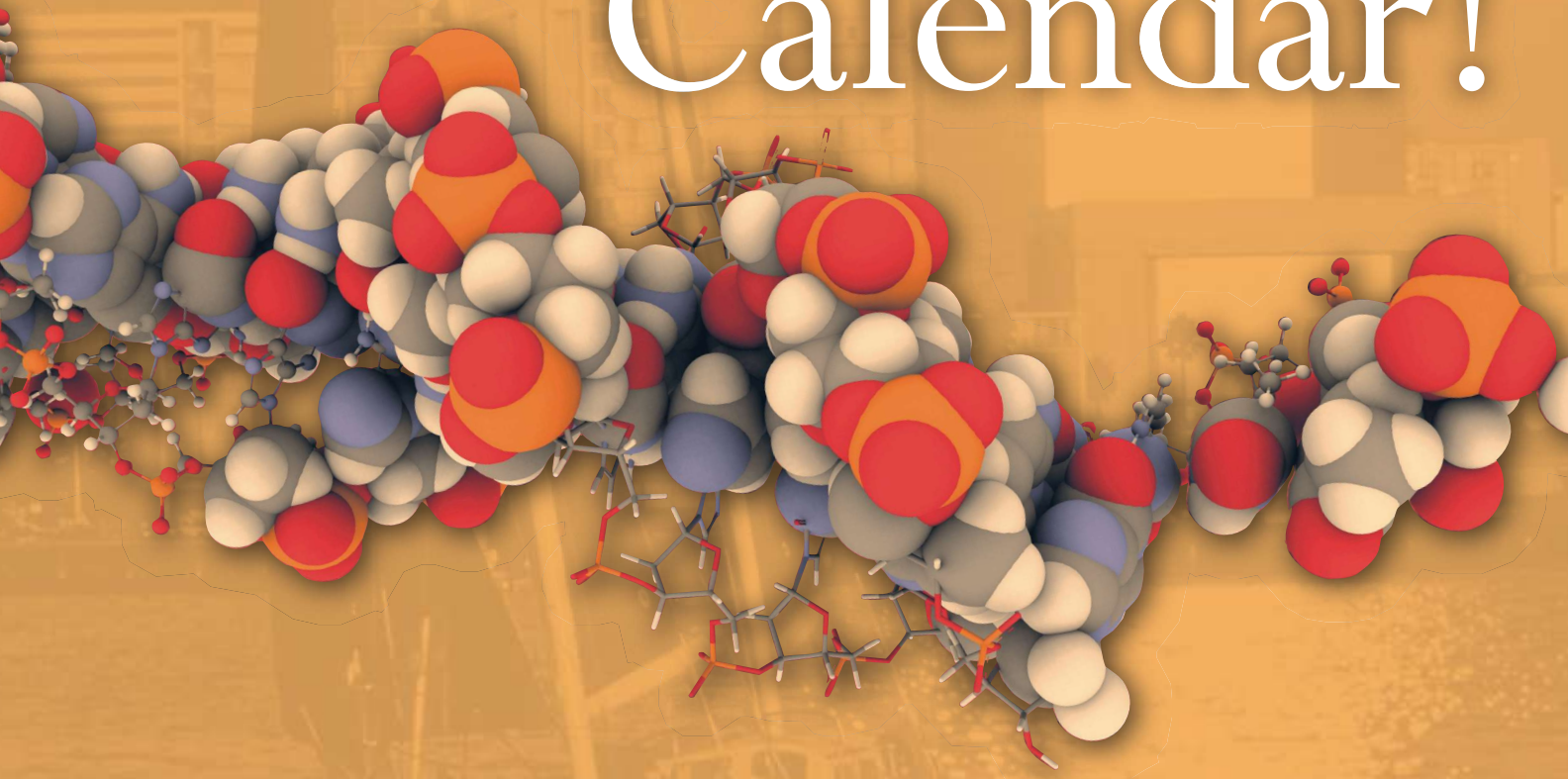

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TAP For CRT — Challenges Due To Product Temperature Criteria

There has been significant discussion over the past few years around TAP (temperature-assured packaging) for CRT (controlled-room temperature). Manufacturers and regulators have not yet decided how they want to handle this type of product, although some countries, such as Saudi Arabia, have already mandated that CRT products be shipped in proper TAP. As with refrigerated products, the regulations vary from strict label claim to acceptance of excursions with stability data. A couple of major questions have to be asked before the individual manufacturer or the industry can decide how to design the TAP. The first question is what temperature is going to be used. CRT has been defined as narrowly as 20° to 25°C through USP (United States Pharmacopeia), 15° to 30°C in some cases, and as broad as 5° to 25°C. To make the temperature decision, the manufacturer must look at its labeling and stability data to see what the company can support as well as regulations around the world. After this decision, the manufacturer must then decide what product needs to be packaged and controlled at what temperature. This decision is crucial to the cost of the package and potentially the profit margin on these products.

TAP PACKAGING — CRT VERSUS REFRIGERATED

The basics for the design of TAP packaging do not change from what has been done for 2° to 8°C products. Main characteristics, such as product temperature criteria, ambient shipping profile, payload size, transport time, seasonal versus universal designs, and conditioning are all the same. Basic materials available for insulation, such as EPS (expanded polystyrene), PUR (polyurethane), and VIP (vacuum-insulated panels), also are the same. Like refrigerated shipments, the PCMs (phase change materials) are critical. The decisions on what to use for insulation and refrigeration are first and foremost dependent on the product temperature criteria chosen, which can adversely affect cost and determines the insulation and refrigeration use.

CONSIDERATIONS BASED ON PRODUCT TEMPERATURE CRITERIA

As discussed above, a CRT product can have various temperature ranges. As also mentioned, this temperature criteria has a major effect on TAP costs and materials chosen. Like 2° to 8°C solutions, the type of insulation needed is most dependent on duration, with more insulation needed the longer the duration. Universal versus seasonal packouts are similar to that of other temperature classes in that universal is always more expensive. With CRT versus 2° to 8°C packages there can be a larger difference in packaging costs between summer and winter. With CRT the summer packout can be very inexpensive because much of the temperature profile is within or very close to the product temperature range. Winter is the challenge, as the product temperature for anything above 15°C is far from the winter profile temperatures, necessitating more and most likely advanced refrigerants, which can add significant cost. If the product temperature range is opened up to something like 5° to 30°C, the packaging becomes less challenging and therefore less costly than 2° to 8°C packaging, utilizing less-expensive water-based refrigerants or combinations of water-based and advanced refrigerants. One final challenge with a strict USP definition (20° to 25°C) for product temperature is that you actually need 1°C tighter control than 2° to 8°C, and the distance from 0°C virtually eliminates water-based refrigerants as a choice, as the package then becomes unreasonably large and heavy.

Ken Maltas

Ken Maltas is VP of engineering for Tegrant Corp. ThermoSafe Brands. Prior to joining Tegrant, he spent 27 years in the medical device industry in various positions related to engineering, operations, and quality management. For the last 18 years, Ken owned and operated his own medical device manufacturing company.

Iftekhar Ahmed

Iftekhar Ahmed is a senior design engineer for Tegrant Corp. ThermoSafe Brands. He previously spent 24 years in CAE (computer-aided engineering) software development and application with an emphasis on heat transfer.

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Tips To Reduce Timelines In Integrated Summaries Of Safety And Effectiveness

An ISS is an integrated summary of safety, and an ISE is an integrated summary of effectiveness. An ISS combines the safety results from different studies conducted in a compound, while the ISE combines efficacy results. The regulatory authorities state both the ISS and ISE are critical components of a submission.

WHY ARE AN ISS AND AN ISE CONSIDERED NECESSARY?

The combining of data in integrated summaries helps to address safety and efficacy concerns that are difficult to address using the data from individual trials. However, the regulators make it clear that a statistically significant result in an ISE is not sufficient to replace positive results in individual trials.

Combining the results from a number of different studies provides considerably more power for these important comparisons of safety and efficacy, while not taking away from a study's primary endpoint. The increased power in an ISS enables identification of rarer adverse events (AEs) that may not be evident from a single study.

PLANNING THE ANALYSES AND SUMMARIES REQUIRED IN THE ISS/ISE

Early planning of the ISS and ISE and the use of a statistician in the planning can help to identify and resolve potential problems at an early stage. This will make the process as efficient and cost-effective as possible. Planning an ISS and ISE prior to starting your pivotal studies enables you to introduce efficiencies, allowing data to be collected to answer specific questions. Producing a submission that is complete, consistent, and easy to follow will make the review process for the regulatory authorities easier and therefore quicker.

For the statisticians and programmers working on the integrated summaries, one of the most time-consuming tasks is the production of a database containing the combined study data. Differences in how the data is collected may determine if it is sensible to combine the data or what the results of the combined analyses actually mean.

As each submission is different, there are key messages you will need to address or specific statistical methodologies that are required and are unique to your submission. Early identification of these enables the statistician to address them prior to combining the results.

Combining results from independently designed studies that often address slightly different objectives is always going to be difficult. For example, study A may dose patients for three weeks, compared to study B that doses patients for six weeks. A combined summary of the number of patients who reported an AE may not be appropriate as one group of patients was 'at risk' and followed up for a greater time period. The statistician can help identify an appropriate methodology for addressing such issues. In this example, a solution may be to present AEs based using a denominator that adjusts for time at risk.

REPORTING OF THE STUDY

Once planning of the integrated analyses is complete, the statisticians and programmers will be involved in the production of the results based on the planned analyses. At this stage, close collaboration between the biometric team and the rest of the study team is still vital to ensuring a successful submission.

It is surprising how difficult it can sometimes be to locate the validated datasets and full supporting documentation. Production of combined derived datasets can be a lengthy task, and you should take into consideration the standards of older studies compared to newer.

In a well-planned submission, once the datasets are final, you can use macros to reduce the complexity of the output production for the ISS and ISE. If the biometrics of the ISS/ISE and pivotal studies have been centralized, then these macros can be used to produce the results from the pivotal studies too. As well as significantly reducing the time to reporting once the pivotal studies unblind, this can help to ensure consistency in the presentation of the results.

The integrated database is also essential for allowing rapid turnaround of questions from the regulatory authorities, as it simplifies production of outputs from the central database.

David Underwood

David Underwood is CEO and chairman of Quanticate. He has been in the pharmaceutical industry for more than 30 years.

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How To Decontaminate Your Decision Processes

By Chris Hitch

Whether you are evaluating an M&A candidate, creating a strategic alliance, analyzing licensing deals, or determining what to do about a leaky and eroding pipeline, how you set up the discussion with your senior team has an immediate and lasting impact on the decision. How can your team make the best decision? Avoid these contaminants, and use these tools to decontaminate your decision-making processes for your most critical decisions.

Decision-Making Process Contaminants

Information availability: *Avoid basing your decisions upon information you either have recently recalled or you vividly remember.* Suppose you decide to select a new vendor for part of your manufacturing process. You're guilty of this contaminant if you choose a vendor with whom you are comfortable and familiar, to the exclusion of others, based upon your requirements.

Confirmation Bias: This occurs when you look for data that confirms your theories about what should be done. You avoid (unconsciously) seeking information that disconfirms the evidence or process.

Anchoring and Adjusting: Once you commit to a course of action, even preliminarily, by saying "I think," you anchor and adjust all discussions around that initial decision point. You see this with budget targets that start with last year's numbers and then adjust upwards or downwards from that initial starting point.

Decontaminate Your Decision-Making Processes With These Tools

Question assumptions. Ensure assumptions are written and validated before deciding upon a solution.

Ask "cui bono" (to whose benefit). You want people to be passionate about the recommendation, yet you must solicit diverse opinions as well.

Validate what the problem is and when it needs to be solved. Clarify what success looks like, then review the process to confirm or disconfirm the proposed strategy to solve the problem.

Ask "what if that (the assumption) is not true?" Look for data that does not simply confirm the prevailing decision option.

Build consensus around understanding the issue, then look for diverse opinions on the solution. Take the time to ensure that everyone involved understands the issue and parameters at the outset. Follow that by looking for multiple solutions.

Question the numbers on spreadsheets or presentations. Dig into the numbers to determine underlying assumptions.

Allow all others to speak before you. Perhaps the best wisdom comes from a retired Navy Rear Admiral, who, during one of our seminars, reminded everybody, "When the boss says 'I think', the thinking stops."

Chris Hitch, Ph.D., is program director at UNC-Chapel Hill's Kenan-Flagler Business School. He has helped more than 2,000 C-suite executives improve organizational performance through strategy reviews, executive development, and organizational alignment. Contact him at chris_hitch@unc.edu.

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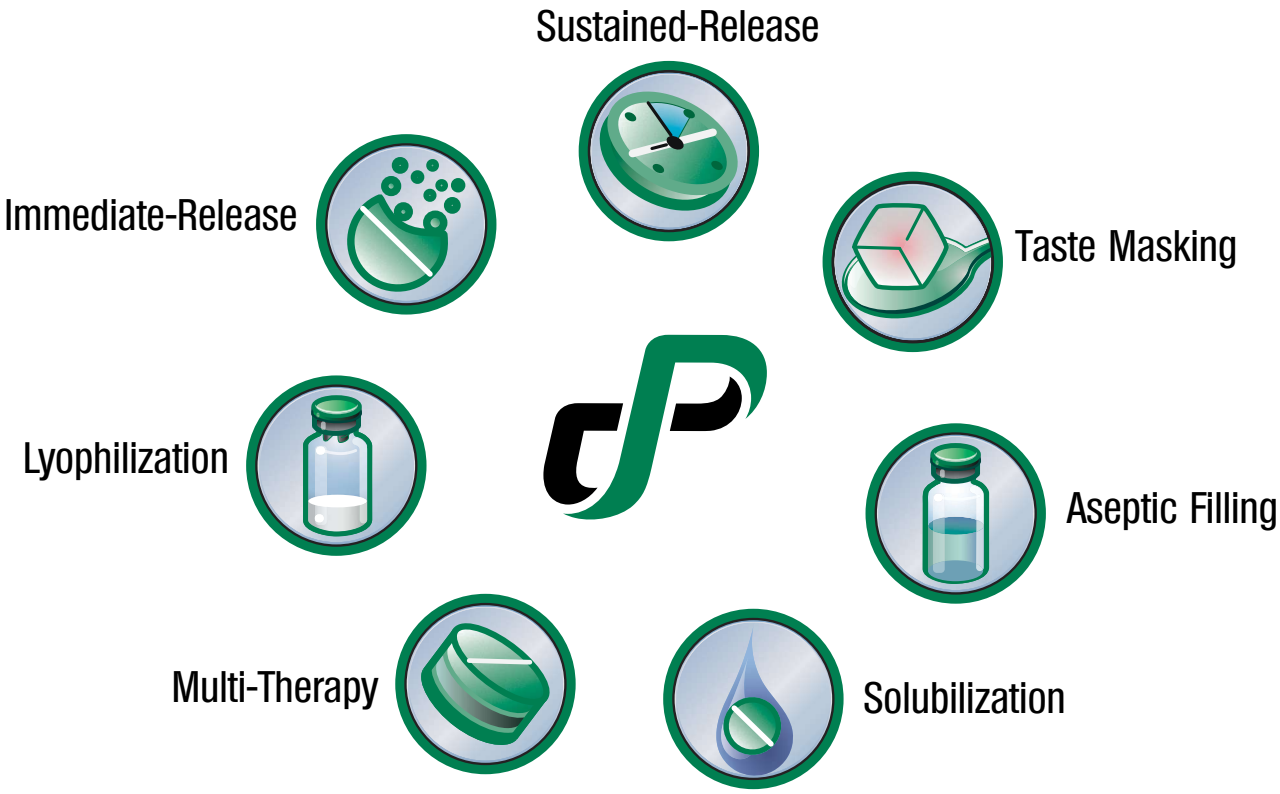

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