Life Science Leader
December 2013

COMPANY TO WATCH: Proteon Therapeutics

p. 13

Shire's Single-Use Gamble

"We cannot let fear push us in another direction, especially if we have a contingency plan." p. 18

Bill Ciambrone, Executive Vice President of Global Technical Operations, Shire

MPI RESEARCH

ONCOLOGY

ENDOCRINOLOGY

INFECTIOUS DISEASES

NEUROSCIENCE

ANALYTICAL/BIOANALYTICAL

CARDIOVASCULAR

DRUG SAFETY

GOING BEYOND

CANDIDATE SELECTION

Beyond Expectations.

MPI Research is more than your typical CRO. We are leading the way in drug and device development, from discovery through early clinical testing.

Beyond Transactional.

At MPI Research, our broad scope of preclinical and early clinical services are supported by excellent scientific expertise. As the world's largest preclinical research CRO in one location, our depth of experience enables us to offer a collaborative environment, the knowledge base to handle all types of studies, and the capability to smoothly transition from preclinical to clinical testing. Our Sponsors appreciate our ability to be their strategic partner in moving their drug or device along the development pathway.

LEAD OPTIMIZATION

Ready to Go Beyond?

OPHTHALMOLOGY

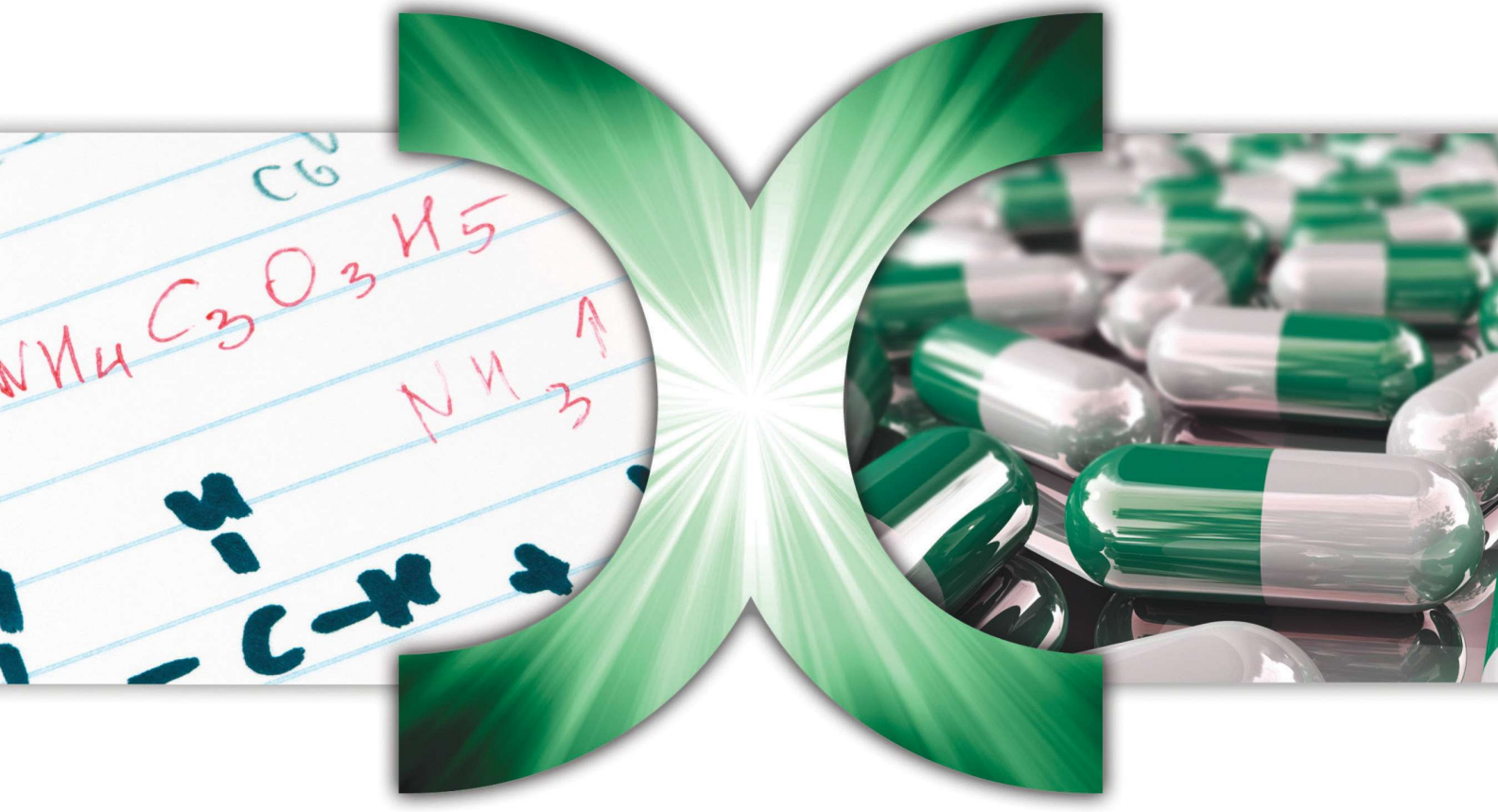
DRUG EFFICACY

For more information, visit **www.mpiresearch.com**

IMMUNE DISORDERS

RENAL

TARGET ID & VALIDATION



AT LAST

Early drug development made easy

Xcelience® is your premier source for formulation development and clinical supplies manufacturing and packaging solutions.

Since 1997, Xcelience has been known for reliably expediting drug product development and clinical manufacturing for oral solid, semi solid and liquid dosage forms. Our formulation development scientists have considerable experience overcoming challenges associated with physical and chemical properties of drug substance, or limited quantities of active pharmaceutical ingredient, in a manner that results in compounds with improved solubility and bioavailability.

Services include preformulation, analytical, method development/validation, formulation development, clinical supplies manufacturing, clinical supplies packaging and distribution.

We are more than just a service. We are formulation development, clinical manufacturing, clinical supplies packaging and distribution made easy - at last. Contact us today at **info@xcelience.com**, or call **813-286-0404.**

Xcelience®

www.xcelience.com

5415 West Laurel Street
Tampa, Florida 33607

Thank You

THE CMO LEADERSHIP AWARDS 2013 Quality Award

THE CMO LEADERSHIP AWARDS 2013 Innovation Award

THE CMO LEADERSHIP AWARDS 2013 Productivity Award

THE CMO LEADERSHIP AWARDS 2013 Regulatory Award

18 FEATURE: SHIRE

Bill Ciambrone, EVP of global technical operations at Shire, gives the backstory on the company's new $210 million single-use facility.

December 2013

Welcome to *Life Science Leader*

CONTENTS

Life Science Leader
A LIFE SCIENCE CONNECT BRAND

DEPARTMENTS

@RFWrightLSL
linkedin.com/in/robertfwright
pinterest.com/rfwrightlsl
facebook.com/LifeScienceLeader

GE Healthcare
Life Sciences

Stir up the fermentation game

The single-use XDR-50 MO system is purpose-built for microbial cultures to deliver performance you can trust, even under demanding conditions. With a robust design, the system exhibits powerful mass transfer, efficient temperature control and excellent gas dispersion. The flexibility of single-use technology maximizes your process efficiency.

Download the application note: Cultivations of E. coli and Pseudomonas fluorecsens in XDR-50 MO at **gelifesciences.com/upstream**

Xcellerex™ XDR-50 MO
single-use fermentor system

imagination at work

GE Healthcare Bio-Sciences Corp.
800 Centennial Ave., Piscataway, NJ 08855, USA

11/2013

Life Science Leader
A LIFE SCIENCE CONNECT BRAND

DECEMBER 2013

Life Science Leader
5340 Fryling Rd., Suite 300
Erie, PA 16510-4672
Telephone: (814) 897-7700 ● Fax: (814) 899-4648

LIFE SCIENCE LEADER (ISSN: 21610800) Vol. 5, No. 12 is published monthly by VertMarkets at Knowledge Park, 5340 Fryling Road, Suite 300, Erie, PA 16510-4672. Phone (814) 897-9000, Fax (814) 899-5580. Periodical postage paid at Erie, PA 16510 and additional mailing offices.
SUBSCRIPTION RATES for qualified readers in the U.S. $0. For non-qualified readers in the U.S. and all other countries $97 for one year. If your mailing address is outside the U.S. or Canada, you can receive the magazine digitally if you provide a valid email address. POSTMASTER: Send address corrections (Form 3579) to Life Science Leader, Knowledge Park, 5340 Fryling Road, Suite 300, Erie, PA 16510-4672.

What Is The Solution To Drug Shortages?

When I interviewed David Meeker, M.D., CEO of Genzyme for the October 2012 cover feature article, the focus was on how the company was helping Sanofi to break free from the blockbuster model. However, during our conversation, Dr. Meeker shared that one of the most difficult lessons learned in his career was failing a patient community by not being able to provide an adequate drug supply. This lesson involved Genzyme receiving FDA warning letters necessitating a shutdown of its Alston, MA, site in 2009. The result was a severe drug shortage for two life-sustaining rare-disease medications. When the article went live on the *Life Science Leader* digital edition, I tweeted about it. This resulted in one of my Twitter followers replying to the tweet — focusing *not* on the article but instead on Genzyme's failure.

Having worked in the industry for nearly 20 years, I am of the opinion, and perhaps naively so, that companies strive to invent life-sustaining drugs in order to help patients while, of course, making a profit. I do not believe Genzyme's failure to have been deliberate. That being said, the shortage not only damaged a company's reputation but also resulted in litigation and, most importantly, preventable patient pain and suffering. When I worked at Organon Pharmaceuticals, in 2004 we experienced a drug shortage for the neuromuscular-blocking agent Zemuron (rocuronium) — resulting from a manufacturing problem. The frustration on the part of the hospital sales team responsible for Zemuron was equal to that of clinicians clamoring for a resolution to the shortage. Nearly 10 years later, drug shortages seem to be getting worse. A recent *New York Times* editorial notes that as of July 31, 2013, 302 drugs were in short supply — up from 211 a year earlier. According to the article's authors, the drug shortage is not the result of numerous manufacturing issues but of something far more sinister.

In 1987, Congress enacted the Medicare anti-kickback "safe harbor," which exempted buying groups from criminal prosecution for accepting vendor kickbacks. A study in the fall 2011 issue of the *Journal of Contemporary Health Law and Policy* found that group-purchasing organization kickbacks inflated supply costs by at least $30 billion annually. Because these giant purchasing organizations control the procurement of up to $300 billion in drugs, devices, and supplies annually for some 5,000 healthcare facilities, it can be difficult to distinguish how these activities differ from those of a cartel. The Government Accountability Office (GAO) is investigating the role of group purchasing organizations in the drug shortages with a report expected in 2014.

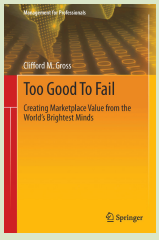
In the meantime, if you want to learn more about some of the causes of drug shortages and possible solutions, check out Cliff Mintz's article on page 44. Some might argue the solution to rising drug shortages is not as simplistic as reigning in healthcare GPOs (group purchasing organizations). The fact that most of the problem involves cheap sterile injectables sold through hospital-purchasing organization contracts, we need to realize — if it walks like a cartel, quacks like a cartel, looks like a cartel — it's a cartel. And the best way to deal with a cartel is not by enabling its activity through government legislation.

Rob Wright
rob.wright@lifescienceconnect.com
@RFWrightLSL

SOUTHWEST CARGO
RELENTLESSLY RELIABLE®

Outrageously *fast* shipping.

Southwest Airlines Cargo® can handle your expedited air cargo needs. With Next Flight Guaranteed (NFG℠) service and the Southwest Airlines® network, your time-critical shipment will arrive at its destination ontime. Our service is so reliable, we guarantee it. Visit **swacargo.com**® to open an account today!



WIN A COPY OF THIS BOOK!

Ask the Board wants to hear from you. Have a question that you would like to pose to our editorial advisory board of experts? Send it to atb@lifescienceconnect.com. If we select your question for publication, we will provide you with a complimentary copy of a business book or CD, such as *Too Good To Fail* by Clifford M. Gross.

ASK THE BOARD

Have a response to our experts' answers or a question of your own? Send us an email to atb@lifescienceconnect.com.

Q: When you first became a CEO, what is the one thing you wish you had done differently and why?

When I first became a CEO, the biggest shift was not the change in my duties, but the way in which I was perceived as I carried them out. I had to quickly formulate a blend of the legacy culture with my own leadership style and vision. Initially, I did not appreciate how uncomfortable the stylistic change of a new executive would be for many employees — it took several months before everyone was completely integrated and up to speed. If I were to do it again, I would have made more time very early on for one-on-one interactions to build rapport with my senior staff. While doing this would have required more investment at the beginning, it would have created a much more decisive and immediately effective start to my tenure.

Heather Erickson
Erickson is President & CEO of the Life Sciences Foundation, the independent steward of biotech heritage. Previously, she was founding president of MedTech Association, serving New York's bioscience community.

Q: What is one of the mistakes you have seen destroy a clinical collaboration, and what should have been done to avoid it?

Clinical collaboration generally breaks down when team relationships fray, and unless there is a personality conflict, the general cause of this deterioration is a misalignment of performance and expectations.

Increase the likelihood of a successful collaboration by augmenting ongoing open and frank discussions among teammates and their leaders with a lessons-learned process. Make a product of the kickoff meeting a well-designed lessons-learned document. For a Phase 2/3 study, perform the first lessons learned early — at the end of study start. The timing of other lessons-learned meetings is dependent on the length of the study and could be quarterly or milestone driven. I prefer face-to-face quarterly meetings to build the team with lessons learned as part of the agenda.

Tim Krupa
Krupa is president of TSK Clinical Development, LLC, a consulting firm providing leadership and solutions in clinical planning, project management, clinical operations, and outsourcing. He began his career with Eli Lilly, and he most recently served as executive director, project management with Quintiles.

Q: What is a common pitfall you have witnessed biotech entrepreneurs encountering, and what should they do to avoid it?

New biotech entrepreneurs often fall back on their scientific training and strive to tweak their work until they are 100 percent satisfied. It can be difficult for them to move quickly in a commercial setting and either "let go" of a project and allow the idea to move through the commercialization process or to decide to "kill" the project. Entrepreneurs need to rely on their network of colleagues and experts whose opinions they trust to help them know what to move forward. Holding on too long to a project that may not be commercially viable can be the death knell of a company. New entrepreneurs need the passion to champion their project but also the wisdom to know when to change course or direction.

Lynn Johnson Langer, Ph.D., MBA
Langer is president emeritus of Women In Bio (WIB) and the director of enterprise and regulatory affairs programs in the Center for Biotechnology Education at Johns Hopkins University where she teaches graduate courses in biotechnology leadership and management.

inVentiv Health Clinical

Advancing Clinical Innovation

inVentiv Health Clinical combines state-of-the-art clinics and bioanalytical labs, leading therapeutic expertise in Phase II-IV, and customizable strategic resourcing approaches to provide a full range of clinical development services to accelerate drug development.

- Global Footprint: A top 5 CRO operating in more than 70 countries
- Therapeutic Excellence: Leading therapeutic expertise aligned to all stages of development
- Patient Recruitment and Retention: Data-driven and research-informed communication strategies to maximize effective patient recruitment and retention
- Late Stage Expertise: Effectively generating and persuasively communicating evidence of real-world safety and value
- Strategic Resourcing: Adaptive, cost effective solutions from contingent staffing to functional models and staff lift-outs

inVentiv Health clinical

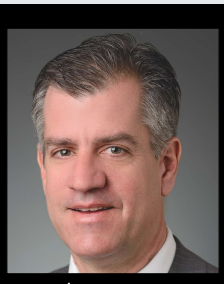
inVentivHealthclinical.com/innovation

Meeting The Antibiotic Pipeline Challenge

"For a long time, there have been newspaper stories and covers of magazines that talked about 'The end of antibiotics, question mark?' Well, now I would say you can change the title to 'The end of antibiotics, period.' We're here. We're in the post-antibiotic era. There are patients for whom we have no therapy, and we are literally in a position of having a patient in a bed who has an infection, something that five years ago even we could have treated, but now we can't."

This is the recent scary report from Dr. Arjun Srinivasan, the associate director at the CDC, told to PBS' Frontline. It's truly incredible we have reached this point, but it's been validated by many other sources.

Sally Davies, the chief medical officer for England has said, "There is a broken market model for making new antibiotics, so it's an empty pipeline," and Dr. Margaret Chan, the director-general of WHO, announced that the "R&D pipeline for new antimicrobials has practically run dry. In the absence of urgent corrective and protective actions, the world is heading toward a post-antibiotic era."



John McManus,
The McManus Group
jmcmanus@mcmanusgrp.com

These health leaders are right — multidrug-resistant bacteria are killing tens of thousands of people every day, while major pharmaceutical interests have exited the business. The Infectious Diseases Society of America reports that the FDA has approved just two antibiotics in the past two years compared to 16 between 1983 and 1987. And even these two products were not meant to combat the most pressing pathogens, gram-negative bacteria that are resistant to most existing therapeutics.

FEW FINANCIAL REWARDS = LESS INNOVATION

It's not difficult to speculate why companies such as Bristol-Myers Squibb and Pfizer have quit investing in this sector. Maintenance drugs for chronic conditions that require months or even years of therapy can result in substantial returns to a pharmaceutical company. Antibiotics must be used for only a brief duration and on a limited basis, and providers still reserve the most novel products for last-resort-use-only.

Public health advocates, hospitals, and others encourage a fail-first approach with older medications such as vancomycin and penicillin before newer, more powerful antimicrobial agents are applied. There is a legitimate fear that the newer, more effective drugs will be overutilized, and the bacteria will form resistance to these lifesavers.

The CDC report *Antibiotic Resistance Threats in the U.S. 2013* notes that more than two million people are sickened every year with antibiotic resistant infections, with at least 23,000 dying as a result. Almost 250,000 people are hospitalized for Clostridium difficile infections, where the use of antibiotics was a major factor leading to the illness.

Yet in the face of this unmet medical need, pharmaceutical manufacturers are bailing out and not meeting the challenge of drug-resistant bacteria. Brad Spellberg, professor at UCLA and author of *Rising Plague: The Global Threat from Deadly Bacteria and Our Dwindling Arsenal to Fight Them*, commented, "We have what has been accurately termed on Capitol Hill a market failure of antibiotics. The traditional capitalistic market has not supported antibiotic trials. It has collapsed."

"The market for new antibiotics is very small, the rewards are not there, and so the capital is not flowing," commented Paul Stoffels, the head of pharmaceuticals for Johnson & Johnson. "In cancer, people pay $30,000, $50,000, or $80,000 for a drug, but for an antibiotic it is likely to be only a few hundred dollars."

Last year, Congress responded by enacting the GAIN (Generating Antibiotic Incentives Now) Act, which expedites the approval of antibiotics by providing applications with priority review and additional nonpatent exclusivity rights. Yet that legislation does not address the fundamental economic challenges in marketing and commercializing novel products in this area.

One such challenge is how Medicare reimburses hospitals for antibiotics. Hospitals are reimbursed a predetermined amount per discharge, based on a patient's diagnosis and procedures, known as Medicare Severity Diagnosis-Related Groups (DRGs). As new technologies are introduced, DRGs can be recalibrated to reflect increased costs, but that requires time and significant volume use of that technology — two factors absent from the novel antimicrobial marketplace. The present DRG system means that purchase of such products is a financial loser for hospitals.

Scott Gottleib, an economist at the American Enterprise Institute and former senior FDA official, has suggested focusing on reforming the New Technology Add-on

Bringing peace of mind to you, your patients, and the world

At DSM, our goal is to help you achieve your objectives both for today and the future. Consequently, we help you rapidly bring life-saving and life-enhancing medicines to the people who need them. Working with DSM gives you the confidence that you have a reliable, stable partner who can provide services for the entire life cycle of your products.

Services

:: (Bio)chemistry Tech Packages
:: Microbial Fermentation
:: Sterile Dosage Forms
:: Regulatory Support
:: Advanced API's & Intermediates
:: Mammalian Manufacturing
:: Solid Dosage Forms
:: R&D Services

DSM Pharmaceutical Products
45 Waterview Boulevard
Parsippany, NJ 07054-1298
Tel: +1 973 257 8011
www.dsm.com/pharma

THE CMO LEADERSHIP AWARDS 2013 | WINNER

QUALITY RELIABILITY INNOVATION PRODUCTIVITY

Quality for Life®

For DSM, quality is a way of life. This is the core of Quality for Life™. Quality for Life™ is the mark of quality, reliability and traceability. It means that DSM customers are getting superior products and services, knowing the source on which they depend. Quality for Life™ means sustainability. It symbolizes our commitment to our environment, consumers, our business partners, our people and the regulatory framework that governs our operations.

Quality for Life™, peace of mind for you and your customers.

HEALTH · NUTRITION · MATERIALS

DSM
BRIGHT SCIENCE. BRIGHTER LIVING.

Payment (NTAP) program, meant to integrate technology into Medicare sooner. In its 13-year history, only two drugs have received additional reimbursement under that program. The NTAP application process is convoluted and challenging. Even if a manufacturer is successful, the designation is limited to two to three years, and the program provides only partial assistance — still requiring hospitals to eat part of the cost of the new technology.

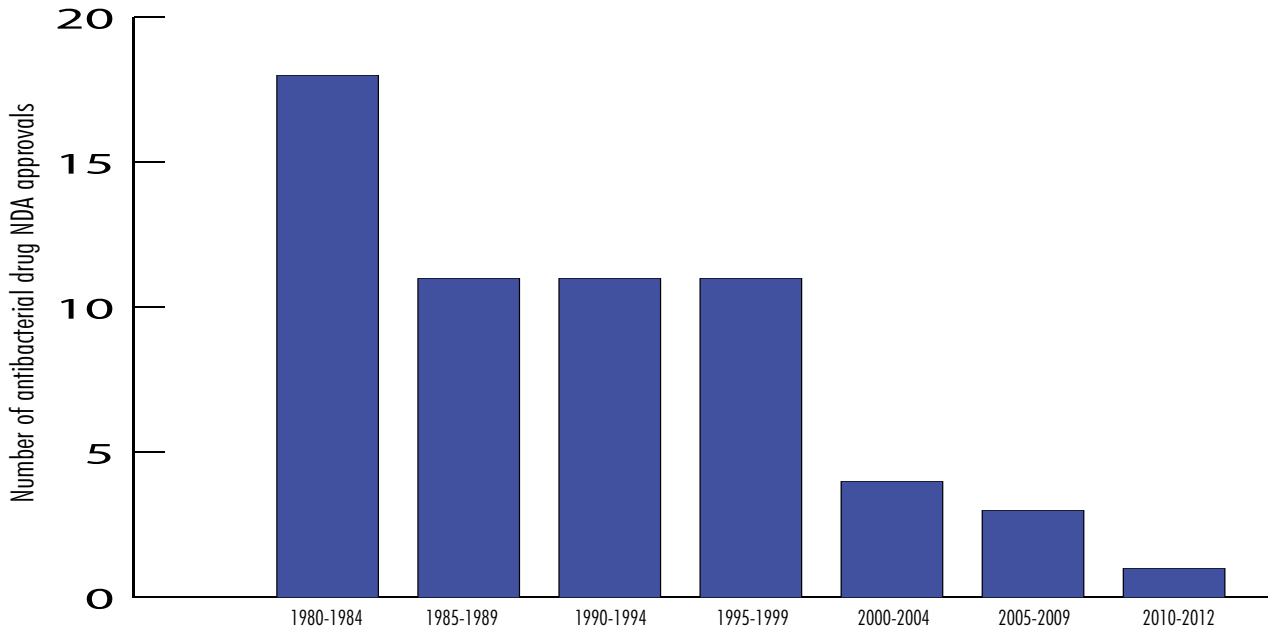
HOW NEW LEGISLATION COULD HELP

Therefore, some in Congress are now mulling a legislative solution that would provide Medicare reimbursement at acquisition cost of new antimicrobial products provided in the inpatient setting for unmet medical needs. Enactment of such a provision means the hospital administrator would decide to purchase the novel antimicrobial on its clinical merits only, and financial considerations would be taken off the table. Because so few products would be affected and their prices are modest, the cost to Medicare would be insignificant. But it would make a huge difference to patients who have run out of options.

Now some pharmaceutical companies are also considering new methods for leaving the commercialization and marketing of new products to third parties and focusing solely on developing new products and receiving commitments for reimbursement for the R&D costs.

These types of out-of-the-box thinking and market flexibilities are necessary if we are ever going to reestablish a vibrant antimicrobial pipeline. Otherwise the "post-antibiotic era" will be permanent and very dangerous.

Number of Antibacterial New Drug Application (NDA) Approvals vs. Year Intervals*



*Intervals from 1980-2009 are 5-year intervals; 2010-2012 is a 3-year interval.
Drugs are limited to systemic agents. Data courtesy of FDA's Center for Drug Evaluation and Research (CDER).

John McManus is president and founder of The McManus Group, a consulting firm specializing in strategic policy and political counsel and advocacy for healthcare clients with issues before Congress and the administration. Prior to founding his firm, McManus served Chairman Bill Thomas as the staff director of the Ways and Means Health Subcommittee, where he led the policy development, negotiations, and drafting of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003. Before working for Chairman Thomas, McManus worked for Eli Lilly & Company as a senior associate and for the Maryland House of Delegates as a research analyst. He earned his Master of Public Policy from Duke University and Bachelor of Arts from Washington and Lee University. He can be reached at jmcmanus@mcmanusgrp.com.

By Wayne Koberstein, executive editor

Proteon Therapeutics

Focusing on a single treatment complication, this start-up is developing a drug to prevent dialysis access failure.

SNAPSHOT

Proteon Therapeutics has the singular purpose of treating the bane of nearly all kidney dialysis patients — stenosis and failure of the surgically placed vascular access for hemodialysis. Access failure leads to thrombosis and surgical interventions to restore blood flow, such as thrombectomy, angioplasty, and often creation of a new access. Proteon's PRT-201, a "locally-acting recombinant human elastase" is applied to the external surface of the artery and vein during the surgical procedure. Having completed a Phase 2 trial and with FDA orphan and fast-track status, the drug is intended to reduce tissue growth inside vessels that causes poor blood flow, thrombosis, and vascular access failure.

LATEST UPDATES

• Q1 2013: Positive Phase 2 results for PRT-201 in chronic kidney disease patients undergoing surgical placement of an arteriovenous fistula in preparation for hemodialysis.

• Q4 2013: Presentation of Phase 2 results at various scientific conferences focused in the area of nephrology and vascular access.

Timothy Noyes, president & CEO

WHAT'S AT STAKE

For this company, everything rides on a single strategy — treat serious, health-degrading, and often life-threatening ancillary conditions in patients with chronic kidney disease on hemodialysis. I picked the company this month chiefly because it highlights a little-discussed fact concerning morbidity and mortality — people frequently suffer and perish, not from the main disease that afflicts them, but of secondary effects of their disease state. Many cancer patients die of pneumonia; diabetes patients, of heart disease; quadriplegics, of pressure sores. In dialysis, the culprit can be a side effect of the treatment itself, for it requires a surgical alteration to large veins and arteries to allow access and exchange of blood with the dialysis machine. Starting immediately after the access is created, a rapid build-up of vascular scar-tissue frequently strangles blood flow and eventually renders the access unusable.

Proteon's central asset is the IP for an invention made at Johns Hopkins University by Nicholas Franano, M.D., who founded the company and still sits on the board as "a spiritual source of energy," according to its president and CEO, Timothy Noyes. Its rDNA-produced enzyme is designed to improve "vascular access outcomes," he says. "When a vascular access site fails, you can no longer get dialysis, which is sustaining your life. Unfortunately, more than 50 percent of patients will experience failure of their vascular access sites in the first year post-surgery."

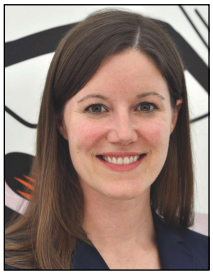
The cause of access failure is typically stenosis and restenosis, actually an aggressive healing response in the affected blood vessels known as neointimal hyperplasia. Kidney-disease patients are already uremic, so neointimal hyperplasia will rapidly narrow the vessels to the point where access is no longer usable. "So a patient comes in for dialysis, but the fistula has failed because it's either clotted or narrowed, and the patient goes off to get a balloon angioplasty. But this is someone who's typically 65 or older, has heart failure, diabetes, hypertension, tremendous GI upset, takes about 20 medications on average, is disabled and infirmed, and is already feeling terrible from all the toxin build-up. The fear and the frustration are immense."

The company's recombinant enzyme is applied directly to the access point during the surgical procedure, and so far it appears to dramatically slow the vessel's blockage. Results of its Phase 2 trial showed about a 50-percent reduction in the access failure rate among treated patients. That could translate into a reduction of nearly one full intervention per patient per year, according to Noyes.

Hinting at further development and expansion of the company's mission, Proteon is mid-way through enrollment of a Phase 1 study of patients with peripheral artery disease (PAD). For the vascular access indication, the company pins many of its hopes on the product's fast-track, accelerated approval status and what Noyes calls, "the real consensus formed in the past 10 years in the dialysis community that, based on overwhelming data, performance of the vascular access is directly related to a dialysis patient's quality and length of life."

VITAL STATISTICS

- Employees: 11
- Headquarters: Waltham, MA.
- Finances: Raised a total of $78 million in a series of private financing rounds (Series A, B & C) since 2006 with participation by TVM, Prism, Skyline, Intersouth, MPM, Bessemer, and Devon Park.



OUTSOURCING INSIGHTS

What Can 2013 Outsourcing Trends Lead Us To Expect In 2014?

By Kate Hammeke, director of marketing intelligence, Nice Insight

As 2013 draws to a close, many of us are wondering what surprises 2014 may bring in the drug development industry. Having a look back at some trends from the past year offers insight into potential changes to come. An important trend demonstrated by buyers of outsourced services was an increase in anticipated spending on outsourcing over the prior year illustrated by the 7 percent upturn among respondents with expenditure between $10M and $50M per year and a corresponding drop in the percentage of respondents whose outsourcing expenditure was under $10M. This increase in expenditure also occurred without a corresponding increase in the overall number of projects or services outsourced. Nice Insight anticipates outsourcing spending to continue to rise modestly in 2014, chiefly because it translates to reduced internal costs.

For the past two years, research data has shown that quality (1) and reliability (2) consistently rank highest among the six key drivers of partner selection.

For the past two years, research data has shown that quality (1) and reliability (2) consistently rank highest among the six key drivers of partner selection. This ranking isn't likely to change in 2014, even though there has been some shuffling in the rankings of other attributes — namely a rise in the importance placed on regulatory track record and a decrease in prioritization of affordability. The CRO and CMO benchmarks for quality and reliability increased by 1 percent and 3 percent respectively from 2012 to 2013, suggesting that these groups recognized the importance of the key drivers in the eyes of buyers and are making an effort to improve accordingly. It will be interesting to see whether there's another increase in these benchmarks in 2014.

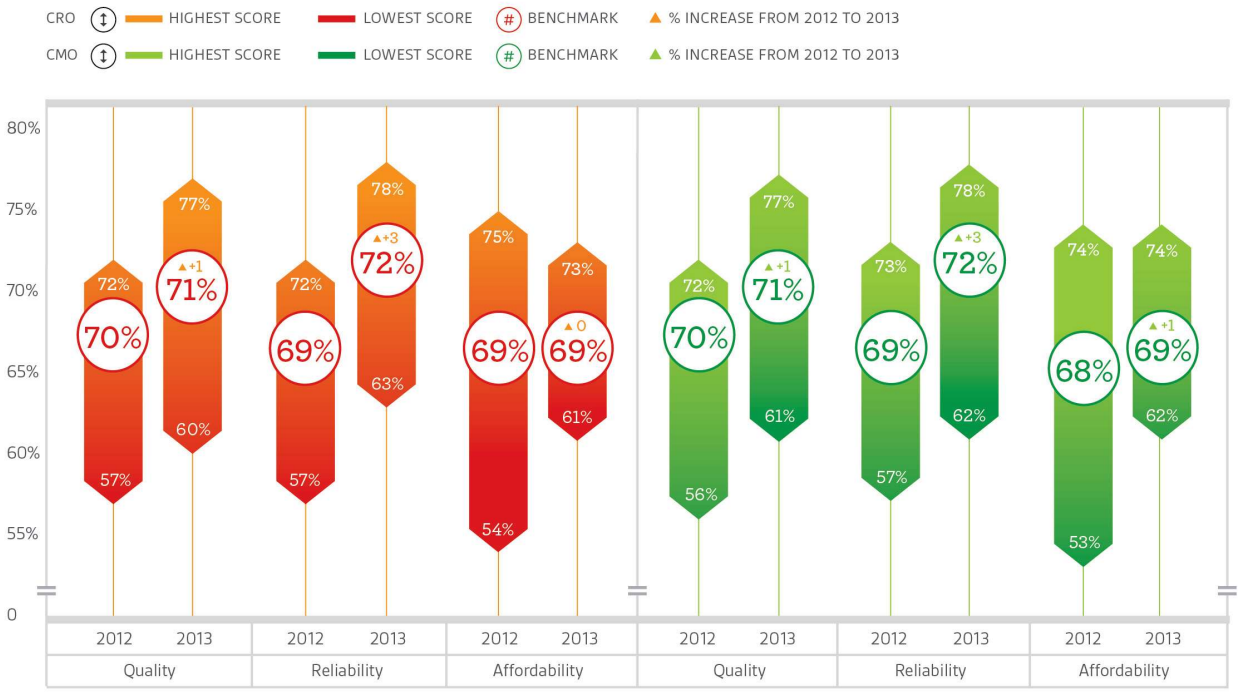
The decline in the perceived importance of affordability when selecting an outsourcing partner to fourth position in 2013 was mirrored by findings from several custom-research projects focused specifically on pricing. It reflects the broader value that a good relationship with a CRO or CMO can bring beyond cost savings, such as the ability to focus on core competencies, access to scientific expertise, and increased productivity. Respondents expressed some pitfalls that occur when too much emphasis is placed on price up front — namely, the frequency of add-on charges or change orders that result in delays. In light of this, it is likely that affordability will continue to decline in priority. The question is, will innovation or productivity take its place?

REGULATORY IMPORTANCE RISES

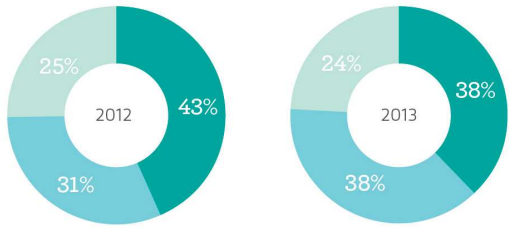
Over the past year there has been an increase in the importance placed on a company's regulatory track record, climbing from fifth position in 2012 to third in 2013. During both 2012 and 2013, a quarter of survey respondents confirmed that their company would engage a CRO or CMO for regulatory support, making this service the fifth most popular in 2012, rising to fourth in 2013. This escalation came shortly after a few well-respected companies received FDA warnings, or worse, product recalls. Nice Insight anticipates regulatory compliance remaining in the top three partner selection drivers in 2014, alongside quality and reliability. The question will be whether sponsors continue to engage CROs and CMOs for regulatory support at such a high rate, or if the challenges of the past few years will prompt innovators to rely more on internal regulatory expertise.

The consistent prioritization of quality and reliability and the escalation in demand for regulatory expertise undoubtedly relate to some well-publicized issues over the last few years, and perhaps some increased scrutiny. As ever, this creates opportunity for companies that approach the circumstances proactively. Drug innovators should seek out the contract service providers that are able to position themselves accordingly for a winning partnership in the year ahead.

Drivers that Influence Outsourcing Partner Selection



Annual Outsourcing Expenditure



Outsourcing Drivers in Ranked Order of Importance

2012		2013
1	Quality	1
2	Reliability	2
3	Affordability	4
4	Productivity	5
5	Regulatory	3
6	Innovation (Accessibility in 2011-2012)	6

Survey Methodology: The Nice Insight Pharmaceutical and Biotechnology Survey is deployed to outsourcing-facing pharmaceutical and biotechnology executives. The 2012-2013 report includes responses from 10,036 participants. The survey is composed of 500+ questions and randomly presents ~30 questions to each respondent in order to collect baseline information with respect to customer awareness and customer perceptions on the top 100+ CMOs and top 50+ CROs servicing the drug development cycle. Over 900 marketing communications, including branding, websites, print advertisements, corporate literature, and trade show booths are reviewed by our panel of respondents. Five levels of awareness from "I've never heard of them" to "I've worked with them" factor into the overall customer awareness score. The customer perception score is based on six drivers in outsourcing: Quality, Innovation, Regulatory Track Record, Affordability, Productivity, and Reliability.


Walker

If you want to learn more about the report or how to participate, please contact Nigel Walker, managing director, or Salvatore Fazzolari, director of client services, at Nice Insight by sending an email to niceinsight.survey@thatsnice.com.

BIO INNOVATION NOTES

Critical Innovation BioProcessing Trends For 2014

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

As 2013 draws to a close, the biopharma industry is looking harder than ever to reduce the sometimes exorbitant cost of manufacturing a biologic. So, using data from our *10th Annual Report and Survey of Biopharmaceutical Manufacturers*, we'll discuss some of the most critical innovations in biomanufacturing and how those innovations will affect the industry in the future.

1. Single-Use Innovation Will Continue To Excite Interest

Much of the demand for innovation continues to center on single-use equipment. Biomanufacturers and CMOs continue to define an extensive list of areas in which they want their suppliers to focus development efforts. In the current study, and in other research, the industry has clearly indicated it needs new and better disposable products. Disposable bags and connectors top the list (44 percent of end users), followed by disposable probes and sensors (40 percent), disposable bioreactors (34 percent), and disposable purification products (34 percent). We expect these rankings will remain consistent in 2014. While stainless-steel equipment remains the dominant paradigm for commercial manufacture, only 5 percent of respondents expressed an interest in innovation in this mature area, putting it at the bottom of the list.

Although few decision makers are actively demanding stainless-steel innovation, trends favor continued improvements in this area, ranging from the use of state-of-the art real-time processing-monitoring-and-control systems to specialized compatibility innovations required by hybrid platforms (e.g. single-use combined with fixed systems).

2. Better Assays: Vendors Need To Focus On R&D

While vendors may be listening when it comes to disposables innovation, end users hoping for better assays might be disappointed. In recent years, we've noted a significant increase in the need for improved assays in a variety of areas. The assay areas most urgently in need of new or improved testing methods, according to respondents of our latest study, include aggregation, bio-assays to assess potency for release of drugs, and biotech drug comparability (for in-house manufacturing changes as well as biosimilars).

But when we asked about which areas were the focus of new product research, it turns out that few respondents were working to fix assay methods or probes. In fact, only around 1 in 10 vendors — in some cases even fewer — is working on testing or assay products. These products ranged from simple probes and sensors to complex raw materials testing (11 percent), to biosimilarity testing (9 percent) and glycosylation analysis (8 percent). As for disposable sensors, the most critical need for innovation pertains to pH sensors, with nearly three-fourths of respondents saying they would like to see improvements in this area. In 2014, vendors will likely heed the call and commit to developing better sensors and probes, although perhaps not to the higher level seen with disposable bags, consumables, and films.

3. Connecting And Integrating Systems In Demand

It's clear from our study that many respondents expect a fully disposable facility to be operational within the next five years. Before that bold vision is realized, the industry will have some very small devices to thank for the ability to use single-use equipment in an integrated fashion — connectors. Disposable connectors, which can link and integrate devices from the same or different vendors, offer great flexibility. These are in demand at the moment both in the U.S. and the EU, and by CMOs and biopharma manufacturers alike. And the rate of interest in innovation in this area has been steadily rising for a couple of years. There's reason to believe vendors respond to this need, and improvements will continue through 2014.

4. Chromatography Alternatives? Not Quite Yet

The slow pace of innovation in assay development is affecting broad areas of the industry. But the problem facing a large percentage of end users is the chronic pain and costs associated with chromatography. End users recognize that current methods work very well (despite the current high costs and purification bottlenecks). Therefore, they may not be pressing for advances as aggressively as in other areas. Some alternative purification technologies are being developed, but few facilities are actually following through on their intentions to switch to protein A alternatives. In fact, intent to switch appears to be waning — and has been for a few years now. Only 1 in 10 respondents said they're seriously considering alternatives for existing production units. That's the lowest figure in several years.

We continue to see a steady proportion of respondents stating that they expect to move away from Protein A over the next 12 months. But in this case, action doesn't always seem to follow intent. For example, despite about one-fourth of respondents saying they'd investigated alternatives to Protein A during the past year to improve downstream purification operations, only about five percent said they actually made a switch. In other words, of the respondents who were considering alternatives last year, only about 20 percent followed through.

5. High-Capacity Resins And Other Downstream Processing Innovations

Facilities may be lukewarm in their pursuit of alternatives to protein A, but that attitude doesn't apply to all downstream technologies. In addition to interest in other high-capacity resins (showing a 10 percent point jump since 2010), decision makers are considering better single-use filters, an area that is also growing rapidly (e.g. from 29 percent in 2010 to 44 percent this year). Interestingly, when it comes to downstream purification, single-use disposable TFF (tangential flow filtration) membranes might be a new technology to keep an eye out for. As mentioned in previous columns, we see CMOs as the catalysts for industrywide adoption of innovative technologies, and they seem particularly drawn to disposable TFF membranes this year.

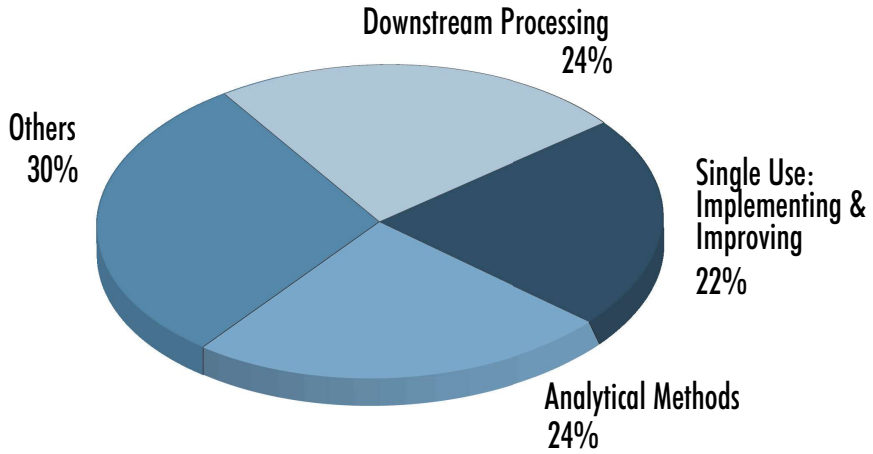
FACTORS CREATING DEMAND FOR INNOVATION

Almost a year ago, we asked the more than 450 global subject matter experts and senior biopharma participants who make up our Biotechnology Industry Council to identify the macro trends in the industry, along with their vision for the future. Here are some of the areas they expect will be driving the "innovation dialog":

- more multiproduct facilities
- more single-use adoption at commercial-scale biomanufacturing
- more continuous processing
- more automation, requiring increased process monitoring
- development of better characterization tools and improved high-throughput, high-resolution glycosylation analysis
- better models for demonstrating biosimilarity
- design strategies that emphasize flexibility, adaptability to new enabling technologies, clone-ability of spaces, equipment separation, and centralized material support.

We are excited to follow where these developments will bring us in 2014.

Biomanufacturers' Top Trends, 2013



450 Biotech Industry Council responses to trends for 2013, Dec. 2012.
Others = platforms, cost reductions, materials sourcing, supply chain regulatory compliance, biosimilars, etc.

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

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

Bill Ciambrone, EVP of global technical operations, Shire

Photos by W. Marc Bernsau

Shire's $210 Million Single-Use Gamble

BY ROB WRIGHT

In 2010, Shire (NASDAQ: SHPG) completed Project Atlas — a biologics manufacturing facility (building 400) on its Lexington, MA campus. At 200,000 gross square feet (GSF) and a total direct cost of $210 million, the facility represents a sizable investment. However, what makes this facility different from most pharmaceutical manufacturing buildings is that it takes significant advantage of single-use systems (SUS). In fact, its entire upstream line utilizes SUS technology. This story is made more interesting when you consider that at the time when Project Atlas was conceived (2007), the company's annual sales revenues were $2.4 billion, with profit after expenses of $82.4 million — $127.6 million shy of the plant's $210 million dollar price tag.

But what really made this a bit of a gamble was that when the plant was designed and construction began, it was with the knowledge that the technology necessary to operate the facility, namely a 2,000L SUS commercially available bioreactor, did not exist! "The closest thing we had was a prototype by one of the vendors," says Bill Ciambrone, executive sponsor of the project. The EVP of global technical operations and 20-year industry veteran, Ciambrone recounts Shire's decision-making approach, the process of gaining buy-in from the team and regulatory bodies, and the various risk mitigation strategies employed.

NECESSITY — THE MOTHER OF DECISION MAKING

In 2005 Ciambrone was working for Transkaryotic Therapies (TKT), which was acquired that year by Shire. He says even back then while he was at TKT the need for a Project Atlas-like facility was evident. "We were a small biotech focused on orphan diseases," he explains. "We knew we would be dealing with mammalian cell cultures, operating largely in perfusion, but there was uncertainty about which products in development would successfully come forward." This uncertainty about which product would get FDA approval proved to be a driving factor for the type of plant to build at Shire. "How do you best deal with uncertainty?" he asks rhetorically. "It is hard to deal with uncertainty if you build a bunch of hard-pipe reactors of a certain size when you aren't sure which products will be approved and will require commercial manufacturing capabilities. If you do create a hard-pipe configuration, you may be operating suboptimally with higher costs than the product really needs." Because Shire was faced not with the prospect of manufacturing blockbuster products for millions of patients but with specialty drugs, the need for increased manufacturing capacity was superseded by an even bigger need — manufacturing flexibility. "The flexibility we needed was for producing multiple products, possibly even multiple scales, but all within a small scale," Ciambrone explains. In addition, the company had a tremendous need for getting the plant up and running quickly. It was even more important to do so considering Shire's competitor, Genzyme, was experiencing manufacturing deficiencies at its Allston, MA plant. An FDA warning letter in March 2009 led Genzyme to shut down the plant just three months later — resulting in a severe drug shortage for two life-sustaining, rare-disease medicines (Cerezyme and Fabrazyme). In addition, the Cerezyme shortage resulted in Shire getting FDA fast-track designation for its experimental Gaucher treatment, VPRIV (velaglucerase alfa for injection). "We thought we had an accelerated schedule of bringing a plant up and running by going with SUS," he states. "The competitor's supply crisis resulted in our having to accelerate everything even faster."

When the Shire team looked at the various approaches to building a new plant, the positives of single-use technology were significant. "There were almost no negative points except for the uncertainty of the technology not yet being in existence," he affirms. "If you believed in what the technology promised, you could build 'a box' [a building with an open floor plan] that could support perfusion over a variety of scales. And then you could decide which reactors to install later without changing the speed at which the plant could be built." To support the decision-making process of building such a flexible plant, Ciambrone's team conducted an algorithm analysis of a number of potential product-mix scenarios. "The algorithm showed the impossibility of the solution," he explains. "There was no hard-and-fast outcome saying, 'install two 2,000s and two 500s, and those reactors will cover enough capacity.'" Further, none of the configurations addressed the speed question. For example, when you build a traditional plant, install utilities, reactors, and equipment, only then can you begin the

WHY NOT SIMPLY OUTSOURCE MANUFACTURING TO A CMO?

Given the rise in popularity of outsourcing pharma manufacturing, it would be natural to ask Bill Ciambrone, EVP of global technical operations at Shire, if using a CMO was considered instead of building its cell-culture manufacturing facility in Lexington, MA. "I don't think there was a single CMO that would have fit the bill because of the small volume of multiple products," he states. "It is very costly to partner with a CMO when you cannot promise exactly what is coming." Ciambrone notes prior to the recent formation of Gallus BioPharmaceuticals, there wasn't a CMO with the SUS capability he was seeking. "We would have had to invest a lot with any CMO, and economically it would not have made sense," he states. "They get different margins on small volumes. With perfusion, you are occupying whatever space they have for a long period of time. No one was able to cost effectively meet the demands our product lines required." Even though it could not find one CMO with the actual capacity for the time period required, Shire conducted a detailed financial analysis to assess outsourcing as an option to further support the decision to build. "Even with the investment of building a $210-million plant, we were able to more cost effectively produce the range of products we needed on a cost per liter, cost per gram basis when compared to CMOs."

Another option considered involved developing a strategic partnership with a CMO. "When we looked at potential partners, they already had a lot of clients occupying space," he states. "In some cases the best deal we could get was to build something for them. This was how we decided having control justified the expansion and expenditure." According to Ciambrone, when it came to trying to broker a strategic partnership, there was not enough willingness for an equitable sharing of costs and risks on the part of CMOs to make a strategic partnership economically feasible. In the end, the need for flexibility became the ultimate deciding factor. "Because the CMO is not the client, you never really have complete flexibility when outsourcing," he notes.

Imagine diagnostic equipment telling you when it needs a check-up.

The AT&T M2M Platform can tell you where equipment is located and how it's performing. See how M2M data can help you optimize efficiency while reducing downtime and costs.

Find out more

For an overview on Machine-to-Machine technology and what it can do, visit us online at www.att.com/m2m

Rethink Possible®

validation process. "You really cannot learn anything about your reactors until they are installed," says Ciambrone.

That conclusion led Shire to a unique proposition for its bioreactor vendor, Xcellerex. To prove that the solution could solve Shire's speed concerns, the pharma company wanted Xcellerex to provide a place where meaningful work could be done on the reactors by Shire staff along with technical support from Xcellerex. The resulting idea became known as the Atlas "Sandbox" Process Line Mockup, which eliminated a number of costly errors and inefficiencies from the finished process line. For example, during tests with Shire at larger scales (1,000L, 2,000L) and long periods of time, it was discovered that the mixing at 2000L was inadequate. Some design changes were needed, including a more robust impeller bearing for the bottom-mount agitator to provide adequate mixing. Had this deficiency not been detected in advance, the bioreactor would not have functioned properly — resulting in costly delays to getting the plant up and running. According to Ciambrone, once Shire and Xcellerex began generating data together in the Sandbox, it became obvious there would need to be some design changes to the bioreactors before the company could take delivery. Furthermore, this testing environment gave the two companies experience with making a lot of sterile connections because the Sandbox was not ISO 7 or ISO 8 certified. In addition, the Sandbox familiarized operators with the systems long before they went live at the plant and facilitated the start of early, offsite commissioning and qualification (C&Q) and SOP development.

Being able to create the Sandbox was the clincher for Ciambrone to choose SUS for the Atlas Project. But when you are boldly going where no one has gone before, you need to gain buy-in not only from your internal team but from regulatory agencies as well.

DON'T FEAR FAILURE — HATE IT

Ciambrone reports directly to the president of the company. So, he only had to convince one person above him once he decided to build an SUS plant. However, the process of gaining buy-in from Shire employees below him, especially those intimately involved and actually helping to make the decision, proved to be a bit more difficult. "It was a matter of freeing them from the fear of failure," he explains. Ciambrone's approach to removing the fear of failure first involved communicating that he, and only he, would be accountable for the decision to build an SUS plant if things didn't go well. "If you stop people from thinking their heads will be on the chopping block, you create excitement," he affirms. In addition, he pointed out that the company not only had the opportunity to do something very different, but also that there were good reasons supporting the decision (e.g. lower costs [as compared to a stainless-steel facility], faster setup time, and the flexibility to change the plant for manufacturing other products in the future). "We cannot let fear push us in another direction, especially if we have a contingency plan," he explains. Having a contingency plan was another key to gaining buy-in from the team. Though the original plan required speccing for SUS, the Shire team also specced a hard-pipe solution. This allowed Ciambrone to communicate that if things didn't go according to plan, the company could still remediate back to a hard-pipe solution with minimal business impact. "It was a matter of letting people know there were a lot of good technical and business reasons to do it this way, but fear of failure wasn't one of them." Ciambrone's corollary to fear of failure is, "You have to hate failure. This makes you plan more and do everything you can so you don't fail." He says fear of failure leads to bad decision making and less risk taking. "Too many people, when setting out on a risky endeavor, feel they have an easy out and are quick to place blame on the decision as being the reason for failure. I utterly reject that," he states. "The decision and risk didn't cause you to fail. It was the fear of failure." Ciambrone ascribes to recognizing and understanding the risks a decision entails, and to plan accordingly.

Just as Shire employees needed to be alleviated of the fear of failure, regulatory agencies needed a thorough understanding to

WHAT YOU NEED TO KNOW IF THINKING ABOUT ADOPTING SINGLE-USE

"Everyone who sells disposable reactors will tell you your capital cost will be a lot less," says Shire's Bill Ciambrone. "You don't have to CIP (clean in place) or SIP (steam in place). You can do SUS in a closet without the air handling." According to the Ciambrone, EVP of global technical operations, when Shire completed the design for Project Atlas, it found going with SUS did save some of the capital costs. "But it was not as dramatic as people would have liked you to believe," he informs. "Operating expenses go down in some areas but go up in others because consumables are not cheap." Ciambrone advises to be sure to take this into account when considering capacity expansion of traditional (i.e. stainless-steel) versus SUS. For example, with a traditional plant, once the piping is in place, it is a sunk cost with some variable operating and maintenance costs. However, with SUS you will be purchasing a greater number of consumables (e.g piping, tubing, bags) every time you use an SUS bioreactor, which will increase your variable operating costs. "The real economic savings which appealed to us were the speed with which we could get the plant up and running by taking advantage of the Sandbox (see main article for explanation) and being able to do some qualification on the bioreactors before they were installed."

Something else you need to consider, which Ciambrone admits he did not have full visibility into until the plant was up and running, is the physical aspects of operating and moving around large totes and collection bags (bigger than the reactors themselves). He advises to be sure to take these factors into consideration when considering the adoption of SUS, as well as planning for adequate space for storing the various disposable consumables you will be using.

feel comfortable approving a new manufacturing process. When doing something new, Ciambrone advises working with regulators proactively. "We met with the FDA and EMA (European Medicines Agency) in the middle of designing the plant," he relates. "Some of the feedback we received was expected, such as challenging us to make sure we had the right protocols in place for leechables, extractables, and other necessary controls." According to Ciambrone, because the company already had been using the same material for storage and buffer, the team felt confident about the protocols in place. What surprised Ciambrone, however, was feedback from the EMA. "They loved the idea," he says. "They thought we were actually doing what should always have been done in terms of contamination control. They liked the idea of getting rid of sterilization and validation and using disposable technology to prevent cross-contamination and carry over." Ciambrone admits that working with regulators was the biggest challenge behind designing the plant and helping the providers of the reactor to develop their prototype into a commercial product. "We needed to demonstrate to the FDA that what we were planning not only made sense, but also that we were able to communicate the technology and due diligence behind the decision with regulators for whom this would be new," he states.

KEY FACTORS OF SHIRE'S SUCCESS

Shire broke ground on the new facility and got its first regulatory agency drug approval within three years. "No one had ever done this before," Ciambrone claims. "The first approval was based on the purification site with the approval of the bioreactors coming later. But the plant would not have been running if we had used the old paradigm of plant building." Shire deemed Project Atlas a success, and so did the industry. In 2011, ISPE recognized the pharma company with an honorable mention in its annual "Facility of the Year" awards program. For Ciambrone, one of the keys to the project's success was effective project governance. "The owners of the project were the decision makers," he affirms. "We didn't spend weeks and months languishing for decisions." Ciambrone admits this may be the benefit of being at a fairly small company. But does it have to be? Leadership governs best when it governs least. Ciambrone subscribes to removing as many layers of bureaucracy as possible. "You cannot have a process by which things have to go through 15 levels in the organization before they get blessed by someone at the top," he explains. "It has got to be quick. If you are asking the team to move really fast, you need to support the team with quick decision making." Ciambrone suggests if you are managing a similar project, put in place effective governance, with an empowered team and ready access to decision makers.

Since the completion of Project Atlas in 2010, which came in five months ahead of schedule and $10 million under budget, product sales revenues for Shire have grown by $1.2 billion. The gamble seems to have paid off. For example, the SUS design resulted in a 38 percent reduction in total facility size and approximately a $50 million reduction in initial capital costs. In addition, the facility uses 87 percent less water, consumes 30 percent less energy, and has resulted in a 95 percent reduction in caustic cleaning chemicals used. Combine these metrics with the fact that the facility has 26 percent less carbon emissions, and you can understand why the Lexington facility stands as a shining example of what it takes to be U.S. Green Building Council LEED (Leadership in Energy & Environmental Design) Certified. Shire seems to be playing its cards right, parlaying its business to 2012 year-end total revenues of $4.68 billion — vaulting the company into the high-roller ranks of Top 50 Big Pharma. Though the folks at Shire are proud of being first, Ciambrone cautions you not to let the perception of being innovative to be the motivation behind any decision, but to be based in logic and the facts particular to your company.

THE BEST LEADERSHIP ADVICE I'VE RECEIVED

Bill Ciambrone, EVP of global technical operations, Shire

"What's the best advice I have ever received? Don't try to be someone else," says Bill Ciambrone, EVP of global technical operations at Shire. During the first nine years of his career, he held a number of lower-level leadership positions. Feeling he wasn't a good leader, he decided to get out of leadership, seeking roles as an individual contributor. When a mentor asked why he was looking to leave leadership, Ciambrone was the benefactor of the best leadership advice he had ever received. "The reason you do not like it and are struggling with leadership is you are trying to be a leader that is not you," he recounts being told. According to Ciambrone, if you want to be a great leader, you need to be yourself and not try to be like someone else. The message was to be more natural and genuine. "Authenticity is a great leadership characteristic," he states. "I have never seen a fake leader maintain authenticity. You have to be leading naturally and not everyone does this the same way." In addition to trying to stay true to his natural leadership style, Ciambrone takes care not to take himself too seriously. "Take your job seriously, but not yourself," he says. "Your title does not make you special. The job is special, not you."

Boehringer Ingelheim **Bio**Xcellence™

Producing value - Boehringer Ingelheim BioXcellence™, your trusted partner

Boehringer Ingelheim Contract Manufacturing has now evolved into **Boehringer Ingelheim BioXcellence™ -** your dedicated biopharma contract manufacturer.

Boehringer Ingelheim BioXcellence™ is a leading biopharmaceutical contract manufacturer with more than 35 years of experience – and more than 20 biopharma products brought to market.

We promise clear advantages for our customers by providing:

- Transparent modular approaches geared to provide flexibility
- Tailor-made solutions – where you need us, when you need us
- Secured supply of material throughout the entire product lifecycle
- Seamless integration with every step of your business process

In order to discuss your specific needs in detail please contact us – we will make your product our passion!

Contact us: www.bioxcellence.com

Boehringer Ingelheim

The Micro-Innovators

Small Enterprises Make Outsized Contributions With Novel Drugs.

By Wayne Koberstein, executive editor

So simple in concept — interview three CEOs of companies developing novel drugs — so challenging in execution. Who would have guessed there is such a strong correlation between novel-drug development and small-company volatility? Since my investigation began, one company replaced its CEO and changed its name, another's stock rose and fell repeatedly on news of a competing product, and a third one joined late in place of another that dropped out. All of those events are among the most common disruptions in business and communications for the micro-enterprises focused on unique paths of medical innovation. Thus, I stumbled upon a key insight into the lives of this industry's *micro-innovators* — it's never easy.

Examined from multiple angles, the three companies illustrate the essential capabilities, strategies, and stages small enterprises must master to discover and develop unique therapeutics for the industry's innovative portfolio, despite all the obstacles. Overcoming hurdles in funding, clinical development, manufacturing, and many other areas, the companies teach valuable lessons in how to survive, grow, and bring potential breakthroughs to the world of medicine.

Many other companies may deserve coverage under the definition of "unique therapeutics," however impractical it would be to include them all, and many others may claim membership in the elite club of micro-innovators. But the key, definitive point here is this: The featured companies discovered the entities they are now developing, rather than licensing or acquiring them. This article also excludes companies that have reformulated drugs, combined them, or retrofitted them with new delivery technologies. These three companies have chosen the toughest possible route in the life science industry: taking an innovative path from the earliest stages of research on through the entire course of product development.

I interviewed the CEOs of micro-innovators Sarepta Therapeutics, Melinta Therapeutics (formerly Rib-X), and Advanced Cell Technology (ACT). Sarepta has been in the news often for its Duchenne muscular dystrophy (DMD) drug, mainly concerning whether it will beat the competition, a GSK drug, to market. Melinta has bravely strode into the almost abandoned field of antibiotics with a product based on Nobel-winning research into ribosomes. ACT has pioneered a unique line of human embryonic stem cells for treating age-related macular degeneration (AMD) and other conditions.

From the three companies' collective and individual experiences, a set of tenets emerges, which I have framed as imperative responses to the conditions such companies typically encounter. Like steps in a staircase, the tenets conform to a rough sequence that raises a company from the idea stage to a fully functioning business equipped and prepared to take a product through development. The steps generally range from initial management and funding through proof-of-concept (PoC), clinical development, and regulatory review.

BUILDING IN BEST PRACTICES

There was an old scientist who lived in a shoe — a tightly laced refuge from the world, where all incoming funds for the scientist's new company went into his lab. No taxes. No insurance. No administrative expenses. It was a wonderful fantasy land, but of course it was bound to collapse unless the scientist awoke to the realities of business. This sounds like an extreme and unlikely story even as I write it down, but in fact I've witnessed it or its close equivalent many times. In fact, I may have spotted a corollary: the more original the research, the more isolated the scientist-founder from commercial reality.

The point here is not to teach an entire course in business management but to draw lessons from experience. Among the basic elements that can determine a company's fate is the quality of its leadership — a combination of board members, scientific advisors, and top executives. Much praise is heaped upon wearing different hats in entrepreneurial environments, but in companies formed to conduct original drug development, each of those functions should be filled by relevant experts.

Unfortunately, it seems few companies get it right from the beginning. All of our featured micro-innovators have gone through multiple management turnovers. One was as recent as April, 2013; Melinta, founded in 2000, is now on its third CEO — Mary Szela, who succeeded Mark Leuchtenberger after his three-year tenure, and after she had briefly served as board chairman.

But the company, whose cofounder is Nobel laureate Thomas Seitz, had taken a long time to meld science and business. Arguably, although no one can doubt the primary importance of a company's scientific leaders, much of their value may be, in curiously apropos syntax, effectively wasted under effectively ineffective management. It is hard to put specific blame on the previous chief execs, who generally received good reviews at the time. But for well more than a decade, the company had not met its main goal of a successful commercialization.

Leuchtenberger represented a culture change from the previous CEO and cofounder, Susan Froshauer, a scientist who retained her position as CSO upon his arrival. He helped focus the clinical program on key development targets for commercialization. Szela was a further leap in the same business-oriented direction. Leuchtenberger had run a couple of small biotech companies that never achieved an approved product. Szela is from Abbott, where she helped launch Humira. Her appointment signals a hardened commitment by the board to get on with the commercialization of Melinta's lead product, eteplirsen.

Another company languished for years in a kind of technological limbo, plagued by a lack of management focus on specific development targets. "Sarepta was not doing the critical path activities such as manufacturing, long-term animal tests, or study design, so there was some skepticism of its PoC data and whether its product candidates could be brought to fruition with the management teams in place," says the company's president and CEO, Chris Garabedian.

Consequently, he says, Sarepta was failing to land a key partnership or advance any development program. Once it turned its focus to DMD, and after Garabedian joined as CEO in 2011, the company restored trust among investors and potential partners, helped by his prior industry experience at Celgene, Gilead, and Abbott. Garabedian also continued to rally the company around a single development program.

Gary Rabin, CEO of ACT, spent some of his first years on the job cleaning up legal entanglements left by the previous manage-

ment involving lawsuits over its private-investor stock pricing. There was no romance in the cleanup, according to Rabin. "It was just blocking and tackling," he says. "You just have to go to the office every day and deal with it." Rabin also inherited a financial hangover when he came to ACT in 2010 — the result of a weird funding history, which we'll get into in Part Two. Good thing he is an economist, having spent most of his career raising funds for life sciences companies.

If putting the right top executives in place is a best practice, recruiting and keeping talent at all levels of the company is an absolutely critical one. Melinta has won several "Best Places to Work" awards that cite its loyalty to the people who helped build it, as well as its readiness to listen to even the newest recruit. Lesson: You can't just relax and say your company is a cool place to work because it is entrepreneurial. You have to work at creating an environment that rewards people for going the extra mile in their jobs. People will be inspired by the common cause of developing a unique product, but inspiration is vulnerable; it will fade quickly if not accompanied by positive treatment in the workplace.

FROM EXPERIMENT TO DEVELOPMENT

A common failing of micro-innovator companies is to languish in the experimental stage without ever breaking out and moving toward a clear product goal. Sarepta is a particularly good example. Garabedian recalls how the company spent years investigating numerous disease areas — such as West Nile virus, polycystic kidney disease, HCV, and coronary artery disease — before settling on DMD.

"When I came on board, the company hadn't yet done the type of early development, translational work that you need to optimize a drug and ensure you have an active dose and regimen in the clinic. Also, the company wasn't attracting the right level of talent. Like many companies that exist on limited cash, the work is all science experiments, almost academic, and as private-enterprise businesses, they fail to achieve any success. We quickly homed in on the area with the most value."

One of Sarepta's experiments in the U.K. hit its target, yielding evidence that, with systemic delivery, an antisense drug could enter the cell and produce a desired protein, in this case, the dystrophin protein in Duchenne muscular dystrophy. Even though the study elicited a rather low dose response, Garabedian says, "It showed a hint of a promise." He says the previous management could not envision the complicated path it would take to develop the drug further and sought to sell off the worldwide rights. But without further development work, they found no one was buying.

"They were prepared to give this program away," he says. "I took the job because I believed we found the right application for this technology, and I wanted to put it on a fast track." In December, 2010, Garabedian announced cancellation of a scheduled dosing study, saying it was the wrong study design, and the delay of a Phase 2b study. He spent his first month with his manufacturing heads and started producing more drug, while at the same time, directing the head of preclinical to start the long-term animal toxicology work. He spoke with key opinion leaders in DMD and used their advice to help design an optimal study. With a still limited supply of the drug, the study had a small sample size, eight patients treated and twelve patients in total when it began in 2011.

Additional evidence also encouraged Sarepta's focus on DMD. Knowledge about the dystrophin gene had increased; academic researchers had done "micro-walks" along the genome to find the gene and were figuring out how to silence a part of the gene, called exon 51, and thereby correct translation of the gene to the protein in patients with certain genetic mutations.

Sarepta seized on the unique mechanism of using phosphorodiamidate morpholino oligomer (PMO) antisense technology to target precursors to messenger RNA, with the aim of skipping over an exon in the gene to restore dystrophin production. It also made the fateful decision to make dystrophin levels the primary biomarker and basis for regulatory approval. Now, news stories on Sarepta's approval strategy, the regulatory response, and the fortunes of its DMD competitors appear almost daily. It has become a stock to watch as all of those variables play out.

All of our featured micro-innovators have gone through multiple management turnovers.

(In September, Sarepta announced favorable data from the Phase 2b eteplirsen study at 96 weeks, showing a "continued stabilization of walking ability" in treated patients on a standard six-minute walk test. The company had previously reported the study met its primary endpoint of increased novel dystrophin. But in November, the FDA directed Sarepta not to file for accelerated approval for eteplirsen and asked for a new placebo-controlled trial, inevitably delaying a long-term follow up on the 2b study and causing the company's stock to free-fall. No doubt the news-sensitive dynamics will continue indefinitely.)

As with Sarepta, Melinta might have chosen to build a business or partnership with its ribosome crystallography platform that targets the large (50S) ribosomal subunit of bacteria, leaving the drug development work to someone else. But the scientific DNA of the company obviously propelled it into using the platform to discover and develop

its own antibiotics. At some point, most micro-innovators face a similar choice — sell the research, sell the platform, or bet the farm on product development. All of them, by definition, choose development.

ACT's Rabin makes it clear why the company went beyond the platform-business model. "We see ourselves as a regenerative medicine company focused on the development of treatments, and as such, are oriented as a product-development company," he says. "Because of our size, we tend to use common pluripotent cell platforms as our starting materials for our various product development efforts, such as embryonic stem (ES) cells and induced pluripotent stem (iPS) cells. However, in the end our focus is much more on the therapeutic product opportunity than on the underlying cell source we use as a starting material for manufacture."

Once committed to the product-development path, companies typically begin to refine each product according to their understanding of how it will be used in practice — a step I have taken to calling "market modeling."

For example, Melinta selected specific formulation and dosage/delivery forms in consideration of how patients with serious infections receive treatment. Its lead clinical candidate, delafloxacin, has both IV and oral formulations, allowing patients who begin IV treatment in a hospital to transition to oral dosing for home-based care. "We believe this IV-to-oral switch has the potential to increase patient convenience, lower the overall cost of treatment, and reduce the length of hospital stays," says Szela. Delafloxacin covers a broad spectrum of pathogens, and Melinta expects it to be a preferred treatment in hospitals because it avoids the need for doctors to specifically identify the pathogen and change medications in mid-treatment, adding cost and complexity.

WHERE THE RUBBER MEETS THE ROAD

We pause here, because I thought a normal article length was insufficient to share all the valuable experiences and lessons gathered from our three micro-innovator companies and their CEOs. When we return with Part Two, we'll look at how the companies have embarked on the often rough road of drug development, paying for translational research and clinical trials, planning the development pathway and designing the needed studies, and conducting the trials aimed at regulatory approval. Please stay tuned for the next installment of "The Micro-Innovators."

A Bullish Season At The BIO Investor Forum

By Wayne Koberstein, executive editor

To tweet or take notes — that was the question at this fast-paced, multitracked round of company pitches and plenary sessions that filled two whole days in the City by the Bay during October. As it happened, my tweets at #BIF13, along with selected input from others in the "hashtag" group for the BIO Investor Forum (BIF), yielded all the notes I needed.

Those notes play out some general themes, along with specific company details that, all together, reflect the unique mood and makeup of this year's forum. Enthusiasm ran high, in sharp contrast to the past half decade of down times in angel/VC funding and IPO action for the life sciences industry. Yet caution remained on everyone's mind, and many people's lips, amidst the celebratory feelings.

Although partnering still held primary importance at BIF, a subtle but palpable shift back to investor funding appeared in the content of plenary sessions and types of companies in the lineup. Perhaps the shift at least partly accounted for the reduced proportion of targeted cancer drugs presented, with noticeably more time given to noncancer conditions and new cancer-treatment modes such as RNA-based (ribonucleic acid) and immunological therapies. In fact, the RNA and immunology approaches spilled over into other areas such as anti-infectives.

INVOKING CANCER IMMUNITY

Cancer immunotherapy combinations gained support in a related panel discussion by executives and scientists from Bavarian Nordic, Inovio, immatics biotechnologies, and the UCSF Medical Center. Panelists answered some sophisticated technical questions regarding the side effects, variety of approaches, and need for carefully managed combinations of immunotherapies to rally all the right forces in the immune system. Including the still-elusive multipatient cancer vaccine, such "mass immunotherapy" — moving immunotherapy away from patient-customized treatment to something more like the normal drug or vaccine supply chain — is likely the wave of the future.

A number of presenting companies are developing immune-based therapies, including therapeutic vaccines. Alas, I could not cover them all, but I managed to hit a somewhat random half dozen that suggest the range of approaches and areas companies are exploring.

Immune Design threw me off at first by using the term "tumor-specific" to describe the MOA (mechanism of action) of its cancer vax technology. Rather than a patient-specific vaccination like Provenge, however, Immune Design's vaccines target dermal dendritic cells (DCs) in vivo to stimulate production of cytotoxic T lymphocytes (CTLs) that home in on antigens commonly expressed in certain tumor types. Thus, they would be deployed as any conventional vaccine.

MabVax Therapeutics has produced polyvalent vaccines from monovalent forms in-licensed from the Livingston research team at MSKCC (Memorial Sloan-Kettering Cancer Center). The vaccines are based on pooled samples to identify antigens typically expressed in adjuvant (postsurgical or chemo) settings, which is where the vaccinations will occur. Another MabVax program is mining antigens from successfully immunized patients as targets for future therapeutic antibodies.

Similarly, **Galena Biopharma** aims to vaccinate patients against circulating cancer cells to prevent recurrence, but using a peptide to induce immune response, starting in breast-cancer patients with the HER2 (human epidermal growth factor receptor 2) mutation but not indicated for Herceptin. Galena has also hedged its bets by licensing and marketing a sublingual cancer-pain drug. I got the impression both MabVax and Galena are lone wolves operating outside the emerging combo-immunotherapy consensus.

On the other hand, **Lion Biopharmaceuticals** and its now-parent **Genesis Biopharma** believe patient-specific T-cell stimulation and enhancement — "autologous cell therapy" or "adoptive T-cell therapy" — are the only viable solutions for tumor heterogeneity and immune suppression, considering the relatively weak response to ipilumimab and other CTLA (cytotoxic T-lymphocyte antigen) or PD-1 (programmed death)

inhibitors that "take the brakes" off T-cell production (also the rationale for combination therapies). But it remains to be seen if such a complex "regenerative medicine" model can translate to a practical business proposition.

Mirna Therapeutics represents the RNA wing of new cancer-Tx approaches. Its technology employs tumor-suppressor microRNA technology to "kill cancer cells by regaining control over multiple oncogenic pathways." This involves restoring and regaining control of the cell's messaging system — a network that stubbornly resists manipulation. As with all RNA-based therapeutic modalities, Mirna faces an uphill battle proving safety and efficacy in human cancers.

But of course the RNA crowd is not alone. I offered this tweet in the midst of the cancer-related presentations: "All new cancer drugs invoke the same sad memory of this: 'We've cured cancer thousands of times — in mice!'"

DISEASE-AREA DIVERSITY

Another notable trend at BIF this year was the greater representation of non-cancer-niche orphan drugs. Cancer and cancer niches have dominated past events because of the dominant interest of Big Pharma in oncology partnerships. In fact, orphan drugs or not, it was refreshing to see a more diverse lineup of companies in general this year.

Orthera is developing its lead product Oxabact for hyperoxaluria, which creates stones and damages liver cells, possibly to prevent dialysis or transplant. It is seeking FDA accelerated-review status for the drug, now in Phase 2, because there is no other treatment option for patients.

ContraFect, which like many VC-founded start-ups that sport a board and management full of ex-Big Pharma execs, is going for the (blockbuster) gold with a lead drug to fight blood-borne infections.

Labrys Biologics is going up against Amgen, Alder, and Arteus in chronic migraine with a mAb to block binding of human CGRP (calcitonin gene-related peptide) to the CGRP receptor, which causes vasodilation — saying the more than four million chronic patients represent the major unmet need in migraine. Toxicology is a big issue in chronic care, and Labrys' LBR-101 looks good in preclinical tox studies; now, on to Phase 1.

Zafgen's beloranid, having yielded supporting data from a Phase 2 study in obesity, uses the MOA of reducing weight, inflammation, and cardiovascular disease by changing how the body processes fat. Weight loss and cardiometabolic data served as biomarkers to make a strong, if early, case for the drug. Zafgen plans to launch beloranid with narrow labeling for severe obesity, then expand to cardiometabolic disease — a classic case of an orphan- or niche-drug's potential to open up a blockbuster space.

Aquinox seeks to correct disorders in the blood and immune systems by activating or inhibiting the SHIP-1 (SH2-containing inositol 5-phosphatase) enzyme, which regulates a key blood-cell pathway. The company wants to first introduce its lead drug with an indication for the rare bladder inflammation, Cystitis/Bladder Pain Syndrome, then expand the labeling to COPD. Small beauty to big bonanza — a start-up's dream.

Proteon Therapeutics is addressing a common problem; disease mortality and morbidity are often related to secondary conditions rather than the primary disease that often gets the blame. In this case, the condition is dialysis access-site failure, one of the most harmful and potentially deadly complications of kidney disease. Proteon's drug PRT-201 prevents or delays decay of the tissue in the surgically prepared dialysis entry site.

The world has long awaited stable oral peptides as a potential replacement for many injected drugs. Will **Protagonist Therapeutics** be the hero? The company is aiming for the first logical target of opportunity, the GI tract, with one of its new-generation peptides capable of storage and oral delivery.

A subtle but palpable shift back to investor funding appeared in the content of plenary sessions and types of companies in the lineup.

PLENARIES IN PLENTITUDE

Besides the cancer immunotherapy panel, I attended several of the many plenary sessions, workshops, and roundtables at BIF that got people talking about the wider context and major influences on the business they are there to develop. Particularly topical were the funding-related sessions described in the following:

"IPO Frenzy: Are the GoGo Markets Here to Stay?" gave a roundup by an expert panel of venture-fund partners. In the past year, the panel agreed, although life sciences funding continued to decline as a whole, the small-cap sector did fairly well, sparking an influx of large funds and first-time individual investors, while many dedicated investors in the sector remained active. But BIO's Dave Thomas warned initial financing of U.S. biotech start-ups is on a downward track to reach a 15-year low in 2013.

None of the IPO panelists were willing to predict a sustained flow of small-cap VC or IPO financing in 2014. But the high-profile flush of cash has some companies asking for money they don't really need yet, some of the panel agreed. Meanwhile, all investors will keep a close eye on further evidence that the companies receiving major infusions, especially on the stock market, can continue to prove their case. Too much negative news in the sector could derail the train of bullish generosity.

"Crowdfunding in Healthcare & Biotech: Will It Bridge the Valley of Death?" had a small-company exec from Novita heading a panel representing traditional funders Knobbe Martens and Delphi, together with innovative funds Poliwogg and Breakout Labs. The panel agreed on one characteristic of early crowdfunding advocates: an idealistic commitment to making investment available to non-elite investors using the increased freedom to communicate opportunities under the JOBS (Jumpstart Our Business Start-ups) Act.

One thing crowdfunders share in common with all investment funds, however, is the challenge of raising money from people they don't know. Companies must be ready to spend time communicating their case, as Andrew Merikel of Knobbe Martens suggested: "If you want people to invest in your company, you must invest in them!"

"Early Stage Venture Financing: Will Current Trends Continue in 2014?" was moderated by Luke Timmerman, the well-known columnist and vice president of life sciences initiatives at Xconomy. The panel covered a diverse lineup of VCs — Sofinnova, Versant, Third Rock, AbbVie, and 5AM. One common theme: VCs are still unhappy, despite the IPO boom. Even with some top performers in bio, returns for the venture crowd have not been great. Early-stage funding still depends on risk takers with rich pockets, but the multiple mid-stage failures are sinking in; there are fewer dreams, more sobering knowledge.

Another problem VCs have these days is with life science entrepreneurs who use the current bull climate for early-stage investment to drive a hard bargain in exchange for funding. "It's actually better for VCs when the market sucks," quipped one of the panelists.

Timmerman was brave enough to bring up a political threat to early-stage research and investment, and to life sciences R&D in general: the Congressional shutdown and near default of the U.S. government, on top of a sharp downward trend in research spending led by the same faction. In a nutshell, what I heard at BIF suggests a message the shutdown faction should heed: The life sciences industry hates politics in general, but it loves the NIH and the industry/government partnership the institutes represent.

BIF is a world where large pharma companies come as guests and are mentioned only in passing. On the West Coast, far from the old pharma centers of New Jersey, and now on the East Coast, but with Boston leading, Biopharma dominates all discussion of the industry's future. Still, I believe it's a mistake to count Big Pharma out, as some observers would like to do. People should remember that, in financial terms alone, Biopharma is still spare change in Big Pharma's hip pocket. Although they weren't talking much about big-company money at this year's BIF, it may well be top of the agenda at next year's forum.

Society of Toxicology

53rd Annual Meeting and ToxExpo™

2014 Themes

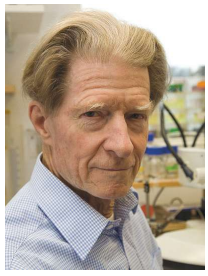
- Advancing Clinical and Translational Toxicology and Application of Biomarkers
- Enhancing Strategies for Risk Assessment
- New Science and Perspectives Surrounding Environmental and Occupational Exposures
- Safety Assessment: Mechanisms and Novel Methods
- Stem Cell Models for Integrated Biology

Opening Plenary Lecturer

Dr. John B. Gurdon

Monday, March 24
8:00 AM to 9:00 AM

The Origins and Future of Pluripotency and Cellular Reprogramming



toxexpo.com

ToxExpo is the profession's largest exhibition. Toxicologists and industry professionals have the unparalleled opportunity to gain first-hand knowledge on the latest advances in products, services, and technology from more than 350 exhibitors. Visit www.ToxExpo.com for details.

Supporters help SOT keep registration fees low. Learn more about becoming a Supporter at www.toxicology.org/support.

2014

Phoenix, Arizona

March 23–27, 2014

Phoenix Convention Center

Some Phoenix photos are courtesy of Greater Phoenix Convention & Visitors Bureau unless otherwise noted. Some photos by Jill Richards.

Style & Substance In The Supplier Space

By Wayne Koberstein, executive editor

This theme has been on my mind so much I'm starting to repeat myself: What is real, and what is illusory in the world of drug, diagnostic, and device development? How do we know one project will succeed and another fail? From what spring might we even draw some measure of assurance? It is not a matter of random chance. Products going through development do not exist as ideal forms floating in a vacuum. Like a space-probe launch, or the maiden flight of a new airliner, countless components have come together to create a product of life science, and any one of them can go wrong.

Every time a purchaser faces a supplier with a sales pitch, the inevitable question must be, "If I buy this, am I creating a potential weak point, or am I adding another lever of advantage?" Whatever the component — a patient-enlistment plan or data-entry form, a biomarkers study or a human-factors analysis — and whatever factors affect its quality, reliability, and cost, the buyer must know the supplier's goods or services increase the product's odds of success.

ONE PLUS THE OTHER

The thought came to me from a seemingly unrelated marketing research study on why mobile advertising is generally less effective than its Web or print counterparts. Forget the study itself, because I didn't stick around for the conclusions, but instead wandered off in my own mental direction. Of course, mobile ads are tiny, intrusive, and most often incongruous with whatever app you happen to be using. So, when would you be most likely to break stride and pay attention to one? Remember, *style* is important, if only to compensate for the small screen and thumbs-on operations of phone or pad. But *substance* is equally or even more important to overcome one's natural resistance to any intrusion into the immediate task at hand.

Sadly for me, the first time I clicked on a mobile ad, it led to a dead end. The ad was simple and clean, a picture of a sleek, little device promising "cool connectivity," which caught my eye because I was looking for a better way to input audio into my mobile devices. Despite the disappointment when I found only a decorated plug-converter at the other end of the ad link, I realized something from the experience: It took both (eye-catching) *style* and (need-answering) *substance* to move me to action. Whether by lucky accident or devious design, the advertiser had hit both buttons for its target audience, namely, me, and others like me, looking for substantial material behind the stylistic pitch.

The lesson here is that the supplier might do what the mobile advertiser did — hit the right buttons of style and substance, promising in the buyer's own language what the buyer wants to hear, but not delivering on the promise. Or, the supplier could take the high road, communicating in the buyer's language and offering solutions it knows it can deliver, reliably and over the long term. In that case, style and substance work together to form a strong client/supplier bond. Unless you present your "pitch" in terms the purchaser understands (style), it doesn't matter what you can deliver. But if you cannot deliver what you promise (substance), no matter how persuasively you promise it, your only chance of staying in business is to keep lining up new, short-term customers.

SIMPLE, SOUGHT, & ELUSIVE

OK, that advice sounded obvious and corny. But it is truly funny how real, adult life has a way of confirming old homilies, making youthful cynicism seem foolish in the rear-view mirror of experience. At every event or publication where I've seen this industry's purchasers and suppliers in discussion, each side seems almost to plead for one golden but elusive quality in their relationships: *trust*. Simple human trust. Despite IT-powered statistical analyses, databases, background checkers, and other high-tech systems for evaluating potential vendors or clients, the main thing both sides are yearning for is to do business with people they can trust — and who will trust them in return.

Naturally, the principle of trust extends beyond mobile advertising, which first sparked this line of reasoning for me. Every supplier has a face it turns toward clients and potential customers. What possible means can the purchaser use to see behind the face and know whether it confirms or conceals the truth? Probably the means that is least used — personal engagement. Go

there. Often. Talk to them. Build a relationship — a network of relationships — based on what Genentech calls "value creation," the non-zero-sum game of mutual problem solving and balanced incentives between purchaser and suppliers.

Most suppliers also have their own supply chain. Get to know the secondary and tertiary suppliers your immediate vendors depend on. Plan for contingencies in proportion to the risk you perceive there. Look for weak points, and, if possible, help your primary supplier figure out ways to strengthen them. Stockpiling reserves of raw material as backup for the next-step producer would be the simplest example of how a purchaser might act to protect a supplier. But opportunities for improvement will likely pop up in any such relationship, varying only by the type of goods or services supplied. The idea is to share the problem-solving mindset, with each side supporting the other.

AT ODDS OR AS ONE

There is another helpful approach sponsors can take — do an inventory of the problems you have caused for your supplier. You know what I'm talking about: rapid-fire, course-reversing changes; punting on regulatory issues and shifting responsibility to the supply side; forcing the other side to absorb unexpected costs… All that and more happen every day in this industry, effectively destroying any collaborative spirit or value creation that might already exist with the supplier, and certainly arresting any development of the relationship in a collaborative direction.

The more damage you do with one or a few suppliers, the more difficult it will be to find new ones that will cooperate with you in a substantive way. Disappointment and cynicism breed deceit; as your reputation for problem-causing spreads in the supplier community, people will feel OK about feeding you the BS you want to hear without delivering the goods they lead you to expect.

You may notice I've used the word "you" interchangeably to mean either purchaser or supplier, depending on the context. This is a journalist's privilege, or conceit, but also the most direct way of addressing both sides with equal engagement. For either, the style of communication determines how well your message is received and interpreted by the other; the substance of trust and reliability determines where the message leads. Will it be purchaser *versus* supplier, or purchaser *and* supplier — plying that great curved sea of product development together?

How To Develop A Successful Supplier Management Program

By Fred Olds, contributing editor

"In today's world, a company can no longer be good at everything," says Hans Melotte, VP and chief procurement officer (CPO) at J&J. He says J&J came to realize that vertical integration no longer worked for them, and they needed to seek expertise through partnerships with outside entities. With tens of thousands of suppliers, horizontal integration posed a challenge to Melotte and his staff. His answer was standardization of their approach to suppliers and the development of business relationships with strategic suppliers.

In an interview in 2012 following Melotte's selection as Chief Procurement Officer of the Year by procurement leaders, he said procurement had to maneuver itself into new business models. He said CPOs needed to build competencies around developing relationships with suppliers, and he launched J&J on a course to do just that. It is a process that continues today.

"A couple of years ago, we set up procurement processes that could be applied across the enterprise in a consistent manner," says Melotte. Procedures were standardized, and common language introduced so employees in J&J procurement would understand what governance, resource, or effort would be required in specific situations.

A supplier management program was developed to clarify how to interface with suppliers. There are three components to the program: Shape the supplier base and ensure the right mix and size, focus on relationship management, and build engagement with suppliers. The program delineates how to stratify suppliers based on strategic importance, the type and frequency of meetings, and where the company should be involved with the supplier.

The goals, says Melotte, are to 1. present J&J in a consistent and institutionalized manner to all suppliers, 2. allocate time appropriately by segmenting suppliers according to strategic needs, and 3. engage suppliers in a way that inspires them to not only want to work with J&J but view it as a customer of choice.

ENGAGING SUPPLIERS

One of his key objectives is to engage J&J's supplier partners in long-term conversations. J&J segments suppliers in three groups using multiple criteria. "Where I think we are different is in our focus and philosophy on managing *relationships*, rather than managing suppliers." He feels the latter could imply a patronizing approach to suppliers.

The term "business relationship" implies two parties on equal footing. Each side has interests and needs that the other helps fulfill. "If you think of a company the size of ours," says Melotte, "it's like extending J&J's supply chain into an ecosystem of partners."

Engagement begins with an invitation to discuss strategic goals and needs with a supplier. It's not a discussion about payment terms or delivery schedules. "These relationships are about developing a long-term conversation," he says. "Our relationships are two-way and 'multi-multi' where no one party has control over everything."

Melotte always wants to hear how suppliers view J&J as a customer. He also wants to know new and better ideas from other companies, and what J&J can do to become a supplier's customer of choice.

The hope is that partners will come to you when they have business opportunities or ideas to share. This could present in the form of marketing new products, exploring new markets, or R&D. Melotte says, "If you do the math, J&J spends about $30 billion with suppliers. This is an expense to us, but it is revenue to the suppliers. Of that revenue, they reinvest about 3.8 percent in R&D, which equates to a little more than $1 billion of R&D investment. We would prefer to see that investment flow back to J&J, augmenting our own R&D investment."

GROUND RULES FOR SETTING UP THE RELATIONSHIP

There must be an honest, transparent, and specific conversation. "Any supplier will say, 'J&J you're important to us,'" Melotte says. "But let's face it, there are degrees of *importance*. Companies need to sit eye to eye and ask, 'How important are we to you, really?' Then ask why, and to what degree." J&J may say it's because the supplier has contacts in Latin America, for example, while suppliers may say it's because J&J is their most profitable account. Knowing the basis of the relationship is important because it defines

Actionable, Practical Instruction for Life Science Professionals

10% DISCOUNT with promotional code **LSTI1213** (valid until 1/31/14)

register today at **lifesciencetraininginstitute.com**

In the **Pharmaceutical**, **Biopharmaceutical** and **Medical Device** industries, job training is critical. The Life Science Training Institute (LSTI) offers a blend of convenience and affordability with the highest-quality content.

- **Practical, actionable takeaways** include handouts, templates, guidance documents and more.
- **The best instructors** – We staff only the most accomplished industry veterans who tackle the same challenges you face every day.
- The perfect blend of **technology**, **convenience**, **content** and **quality** lead to a superior learning experience, tailored to the busy life sciences professional.

LIFE SCIENCE TRAINING INSTITUTE

www.lifesciencetraininginstitute.com
5340 Fryling Road, Suite 300 | Erie, PA 16510
PH: (215) 675-1800 ext. 123

the dialogue and the evolution of the partnership.

Each side also needs to bring top leadership to the table. That demonstrates a company is serious about working together and has enlisted the people with the authority to make decisions and resolve issues. The dialogue in early meetings should describe and compare the two companies' businesses and goals. "This doesn't mean the goals have to be aligned," says Melotte. "But it does mean they cannot be exclusive." The point in establishing the relationship is to further their mutual goals and discover how they can strengthen each other.

"It takes time, failures, and successes to learn to manage business relationships with other companies, but any enterprise needs other companies to succeed in today's world."

Hans Melotte, VP and chief procurement officer (CPO), J&J

Melotte recommends that, when you can, work on creating a joint charter. Such an agreement could involve building a manufacturing facility or redesigning a product. The charter sets goals for an initiative or project, describes what success looks like, and delineates responsibilities, time lines, and resources.

SEGMENTATION AND SELECTING PARTNERS

"Shape your partner base so that it complements who you are and your business needs," Melotte says. Neither volume of business, history, or size necessarily moves a supplier to Segment 1 status. Instead, it's a matter of the supplier's strategic importance to the partners.

First, look at your supply chain and determine if your supplier base has the right mix to offer what you need. This isn't merely a question of whether your company gets enough pens, bolts, and equipment. Examine if the base meets the company's strategic business plan. For instance, a company that wants to expand into Asia might need to complement its current supplier base with suppliers in Asia. The new partner becomes a Segment 1 supplier because of its strategic location or expertise.

"Another consideration in segmentation is your vantage point," says Melotte. "I might designate a small supplier as Segment 3 in the overall J&J universe. Yet that supplier might be ultracritical to our baby business in India. So, the supplier may end up as a Segment 1 relationship."

Segmentation is a dynamic process. It has to keep pace with changing markets and opportunities. Melotte says, "Our business portfolio, our business needs, and our strategic priorities change, so our supplier base needs to change." He believes their supplier management program provides the platform to meet change. It calls for continual evaluation of the size and mix of J&J's supplier base. If necessary, the staff can resegment suppliers and continue to manage relationships in a consistent manner.

STRENGTHENING THE RELATIONSHIP

Sustaining relationships requires consistent face-to-face contact and feedback. J&J meets regularly with suppliers to measure progress and provide updates on their businesses. These meetings serve as a barometer of how well the relationship is working.

Making progress and experiencing success not only furthers both companies' goals, it strengthens the relationship. On the other hand, "If you meet once a month to 'renew your vows,' but nothing happens, the relationship is bound to deteriorate," says Melotte.

He explains that in addition to these frequent meetings, it is helpful to occasionally gather groups of partners together to conduct an open conversation on the process in general. For example, as part of the launch of its supplier engagement program in 2012, J&J invited the leadership of a select group of its strategic suppliers to a roundtable. The purpose was to provide a venue where the partners could engage with J&J senior leadership in an open dialogue about business strategy and opportunities to drive growth.

J&J brought its top management to the roundtable to meet their counterparts. J&J executive leadership opened the meeting by sharing their business model, products, plans, and strategic imperatives. Further discussions grouped suppliers in a manner that they could share ideas on common issues and facilitate networking. Appropriate representatives from J&J were paired with the suppliers to moderate discussions and record feedback. In follow-up, suppliers expressed their desire to continue the dialogue on an individual basis and meet again in this general forum annually. They also commented that they had not been approached by other companies with such an opportunity.

AN ECOSYSTEM OF SUPPLIERS AND PARTNERS

At this stage of the deployment of a supplier management program, many of the metrics are activity-based. The current proxies are the supplier customer-of-choice survey and a net-promoter score. "About 70 percent of Segment 1 suppliers rate us as one of their customers of choice," says Melotte. "This suggests that more than two-thirds of our suppliers are inclined to dedicate their best and brightest resources to us, or to come to J&J with their innovative ideas." For him, the ultimate test is how the company performs in meeting its goals and doing what is right by its patients and customers.

Melotte says, "It takes time, failures, and successes to learn to manage business relationships with other companies, but any enterprise needs other companies to succeed in today's world. To grow and survive, a company needs to form an ecosystem of suppliers and partners that, in the aggregate, make them a stronger system." He suggests that while this is true for a large company like J&J, it may be even more important for a small company that often has very little room for error.

2014 AAPS National Biotechnology Conference

Advancing Health Through Innovations in Biotherapeutics

Call for Papers

MAY 19-21, 2014

Sheraton San Diego Hotel and Marina

COSPONSORED BY BIOCOM / BAYBIO

Contributed Papers Submission Deadline:
February 12, 2014 ✔

SUBMISSION DETAILS:
www.aaps.org/NBCContributedPapers

aaps®
American Association of Pharmaceutical Scientists

Emerging Markets And Your Global Regulatory Strategy

By Suzanne Elvidge, contributing editor

In the early 1980s, talking about the worldwide pharmaceutical market really meant the U.S., Japan, and Europe, which comprised the bulk of total sales, with the rest of the world (ROW) thrown in somewhat as an afterthought. Today, ROW is a term of the past, and with increasing speed, the concepts have changed from "developing" to "emerging" and now to "growth" markets, with China already today having become a major market, the number two global pharmaceutical market.

THE SIZE, SIGNIFICANCE OF ASIA AND THE EMERGING MARKETS

Asia has a population of around 4.3 billion and is home to about 60 percent of the world's population. China alone has a population of approximately 1.3 billion, which is three- to fourfold bigger than Europe or the U.S. Adding in the other developing markets, such as those in Latin America, this makes for a huge potential market for the pharmaceutical industry, and one important not to miss.

It's more than just taking advantage of a growing market, however, as Joseph Scheeren, senior VP, head of global regulatory affairs and site head of global development Beijing at Bayer HealthCare, explains. "We started positioning ourselves in this market early on. While we are number 14 in the top-20 list of pharmaceutical companies worldwide, we are number 4 in China. It's not just about looking for growth, but also providing access to drugs for patients in these regions on humanitarian grounds, in line with our company mission, 'Science for a better life.'"

The growth markets include Brazil, Russia, India, China, Mexico, South Korea, and Turkey, also known as the BRIC-MST countries. The environment is changing rapidly, however, and the focus is now on China, Brazil, and Russia.

"The GDP is rising in these countries, and generally, as the GDP increases, healthcare expenditure also increases," says Scheeren. "For example, in China, the government is investing heavily in healthcare. It's always important to keep an eye to the future for breakthrough areas, and the next markets to watch are likely to include Taiwan, Indonesia, the Philippines, and Vietnam — these regions combine a large population and a growing GDP."

CREATING AND ALIGNING THE REGULATORY STRATEGY

Pharmaceutical companies such as Bayer have a global footprint and strive for simultaneous global launches at the earliest time, including in growing markets. Aligning the regulatory strategy across many countries saves time and money for drug developers, resulting in earlier access by patients.

"Once a drug reaches Phase 1, it's a good idea to start discussions with global regulatory authorities so that you can begin to create the worldwide development program. The aim is to achieve a single global clinical plan that includes the major markets — the United States, Europe, Japan, and China. This global plan will face challenges from individual market environments and regulatory requirements that can lead to having a separate development for some countries. Once all data is available, and the regulatory dossier has been finalized, we try to submit it simultaneously globally," says Scheeren.

He goes on to explain that creating this strategy is dependent on the different regulatory requirements in the markets. For example, simultaneous submission is usually not feasible in China, where a CPP (certificate of pharmaceutical product) and approval in one of the major markets are typically first required. The basic dossier for Europe and the United States, however, can be adapted to local requirements in the other markets, and the submission requirements overall are gradually harmonizing under the ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) process.

"When the ICH process began, in the 1990s, harmonization started with Europe, the United States, and Japan. Many other countries have now followed suit, and the trend is toward global harmonization," says Scheeren. "As a general rule in growth countries, the Latin American markets tend to be the most homogenous,

but there is variation within Asia. While Australia tends to follow the global guidelines, South Korea, Vietnam, India, China, and Russia have their own special requirements, like the need for local patient data."

In terms of the submission format, countries are beginning to move closer to the international submission template (eCTD — electronic common technical document). Similarly, the trend is toward more harmonization in legal frameworks among the countries. For example, China's regulatory processes are evolving, creating a framework that is more closely aligned to the U.S. and European legislation, and in both South Korea and China, the regulatory agency has been raised to the ministry level.

UNDERSTANDING THE CHALLENGE

Even as the guidelines are becoming better harmonized, some very specific local requirements are becoming significant enough to shape the entire worldwide strategy. These can be as simple as the need for translations, or as complex as the structure of the entire clinical trials.

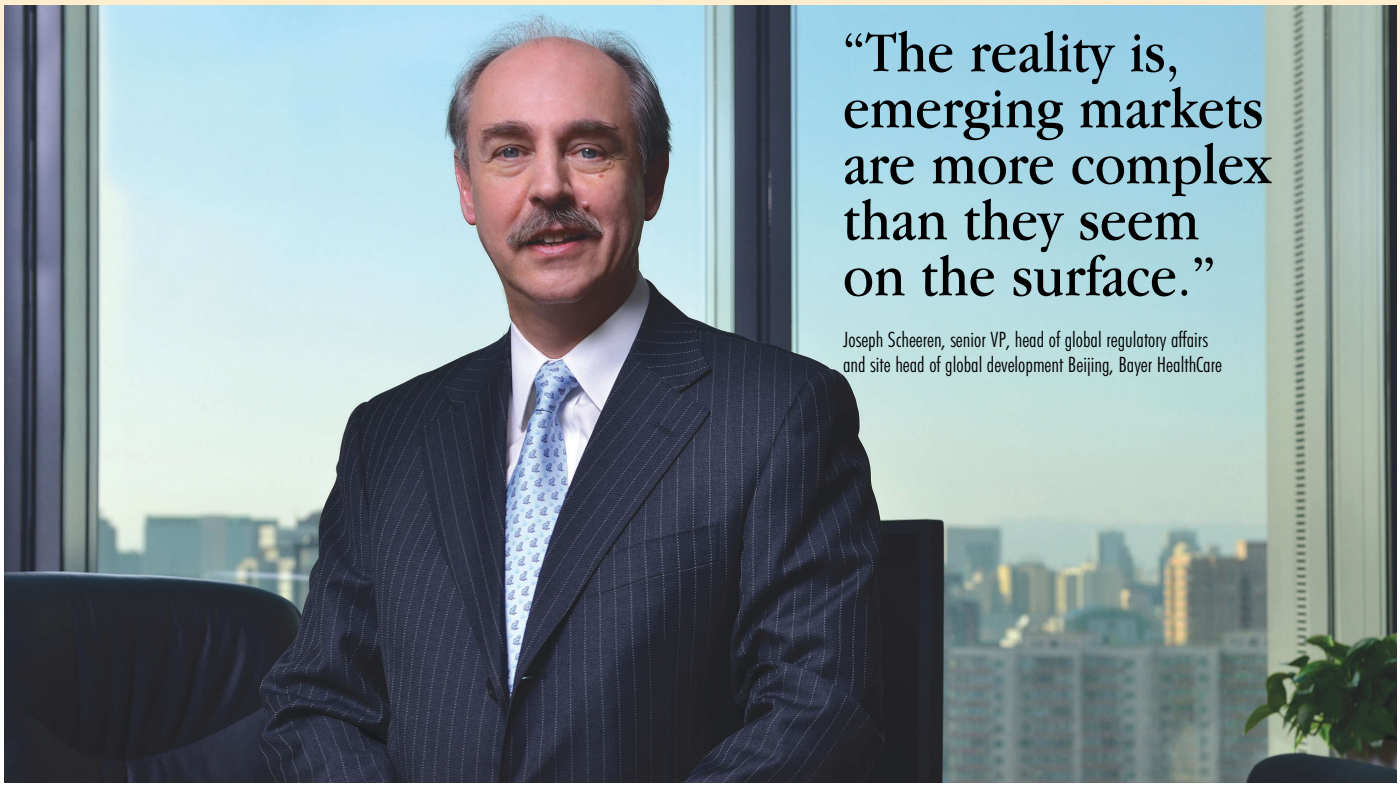
"The reality is, emerging markets are more complex than they seem on the surface. There are thousands of local manufacturers and a staggering number of approved products, all controlled by relatively small regulatory agencies. China is a key example of this," says Scheeren.

Some countries will require translations of the summary or the whole file, whereas others may accept abbreviated files if the product has been approved elsewhere. "For marketing authorization submissions, some countries require very specific local clinical trials. For example, China has minimum requirements of 100 pairs of patients in small molecule trials and 300 pairs in biologics. This is particularly challenging for companies developing drugs for small populations and orphan indications where the global development plan only intended enrollment of a few hundred patients," says Scheeren.

These differences can have a significant impact on time lines, thus incurring delays. For example, if separate trials are needed, this could slow registration by two to four years. The time taken for approval of individual steps in the process may also differ.

"The assessment period for clinical trial applications (CTAs) in China can be long, and may require the drug developer to conduct a national trial, making it a challenge to integrate it into a global clinical program," says Scheeren. "Other emerging markets, such as South Korea, have faster time lines and therefore are easier to integrate."

Most emerging markets do not have electronic filing systems for CTAs and NDAs (new drug applications), and so the need to submit



a paper application slows things down as well. China is expected to move to electronic filings in the near future.

The challenges are not just logistical, though. It's also important to remember that medical practices differ worldwide, and that some populations and ethnic groups may metabolize drugs differently. And it's not over once the drug gets to market, either, as the ongoing regulatory requirements are growing globally. For example, if there is a change in labeling in the drug's country of origin, this needs to be updated simultaneously in other countries.

MAKING IT WORK PRACTICALLY

One of the most practical approaches for managing the different requirements for clinical trials is to work with local partners, and Bayer uses Covance as its preferred partner. The regulatory steps are retained in-house, at one of Bayer's four international hubs (one in the U.S., one in China, and two in Germany).

"To get the best out of our partners, and to ensure that everyone is kept aligned, we work closely together, holding regular meetings to discuss issues and exchange best practices," says Scheeren.

It's important to know and trust manufacturing partners. This is particularly important, as there have been issues reported in India, China, and the other emerging countries.

"There is a new requirement from the EMA for exported products, requiring manufacturers to be certified. The standards for products being exported are quite high, and some local manufacturers are now receiving U.S. and European approval for import," says Scheeren. "China established its first version of GMP in 2000, and implemented the second version in 2010, and the regulatory agencies are validating the manufacturers. Bayer was one of the first to be certified after the second version. The standards for products being exported are pretty good, and deviations tend to be minor."

WHAT CAN WE LEARN FROM EMERGING MARKETS?

While the focus has been on what the emerging markets can learn from the West, there is also a lot that the West can learn from the emerging markets, as Scheeren explains. "China's regulatory agency, though small, has achieved a lot. This boils down to a 'can do' attitude, good communication, excellent working relationships, and willingness to work with industry and other regulatory authorities such as the FDA and EMA."

LOOKING TO THE FUTURE

Moving forward, it will be vital for companies to include Asia and the developing markets in the global development plan, integrating them as much as possible. There have been a lot of changes bringing the requirements and strategies closer to those in Europe and the U.S., but more changes will need to be made to ensure that drugs continue to be developed and marketed with these markets in mind. The FDA has set up offices in many of the developing markets, working to improve overall standards. Benchmarking, collaboration, and cooperation will help to build on this standards effort through formal and informal workshops and meetings.

"It would be great to have China completely integrated into a global development plan for most new drugs, but that would need shorter CTAs and simultaneous submissions, not requiring prior U.S. or EU approval," says Scheeren. "However, the trend clearly is in the right direction, and will increasingly lead to earlier access for patients and increased investment from industry."


Ingredients


Finished Formulation


BioPharma


Contract Services


Technology


Packaging

Meet 34,000* pharma buyers in 3 days

Book your stand

Contact:
Call: +31 (0)20 40 99 544
or visit: www.cphi.com/exhibit

"The visitors are of a very high quality, with many decision-makers attending. We always make a lot of good contacts at CPhI."
Montse Cirera, Marketing & Corporate Affairs Director, Cafosa

CPhI Worldwide is the leading event for the global pharmaceutical ingredients industry. Every year, 34,000* buyers, manufacturers, suppliers and users attend to exchange ideas, form alliances and conduct business on an international scale. More than 2,200 exhibitors represent all aspects of the pharma market from ingredients to contract services, technology, packaging and more.

CPhI worldwide

7-9 October 2014 · Paris Nord Villepinte · France

Co-located with:

icse P-mec InnoPack

*subject to audit

Organised by

UBM

"The world's leading pharmaceutical event & conference platform"

Drug Shortages: Why They Happen And How They Can Be Solved

By Cliff Mintz, Ph.D., contributing editor

Until the mid-2000s, prescription drug shortages were virtually unheard of in the U.S. However, they have been steadily rising since 2006 and are having a profound effect on the delivery of medical care and the regulatory approval of new medicines. "I had never heard of or personally experienced drug shortages until 2006," said Robert Campbell, M.D., co-chair of a newly formed group called Physicians Against Drug Shortages. Likewise, Sean Adams, M.D., a private-practice anesthesiologist concerned about ongoing drug shortages and their effect on patient care, offered, "Until six or seven years ago, I had never heard of drug shortages; physicians were always able to get the drugs they needed to treat their patients." Interestingly, a report from the University of Utah Drug Information Service showed that reported drug shortages grew from 70 in 2006 to 166 in 2009 and 210 in 2011. Many experts, including Campbell, expect the number of drug shortages to exceed 225 in 2013.

Not all drugs are in short supply in the U.S. Most of the affected drugs (almost 80 percent) are sterile, generic injectables used for general anesthesia and pain management or to treat infectious diseases and cancer. "Because of prolonged shortages, physicians are increasingly being forced to either delay or withhold treatment or substitute less effective drugs," said Campbell. He added, "In addition to increasingly jeopardizing patient safety, this is contributing to rising rates of subpar patient care and poorer medical outcomes."

Drug shortages are not only affecting patient care. In many cases, shortages have also had a negative impact on the progress and conduct of the human clinical trials required for new drug approvals. Oncology drug development has been the therapeutic area most affected by the shortages. This is because cancer, unlike other disease states, is typically treated with specific multidrug regimens with narrow therapeutic indexes. Consequently, a shortage of a single component of an approved treatment regimen can effectively eliminate its use as a comparator (control) treatment in clinical trials. "Shortages of specific generic chemotherapy agents continue to interfere with patient enrollment and oftentimes halt or delay the progress of oncology clinical trials," said Ali McBride, PharmD., Department of Pharmacy at the University of Arizona Cancer Center.

In support of this, a survey conducted by the Hematology/Oncology Pharmacy Association for a 12-month period ending October 2011 revealed that drug shortages forced 44 percent of respondent institutions to either halt or delay patient enrollment in cancer clinical trials. The drugs frequently reported as being in short supply included fluorouracil, leucovorin, liposomal doxorubicin, and paclitaxel drugs commonly used to treat ovarian and breast cancers. "Unfortunately, while many people contend that drug shortages are beginning to abate, new drugs are regularly being added to drug shortage lists in the U.S.," lamented Campbell.

CAUSES OF DRUG SHORTAGES

The FDA attributes over half (54 percent) of all drug shortages to quality or manufacturing issues that force drug production facilities to either partially or permanently shut down. These issues have been most pronounced for sterile-injectable drugs (most of which are generics), which are more complicated to manufacture than nonsterile products and, consequently, more likely to experience quality or production problems. To that point, in 2012, it was estimated that nearly a third of the sterile manufacturing industry's production capacity was not being utilized because of plant closings or temporary shutdowns to fix serious quality issues.

Another factor contributing to drug shortages is consolidation in the pharmaceutical and contract manufacturing industries. This has resulted in a dwindling number of manufacturing and suppliers for a growing number of drugs. At present, according to a 2012 FDA report, over 50 percent of drugs in short supply have three or fewer manufacturers. Moreover, Physicians Against Drug Shortages' Campbell emphasized that only three manufacturers are responsible for producing 70 percent of the world's

sterile injectable products. Consequently, when one manufacturer has to shut down even temporarily, the remaining manufacturers are often unable to quickly ramp up production to meet global demand. Likewise, sometimes a scarcity of raw materials or other drug components like excipients can slow down drug manufacturing and cause shortages. These shortages can be devastating, especially when a primary or secondary raw-material supplier delays or discontinues production.

Also, financial challenges have forced many smaller drug manufacturers to scale back production or shut down entirely. According to a 2011 U.S. government report, at least 90 percent of the global supplies of certain drugs are produced by a single manufacturer. Not surprisingly, manufacturing problems at a single provider's production facilities can have severe consequences on drug availability. This was the case in 2011 for the drug Doxil (liposomal doxorubicin) used to treat ovarian cancer, multiple myeloma, and the HIV-related Kaposi's sarcoma. In this instance, Ben Venue Laboratories, the sole provider of Doxil worldwide, was forced to suspend manufacturing operations because of serious quality control problems. This resulted in massive global shortages of Doxil, which continue to persist today despite resumption of manufacturing at the Ben Venue facility. Interestingly, some industry insiders have accused the FDA of causing the shortages, saying that overzealous enforcement and poor communication have caused plants to slow production or close needlessly.

Others contend that many drug shortages are firmly rooted in business practices and decisions made by the companies that manufacture them. Some of the factors that may influence these decisions include profits, intensity of generic competition, market share considerations, manufacturing costs, anticipated clinical demand, regulatory compliance requirements, and costs associated with correcting manufacturing problems or mergers. In addition, economic pressures are forcing many manufacturers to routinely maintain lower drug inventories (no surpluses) or to even consider removing lower-margin drugs from the market.

Finally, some insiders like Campbell and Adams believe that most drug shortages can be ascribed to fundamentally flawed business practices of the so-called "drug middlemen" — wholesalers or distributors, prime vendors, healthcare systems, and group-purchasing organizations (GPOs) — that dominant operation of the global drug supply chain. For example, most of these organizations have embraced the "just in time" business model championed by the automotive and semiconductor industries in the 1990s to reduce inventory costs and optimize cash flow. Critics contend that, while this business model may help to cut overhead costs and maximize profits, there are no drug surpluses that can be tapped when drugs are in high demand and short supply. Others believe that questionable business practices like drug stockpiling (in advance of price increases), delivery delays, preferential selling practices/quotas, contract disputes, and hoarding based on rumors of impending shortages are responsible for the increased frequency of drug shortages.

THE GOVERNMENT OFFERS SOME SOLUTIONS

Growing health concerns about chronic U.S. drug shortages prompted President Obama in October 2011 to issue an executive order that required the FDA to take more action to help alleviate shortages. Recommended actions included more comprehensive surveillance and reporting, expediting regulatory reviews of manufacturing changes and new manufacturing sites, and monitoring the behavior of manufacturers and distributors to prevent stockpiling or price gouging of scarce prescription medicines. In a separate letter to drugmakers, Obama reminded them of their legal and ethical responsibilities and urged them to work more effectively to share information in advance of a possible shortage.

Spurred by the executive order, Congress enacted legislation in the summer of 2012 that increased the FDA's authority to avert drug shortages by requiring drugmakers to report drug discontinuations and supply interruptions, improve coordination between federal agencies, and speed the approval of generic drugs. It is important to note, however, that the FDA cannot require a company to produce a drug, nor does the agency have authority over business decisions related to availability or prices set by manufacturers. Moreover, the FDA has no jurisdiction over shortages that occur because of contractual problems among manufacturers, distributors, or end users. Consequently, it is not clear how much the new legislation will help to curb the frequency of future drug shortages.

Although many believe that the FDA's expanded powers will better help to manage drug shortages, others like Terry Walsh, head of comparator networks at TransCelerate Biopharma (a consortium of 17 pharmaceutical companies), think that industry initiatives such as the Clinical Trials Comparator Network created by TransCelerate will also be vitally important. According to Walsh, the network was created because of the unpredictability and difficulty in sourcing many comparator and cotherapy drugs (especially in oncology, pain management, rare disease products, and anti-inflammatory monoclonal antibodies) that can delay or halt the progress of clinical trials. He believes that the Clinical Trials Comparator Network will help to overcome sourcing problems and allow its members to readily obtain comparator drugs directly from one another when they need them, in appropriate quantities, and with proper documentation. "This will help to prevent delays and expedite new drug approvals," said Walsh.

Another solution to reducing drug shortage—mainly advocated by Physicians Against Drug Shortages and its members—involves legislative action and reforms that curb the financial power and limits the purchasing power of GPOs. Recently, six senior congressmen called on the U.S. Government Accounting Office (GAO) to investigate whether business and contract practices by GPOs are contributing factors to drug shortages.

WHO Comments Signal Support For Compulsory Licensing

By Gail Dutton, contributing editor

The NIH recently made an unprecedented decision in granting the Lacks family some say in how the cervical cancer cells from the late Henrietta Lacks — the famed HeLa cell line — are used. A few months earlier, in May, controversy over ownership of a sample of the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) erupted into a public spat involving the government of Saudi Arabia and Erasmus Medical Center in the Netherlands. In commenting, the WHO Director-General, Margaret Chan, demanded that labs not be allowed to profit from their work.

The underlying issue in both situations is the right to profit from scientific discovery. The ramifications of these incidents may affect not only the use of biological samples but also countries' decisions to use compulsory licenses.

DEVELOPING WORLD UNRECEPTIVE TO PHARMA PATENTS

The WHO appears suspicious of profit-based businesses. As Chan said in her WHO speech in May, "Many of the risk factors for noncommunicable diseases are amplified by the products and practices of large and economically powerful forces. Market power readily translates into political power. When public health policies cross purposes with vested economic interests, we will face opposition, well-orchestrated opposition, and very well-funded opposition."

India, with a strong generic pharmaceutical industry, is particularly receptive to the notion of constrained patentability for pharmaceutical products. Earlier in 2013, India's health ministry committee urged the government to exercise its compulsory licensing rights for Herceptin (trastuzumab). The Indian biopharmaceutical firm Biocon expects to complete Phase 3 trials of a biosimilar for trastuzumab this fiscal year, and Dr. Reddy's Laboratories and Intas Pharmaceuticals indicate they may begin clinical trials soon. One year earlier, in March 2012, India exercised a compulsory license for Nexavar (sorafenib) by Bayer, which was subsequently produced by the Indian firm NatcoPharma.

When Roche relinquished its patent battles in India in August 2013, it cited India's intellectual property environment as a key factor in that decision. Indian generics firms may see a boost from tight patent requirements and the exercise of compulsory licensing, but the results are chilling for innovators operating in India.

India's success in exercising march-in rights has been noted by other nations. South Africa has an active campaign, spearheaded by the Treatment Action Campaign (TAC) and Médecins Sans Frontières (MSF), to remodel its patent laws after the Indian laws. In an August memorandum to the South Africa Department of Technology and Industry (DTI), TAC and MSF charged the lack of competitive markets in emerging regions enabled pharmaceutical companies to charge unaffordable prices that make life-saving medicines inaccessible.

"Although other BRICS [Brazil, Russia, India, China, and South Africa] countries like India and Brazil have utilized these pro-public health safeguards, South Africa is lagging behind and has not amended its patent law to incorporate or implement TRIPS [Trade Related Aspects of Intellectual Property Rights] flexibilities," the TAC and MSF memo pointed out. It advocated a stringent patent examination process that "only grants patents on new drugs. If fewer secondary patents are granted, then more generic versions of medicines will be able to enter the market upon the expiry of compound patents, which will in turn drive down prices. Furthermore, when patents result in medicines being priced out of reach, actions that mitigate high prices, such as compulsory licensing, must be practically feasible to implement." It called on DTI to "broaden the grounds and facilitate the procedures for issuing compulsory licenses." Similar laws are enacted in China and are being planned in Argentina and the Philippines.

W. Murray Spruill, Ph.D., co-leader of Alston & Bird's intellectual property patent proup and the leader of the law firm's biotechnology, chemical, and pharmaceutical team, suggests these reactions are unrelated to Chan's statements at the WHO meeting and that the willingness to exercise compulsory licensing rights in the United States is unlikely to change. "There was a lot of talk about compulsory licensing during the anthrax scare several years ago, but no compulsory license was granted in the U.S.," Spruill says. "I don't think it will be affected now."

To exercise compulsory licensing in the U.S., the government must show that the company is not using the patent, the company is failing to meet a public demand, or the invention was funded partially by the government. The WHO agreement on TRIPS, in contrast, includes all patents.

The exercise of compulsory licensing in the EU is similar to that of the U.S. However, recent legislation allows a Europe-wide health emergency to be announced, with provisions to facilitate ordering vaccines for member states. Although the legislation does not address compulsory licensing, it does broaden the geographic scope of any actions. The EU Parliament says that, "Access to vaccines will be fairer, as they will be purchased at advantageous prices."

SAMPLE OWNERSHIP IS DEBATED

Upstream from the patent issue lies the question of sample ownership. As Deborah Lacks, Henrietta Lacks' daughter, says in *The Immortal Life of Henrietta Lacks*, "If our mother cells done so much for medicine, how come her family can't afford to see no doctors? … People got rich off my mother … now we don't get a dime. I used to get so mad about that …"

The issue with the MERS-CoV is only slightly different. Microbiologist Ali Mohamed Zaki, who uncovered the virus, says the Saudi Ministry of Health tested the sample for swine flu, then ceased testing. Zaki then sent a sample to virologist Ron Fouchier at the Erasmus Medical Center in the Netherlands for identification. The Saudi Ministry of Health says the sample left the country without permission, and disputes Zaki's version of events. But, as Nobel Laureate Sir Richard Roberts, Ph.D., chief scientific officer of New England BioLabs, asserts, "It's ridiculous to ban anybody from getting involved to help solve a disease."

Saudi Arabia also claims viral identification was delayed three months because Erasmus Medical Center filed for a patent on the use of the virus' DNA sequence and host receptor data. Other researchers point out that the virus sample is freely available and, in fact, has been analyzed by labs in many different countries. At that point, the WHO's Chan entered the fray, forcefully telling meeting delegates that countries must not allow commercial labs to profit from MERS-CoV.

Yet, as Tilde Carlow, Ph.D., head of the division of parasitology at NEB, points out, "There must be some profit to drive R&D in our field. The consequence from not deriving profit could be really serious. There is an urgent need for new antibiotics, but because of the potential for meager profits, many companies aren't interested." Carlow predicts there will be a growing number of neglected diseases because of an inability to make a profit, thus hampering knowledge creation.

For-profit organizations aren't necessarily getting involved in orphan diseases to make a profit, Roberts adds. "Some companies, like ours, have no desire to benefit financially, but instead want to solve a third-world disease." For example, NEB became involved in lymphatic filariasis research some 30 years ago, before the WHO launched its own initiative in 2000. "Researchers at New England BioLabs are not interested in the commercial value of this research. We basically give away all the rights to anything we find here. We file patents, but do not charge licensing fees."

SAMPLE SHARING GUIDELINES VARY

The MERS-CoV flap illustrates confusion regarding the international rules for sharing samples, despite the pandemic influenza preparedness (PIP) framework the WHO developed to govern sample sharing. Under that framework, virus strains may be shared internationally with private companies as well as with public concerns. Countries sharing the virus receive equal access to the resulting treatments or diagnostics.

The guidelines for sample transfer and ownership vary, to some extent, by sample type. Within the Ocean Genome Legacy, which Roberts chairs, "There, the suppliers of the samples own the rights. With humans, however, it's difficult to know who is the correct owner." But, he points out, "Unless a researcher is there to isolate and characterize a sample, ownership doesn't mean much."

The question that remains is whether or how Saudi Arabia should benefit from the MERS-CoV. Nothing prevents it from developing diagnostic tests or therapeutics, either alone or in concert with other partners.

In the end, the spats regarding ownership of the MERS-CoV sample and the involvement of the Lacks family in determining who may use the HeLa cell line may be merely sideshows to a greater issue: the stance taken by the WHO and its perception of for-profit corporations. With the WHO's tacit blessing, developing nations become more likely to tighten their patent laws and to exercise their compulsory licensing rights when they determine that medicines are unaffordable.

FSP Or Full-Service Outsourcing?

Functional service provider (FSP) partnerships have been gaining traction in recent years because of their potential to increase efficiency and flexibility in outsourcing without compromising quality. Well-defined services within the scope of a clinical trial project or program (e.g. data management, biostatistics, or medical writing) are good candidates for FSP outsourcing. By outsourcing individual functional services, sponsor companies gain freedom they might not have in a traditional preferred provider relationship or when outsourcing an entire study. However, many factors contribute to a successful FSP relationship, and when evaluating CROs as potential FSP partners, sponsors should look for certain qualities.

First, you must understand the difference between FSP and full-service outsourcing. Traditionally, sponsors have outsourced full-service responsibilities to CROs for their clinical trials, often within the scope of a preferred provider relationship. Recently, some sponsors have moved away from these kinds of relationships toward a "cafeteria-style" outsourcing model, or FSP relationships. In this model, you can pick and choose which services to outsource to which CRO based on the CRO's areas of expertise.

CULTURAL FIT

Start the vetting process for an FSP relationship with a CRO by asking about company values, how conflicts are resolved, communication channels, management oversight, and approach to customer service. The CRO's answers to these questions should be in alignment with your approach to clinical research and collaboration.

EXPERIENCE

Obviously, if you are pursuing an FSP relationship, you want a CRO that has experience with this type of model. That way, it's likely it has worked out the kinks and will be able to hit the ground running with a new sponsor. Experienced CROs also will have recommendations for training programs, which will ensure a seamless integration between CRO and sponsor staff as well as ensure new staff members are trained quickly and efficiently. Ask if the company has suggestions for the best way to work together, including overall program management, rapid start-up processes, points of contact, system usage, process development, deliverable and timeline tracking, and billing.

CONSISTENCY

Sponsors should ask potential CRO partners about company and team turnover rates. In addition, ask about the company's strategy for maintaining and disseminating program-related knowledge across their team (e.g. therapeutic, protocol, and system knowledge) as well as how they handle team member departure/reassignment and onboarding. These strategies should be part of the foundation of the FSP partnership.

FLEXIBILITY AND SCALABILITY

Sponsors should ask the CROs how they plan for and handle the need to scale up quickly, as well as how they avoid underutilizing resources. In both cases, some sort of strategic forecasting and proactive communication should be part of the plan. Program governance meetings are an excellent strategy for managing the resourcing demands of a successful FSP partnership. These meetings can occur as often as necessary to ensure constant communication between CRO and sponsor. Both parties should contribute to the agenda to ensure active engagement and bidirectional communication. These meetings can be beneficial in maintaining a big-picture view of the FSP partnership, and they encourage direct and frequent communication between team members.

All of the previously mentioned characteristics are important when seeking to establish an FSP relationship that has the potential to reduce time and costs without compromising scientific integrity or quality. There are many CROs in the industry that provide FSP services, so it's necessary to conduct a thorough evaluation to identify an FSP partner that is a good match for your project or program. In an industry where the goal is to get approvable drugs to market as quickly as possible, consistency in all of these areas is a winning formula for identifying an FSP partner that sponsors can trust.

Dawn Edgerton

Dawn Edgerton is assistant VP of operations at Rho, a full-service CRO based in Chapel Hill, NC. She has 16 years of experience supporting research within the drug development industry and NIH longitudinal studies. In her current role, Edgerton provides leadership and guidance to project leads across all phases of clinical development and over a wide range of therapeutic areas.

wtg

Biomanufacturing Summit 2014

January 29 - 31, 2014 • Hilton San Diego Bayfront, San Diego, California

Uncover tomorrow's strategies to help you streamline processes, enhance capacity and reduce operational costs

Speakers from

AMGEN · Baxter · biogen idec · Bristol-Myers Squibb · Boehringer Ingelheim · Genentech · genzyme A SANOFI COMPANY · gsk GlaxoSmithKline · Lilly · MedImmune · MERCK · Pfizer · Roche · SANOFI · Shire · TEVA

Save $500 when you register today

Book your place by December 16, 2013

biomansummit.com/biopharm

@biomansummit | enquire@wtgevents.com | +1 416 214 1144 | biomansummit.com

* This delegate offer is not available to solution providers, consultants, or suppliers. A 10% service fee is applied to all bookings.

Using Expert Crowdsourcing To Expand The New Drug Pipeline

By Clifford Gross, Ph.D.

Enhancing a company's product pipeline with compelling new drug candidates has been a challenge for the world's leading pharmaceutical companies. Many corporations have spent billions of dollars on in-house R&D with lackluster results. Clearly a new paradigm needs to be embraced industrywide to address this problem.

Currently, there are 15,000 universities in 160 countries that create approximately 100,000 new technologies every year. Interestingly, roughly 3,300 of these institutions develop 80 percent of the peer-reviewed, published university research, the cost of which is borne by taxpayers in their respective countries.

Open innovation is a corporate strategy of which the basic tenant is that R&D should not be limited to in-house capabilities but must be reimagined to include all of the external research that is conducted and available for acquisition.

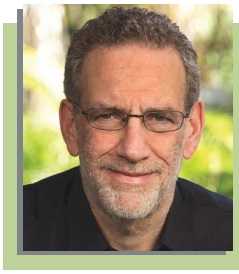
With the development of smartphones and the emergence of social networks, the world has become much more interconnected. This has led to the development of expert networks on a scale never before seen and the coming of age of crowdsourcing. Crowdsourcing is a market-driven approach to pull solutions to defined problems from the interconnected world beyond existing suppliers. In traditional crowdsourcing, a company can push out a problem to a social network in hopes of getting back a practical solution. This actually works quite well for consumer-facing incremental improvements. However, when game-changing technological improvements are needed such as new drug candidates, the crowd at large normally does not have the expertise to solve the problem. In these cases "Expert Crowdsourcing" can be useful. Universities and government research centers are target-rich environments for both these experts and the technological leaps they produce.

Creating a robust pipeline of new discoveries is a good start, as it allows a company to keep its finger on the pulse of new discoveries in its space, but it is not sufficient to augment in-house R&D in a continuous manner. To achieve this, it is necessary to inject two additional layers of expertise: objective external technology review and university-centric transaction experience. The first de-risks technology candidates for consideration, and the second reduces the time and expense needed for the acquisition or licensing of new technologies from not-for-profit research institutions.

The following steps can help to cost-effectively enhance the number of new drug candidates for life sciences companies of all sizes:

1. Build a global network of all major universities and publicly funded research centers that conduct basic research in the areas relevant to your business.
2. Develop an external screening team to provide real-time candidate selection.
3. Build an in-licensing team experienced specifically in university technology transfer.

Collectively these steps can augment any corporate R&D program and help address the pipeline gaps that statistically are unlikely to be met through in-house research alone.



Dr. Clifford Gross serves as the CEO of Tekcapital Ltd. based in Oxford, U.K. and has completed more than 100 technology transfers from university and federal laboratories for a wide range of companies. He received his Ph.D. from New York University and an M.B.A. from the University of Oxford. He can be reached at cgross@tekcapital.com.

To comment on this article, send an email to rob.wright@lifescienceconnect.com.

Gallus Acquires Laureate

Synergy Expands Unique Flexibility

Gallus adds further flexibility to its CMO services with the acquisition of Laureate. We've doubled our biologics clinical development capacity by adding a complementary FDA-approved cGMP facility in Princeton, New Jersey. Clinical and commercial supply capabilities have expanded and include flexible and fixed stainless steel up to 2,000 L and single-use HyClone™, WAVE™ and Xcellerex™ technologies up to 2,000 L, in addition to clinical aseptic fill-finish capabilities. We continue to offer our pioneering and flexible approach, including the SuiteSPACE® virtual ownership model.

Contact Gallus to learn how far we'll go to work for you.
info@gallusbiopharma.com | **www.gallusbiopharma.com**

gallus
Uniquely Flexible CMO™

THE CMO LEADERSHIP AWARDS 2013 | WINNER REGULATORY PRODUCTIVITY

We're Taking Our Strength in High Potency to a New Level

Development to manufacturing – get all the expertise, quality and choices you need to succeed.

Visit www.patheon.com

Patheon is making significant investments in high potency across our global network. Already high potency customers enjoy the same quality, expertise and breadth of resources as all Patheon customers, including an array of solid and sterile dosage forms. Now we're building on that strength with the latest contained equipment and innovative processes. Our goal: elimination of the need for respiratory protection. At Patheon we're not just buying equipment, we're investing in your success.

- Extensive experience and expertise
- Development to large-scale manufacture
- Flexibility to meet customer and regulatory standards
- Stellar quality and regulatory track record

Visit www.patheon.com
Call +1 866-PATHEON
Email doingbusiness@patheon.com

Patheon™
Performance the World Over