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Art Pappas, Founder, Pappas Ventures

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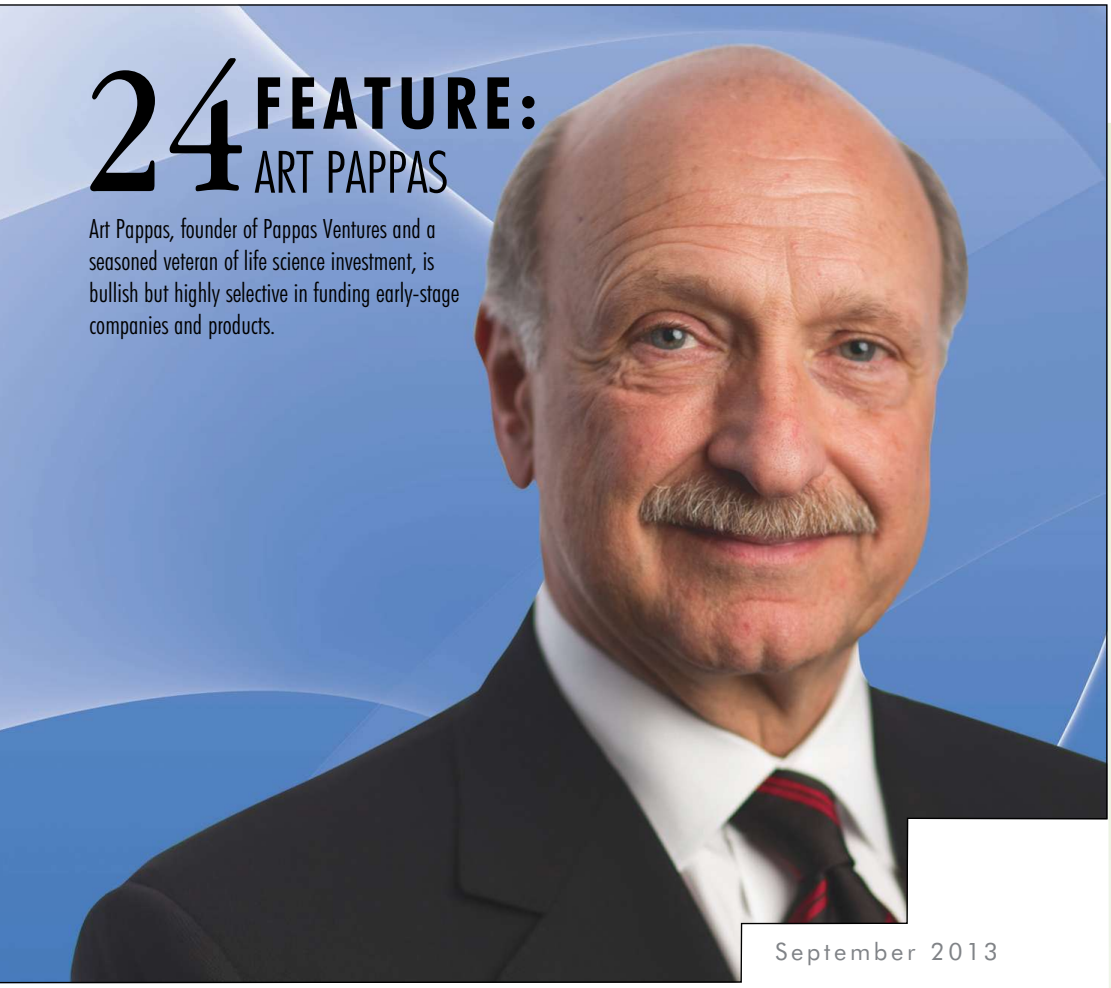

24 FEATURE: ART PAPPAS

Art Pappas, founder of Pappas Ventures and a seasoned veteran of life science investment, is bullish but highly selective in funding early-stage companies and products.

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Welcome to *Life Science Leader*

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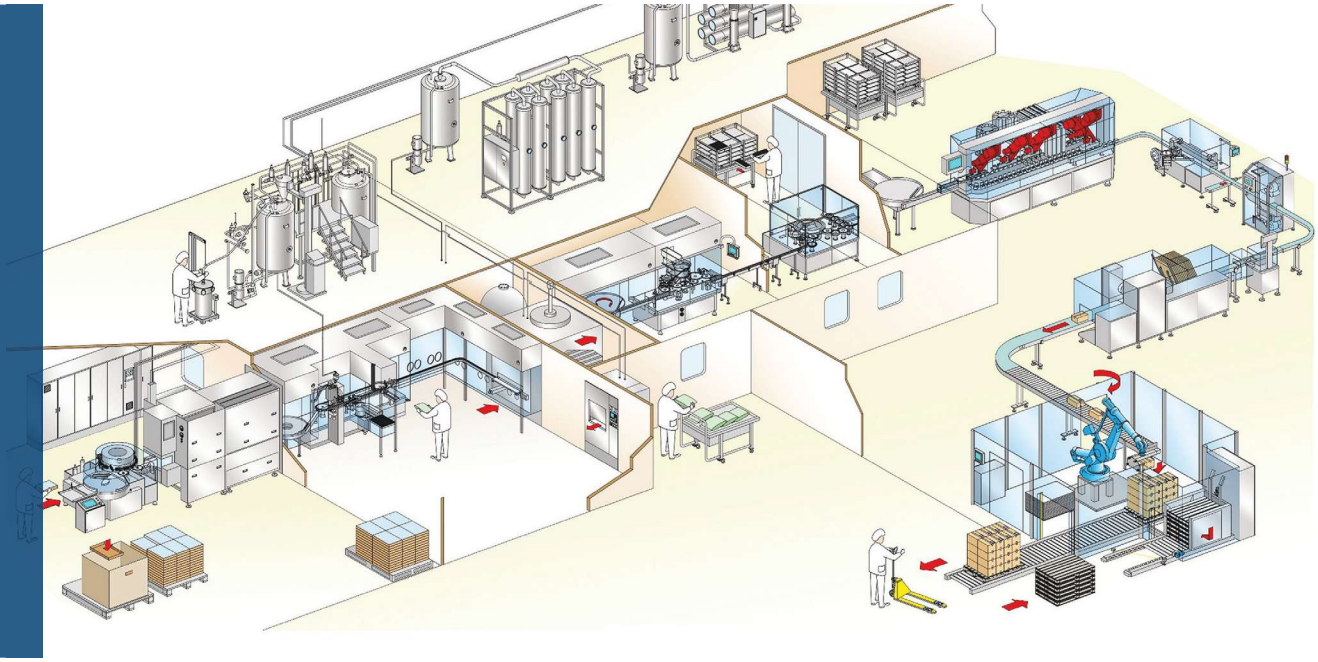

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SEPTEMBER 2013

Life Science Leader
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Erie, PA 16510-4672
Telephone: (814) 897-7700 ● Fax: (814) 899-4648

LIFE SCIENCE LEADER (ISSN: 21610800) Vol. 5, No. 9 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.

EDITOR'S NOTE

Private Or Public? Not Really Even A Question In Life Sciences?

In August, I was invited to attend a NASDAQ opening bell-ringing ceremony as a guest of NeoStem (NASDAQ: NBM), which focuses on the emerging cellular therapy industry. The company was relocating from the NYSE to the NASDAQ — the world's largest electronic stock market. Dr. Robin Smith, M.D., chairman and CEO of NeoStem, saw several benefits for making the change, including enhanced visibility to institutional shareholders. The experience got me thinking about the question many life sciences industry entrepreneurs struggle with when launching a start-up — should we go private or public? According to Punit Dhillon, president and CEO of OncoSec Medical Inc., a small publicly traded biotech, a key driver for the decision to go public is the availability of funding sources and management's experiences and relationships.

To be sure, going public has its benefits in the forms of cash influx, recognition, and prestige. Christopher Helmrath, managing director at SC&H Capital, a CPA and management consulting firm, believes going public should be a last resort because it involves the most scrutiny. There is no doubt there are advantages to staying private — no reporting requirements, no disassociated shareholder to please, and no undue focus on short-term goals. When run properly, private companies can grow to sizes comparable to their publicly traded counterparts. Boehringer Ingelheim (BI) for example, is privately held and one of the 20 largest pharmaceutical companies in the world. The other 19, however, are all publicly traded.

If success is determined by the size of your pocketbook, it is not likely that new drug companies will be able to make a go of it as private companies, because you need a big pocketbook to bring a drug to market. Just to get one clinical trial site up and running averages $50,000. The fee paid by companies to the FDA for filing a new drug application (NDA) with clinical data is nearly $2 million, which is approximately four times the cost of conducting an IPO. In the life sciences industry, the question of being a private versus a public company seems to be less a question of *if* you go public, and more a question of *when*. For some, that *when* is now.

This past July, billionaire Randall Kirk filed papers with the SEC for an IPO for his most recent biotech venture, Intrexon, which is to be listed on the NYSE under the trading symbol XON. Kirk is not alone in seeing the benefit of going public. According to the National Venture Capital Association (NVCA), 21 IPOs were conducted in the second quarter of 2013, raising more than $2.1 billion. This is more than double the volume and dollars compared to the previous quarter's eight IPOs totaling $716.9 million. The second quarter also saw the highest number of biotechnology venture-backed IPOs since the third quarter of 2000. What does this mean? According to William Slattery, a partner at Deerfield Management, a New York-based healthcare investment management firm, it means investors can have more confidence in the potential of biotech today than in 2000, as there is improved understanding of the molecular underpinnings of disease. It also means if you are currently private, best brush up on your knowledge on going public, as well as emerging investment options like those highlighted in Wayne Koberstein's article on page 24 featuring VC veteran Art Pappas.

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Q: What trend will have the biggest impact on pharma/bio?

In my opinion, the use of combination therapies to treat diseases other than cancer will have the biggest impact. The types of diseases where companies could seize opportunity include Hepatitis C caused by the hepatitis C virus (HCV), Alzheimer's, and multiple sclerosis (MS). One of the companies well-practiced and best-positioned seems to be Gilead. Alternatively, companies working on harnessing the immune system to combat cancer could be an interesting growth opportunity. Big pharma seems to be leading the way. For example, a Bristol-Myers Squibb (BMS) study with the two-drug combination (Yervoy and nivolumab) resulted in nearly one-third of 52 skin cancer patients having rapid and deep tumor regressions. Roche's Genentech, Merck, and BMS dominated this year's American Society of Clinical Oncology (ASCO) meeting, though Onyx and BioMarin bear watching.

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

Q: What advice do you have for the FDA to facilitate more cost-effective drug development?

We need an FDA that is equipped to handle both the pace of discovery and the pace of diagnosis. We need to create a 21st century FDA that can speed breakthrough cures and medicines to the patients who so desperately need them, while retaining its position as the global "Gold Standard" for the review and approval of safe and effective medicines. Furthermore, the reimbursement conversation must be focused on the value of providing cures and treatments. There are 10,000 baby boomers entering Medicare every day for the next 20 years. If fewer of them were sick from various diseases, Medicare costs would be driven down astronomically. We need to look at what we spend on chronic conditions. If we could delay the onset of diabetes by even five years, we would save Medicare $50 billion a year.

Alan Eisenberg
Eisenberg serves as executive VP for emerging companies and business development at the Biotechnology Industry Organization (BIO). He manages and directs BIO's services and advocacy efforts for BIO's emerging companies.

Q: Which pharma/bio companies do you think are truly being disruptively innovative?

Many pharma and bio companies are attempting individual approaches that are extremely innovative. I am particularly drawn to those companies investing in internal resources focused on bringing innovation to their clinical research. Such dedication is important as companies otherwise try to draw on existing resources already committed to their "day jobs," making innovation more of a hobby. Dedication is needed in order to bring discipline to innovation and to ensure companies are picking well-developed ideas, running intelligent experiments, and managing the necessary change in order to embed appropriate new tools and approaches in the organization. I appreciate companies willing to be transparent, enabling the entire clinical research field to move forward. Some of the companies participating at the Disruptive Innovation in Clinical Trials program (i.e. Lilly, J&J, and Pfizer) are taking strong positions by these measures.

Craig Lipset
Lipset is head of clinical innovation within worldwide R&D at Pfizer. In this role, he works across units and stakeholders to define Pfizer's vision for the future of clinical trials and enables the initiatives and investments to create that future.

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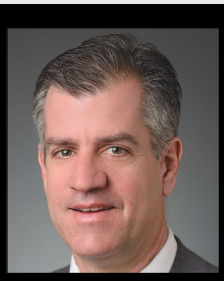
Republicans: Stop Allowing Vocal Ideologues To Dictate Health Policy

While it is understandable why many members of Congress fear crossing their ideological base, it is high time for Republicans and Democrats alike to disregard ideological rigidity and come together on reasonable and modest reforms that can strengthen the health system and bring greater efficiencies.

For decades, when Republican leadership constructed legislation, attention was focused on maintaining support of moderate Republican members, often in Democratic-leaning suburban districts. But three recent developments gave impetus to the conservative base driving negotiations and legislation within the caucus:

1. Redistricting, whereby state legislatures gerrymandered district lines to make Republican districts more conservative (and Democratic districts more liberal).
2. The Supreme Court decision to allow third-party groups to spend unlimited "independent expenditures" educating the public on certain issues or members' votes.
3. The rise of the grass-roots Tea Party.



John McManus,
The McManus Group
jmcmanus@mcmanusgrp.com

Republicans are now more concerned about a primary challenge from their base than a Democratic challenge from the center/left. The primary defeat of prominent main-street Republicans such as Senator Bennett (R-UT), Rep. Castle (R-DE), and Rep. Stearns (R-FL), among others, struck fear in a number of Republicans and now drives their decision making on many matters, but healthcare above all else.

This explains why the Republican House leadership was forced to scuttle a modest bill that would have removed funds from an Obamacare slush fund in order to finance high-risk pools for uninsurable individuals, another Obamacare initiative that had run out of money because too many sick people signed up. The bill was a clever initiative because it simultaneously 1) defunded a slush fund for prevention that Secretary Sebelius was tapping to establish federal health exchanges in those states refusing to set up their own exchanges and 2) addressed a real policy problem with Obamacare, which had low-balled the resources it would take to provide assistance to uninsurable individuals through high-risk pools — a policy proposal Republicans had embraced for years.

The Club for Growth and Heritage Action — two notorious conservative groups known to drop tens of millions of dollars on Republicans they find not conservative enough, or "RINOs" (Republicans in name only) as they dub them — sprang into action. They issued alerts to their members and threatened retribution to any Republican who supported Majority Leader Cantor's bill on the issue. The bill also drew the ire of AARP and several left-leaning groups, so bipartisan consensus could not be achieved, and a floor vote has been indefinitely delayed.

The issue is endemic of a larger problem that Republicans confront in approaching health policy. There is a substantial faction of the Republican party and the base that would like to either repeal Obamacare in its entirety or require the entire statute be implemented precisely as written and watch with glee as the Democrats' law fails to deliver half of its promises at twice the cost. Two score and counting repeal votes in the House have been unsuccessful in getting the Democrat-controlled Senate to move.

Now Tea Party activists Senators Ted Cruz (R-TX) and Mike Lee (R-UT) are demanding that Congress defund Obamacare this fall when it votes on the appropriations bills that fund the federal government. Even if that bill passed the Senate with some Democrat support, it would be vetoed by President Obama and a 2/3 majority from both chambers would be required to override. They simply don't have the votes, and bringing the government to the brink on an issue that has been settled by the Supreme Court and the 2012 election makes no sense.

WHAT SHOULD CONGRESS FOCUS ON THIS FALL?

The Obama administration is scrambling to implement the greatest change to healthcare policy in the history of the country, but by all indications, it will not be ready, and chaos will roil the health sector.

- The Supreme Court made the Medicaid expansion optional to states, and only 24 states with 5.4 million of the 15 million potential new enrollees have affirmatively announced they will proceed with the expansion.

- More troubling, 27 states have indicated they will not establish their own exchanges, which will offer subsidized insurance policies available to individuals above the poverty level. A recent Government Accountability Office report found that implementation of the federal exchanges for those 27 states by October 1 is uncertain

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and that CMS is behind on activities that cross "the core exchange functional areas."

Meanwhile, in a glimmer of hope to end the paralysis, the Energy & Commerce Committee came together this summer and reported out a bipartisan bill to repeal the flawed Medicare physician payment formula, the "SGR." That formula has been overridden more than 15 times in the past 10 years in stop-gap fashion where Congress kicked the can down the road without finding a permanent solution to the pending 25% payment cuts or reforming a fee-for-service system that rewards volume instead of quality.

It would be a real achievement to permanently repeal this unworkable formula and set the system on a path focused on patient outcomes. But how is Congress going to find the $140 billion to $160 billion necessary to fund this change over the 10-year budget window? That's where bipartisan consensus is likely to break down.

A little-discussed option would be to delay implementation of Obamacare spending for one year.

- While the Medicaid expansion and new subsidies for individuals in the exchange cost only $49 billion in 2014, Congress could grab $170 billion of savings over the 10-year budget window because that represents Obamacare spending in 2023 — the last year in the budget window — which would now be pushed outside the window. That is more than enough resources to clean up SGR and other temporary policies that Congress has failed to fundamentally address.

- The one-year delay would give the administration valuable time to ensure that the signature domestic achievement of the Obama Administration gets implemented properly. (Even the Obamacare architects stipulate that the bill that became law was never intended to be the final product, but a bill to get the Senate to conference. The 2010 election of Scott Brown in Massachusetts destroyed the Democrats' 60-vote control of the Senate chamber and compelled the House to enact the Senate bill in its entirety.) But a delay requires Democrats to take their foot off the gas and acknowledge that time is needed to make necessary changes.

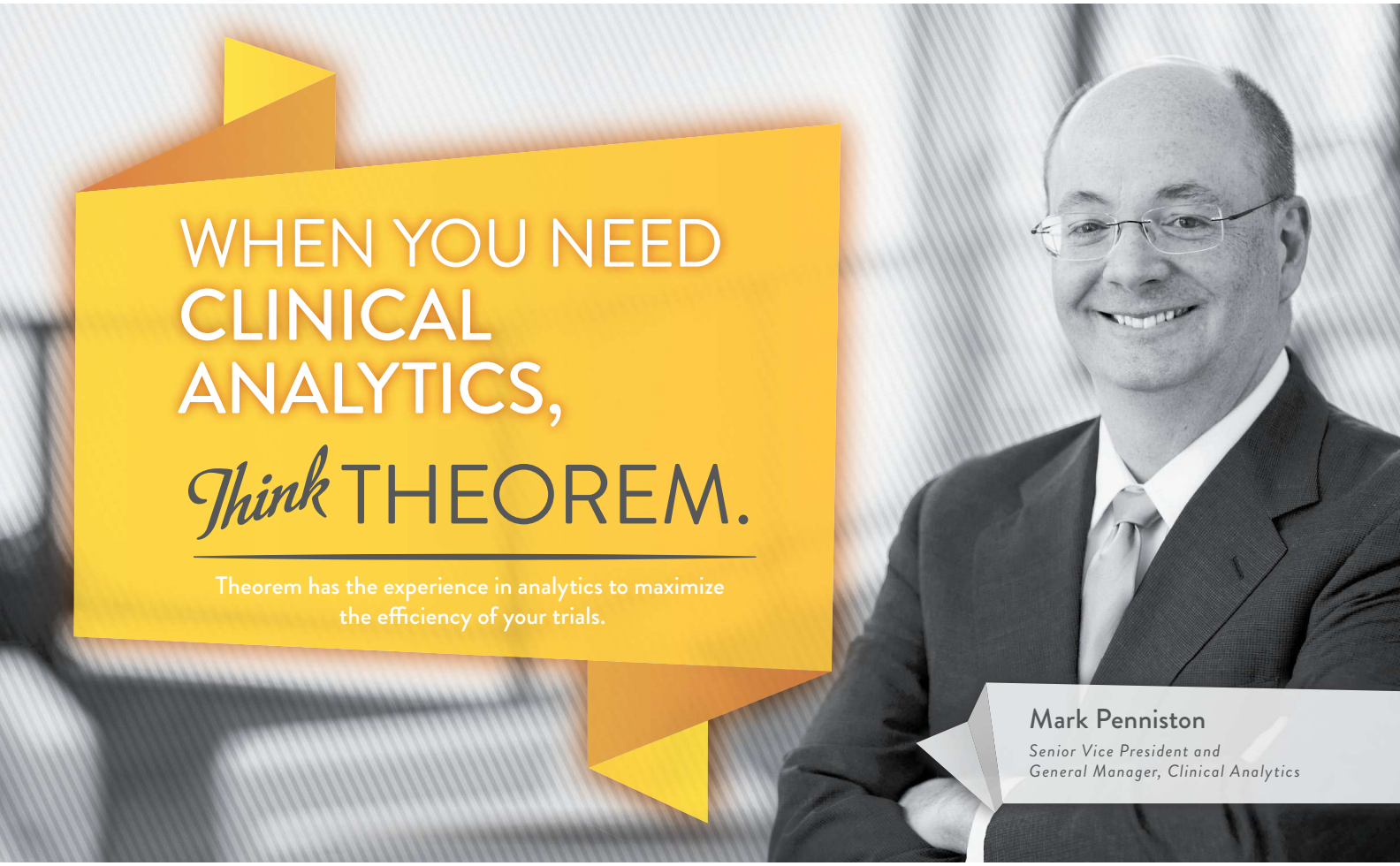
> There is a substantial faction of the Republican party ... that would like to either repeal Obamacare in its entirety or require the entire statute be implemented precisely as written and watch with glee as the Democrats' law fails to deliver half of its promises at twice the cost.

- Republicans would agree to technical changes to make Obamacare implementation more workable. Those fixated on full repeal could view a one-year delay as a repeal-on-installment-plan as it blocks spending in 2014.

- To attract Republican support, Democrats should agree to a policy win for the Republicans, such as repealing the reviled Independent Payment Advisory Board, which can rewrite Medicare payment and coverage policy without congressional input when certain spending triggers are hit.

- Republicans should also reject the Heritage Foundation's assertion that SGR reform should not be linked to "pay for performance" for physicians who meet quality metrics developed by physician medical societies and implemented by Medicare. Far right skepticism of best practices developed by the physician community is unfounded.
- For any of these sensible changes to take place, Republicans and Democrats need to work together across the aisle and ignore the dogmatic radicals of their respective bases calling for outright repeal on one side and immediate, unaltered implementation on the other.

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.



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By Wayne Koberstein, executive editor

Esperion Therapeutics

A small-cap company braves the new world of blockbusters.

SNAPSHOT

Esperion Therapeutics is a relatively young company and newcomer to the public stock market. As such, it provides us with an instructive picture of a life sciences start-up in transition, perhaps to something much bigger — or perhaps to the oblivion many small-cap companies enter when their late-stage trials fail to fulfill early-stage expectations. Esperion is about to begin a Phase 3 trial in the cholesterol-reduction area, a market currently dominated by the "statins," which fail to work or cause serious muscle spasms in millions of patients. Esperion's lead clinical candidate, ETC-1002, using a new mechanism, appears to lower LDL cholesterol (LDL-C) with relatively high tolerance. Could "blockbuster potential" be too strong a term?

Tim Mayleben, CEO

LATEST UPDATES

- *July 2013:* Completed $74.9 million IPO.
- *June 2013:* Top results of Phase 2a clinical study showed ETC-1002 lowered LDL-C by an average of 32 percent and was well-tolerated in patients with hypercholesterolemia and a history of statin intolerance.
- *May 2013:* Full results of Phase 2 clinical trial showed ETC-1002 lowered LDL-C by up to 43 percent in hypercholesterolemic patients with Type 2 diabetes.
- *April 2013:* Completed $33 million preferred financing.

WHAT'S AT STAKE

What could be in store for Esperion Therapeutics, one of the relative few midstage developers of new drugs with blockbuster potential in a sea of niche and specialty products now coming on the market? Esperion was also one of the companies to join the "Biopharma Spring" outpour of IPOs just as it was completing its key Phase 2 trials. At least a half-dozen of the most recent FDA approvals have gone to blockbuster candidates, a significant sea change from last year's wave of niche drugs. Esperion could be headed for membership in that elite club — perhaps, with its drug ETC-1002 helping revive some of the sheer market energy that once made primary care the king of pharma. "Success for Esperion will be if ETC-1002 completes clinical development, is approved, and is prescribed by physicians for the millions of patients who can't tolerate statins or can't get to their LDL-C goal," says the company's CEO, Tim Mayleben.

Esperion has evidently prepared itself for Phase 3 with an extensive Phase 2 program of seven separate studies for proof-of-concept, safety, and efficacy in a multitude of patient populations and ancillary conditions. The common theme, however, is LDL-C reduction in people who either fail to benefit or cannot tolerate statins. As Mayleben suggests, the pool of potential patients runs into the millions, opening up the prospect that Esperion's drug could achieve blockbuster status alongside a continuing statin market. "We don't intend to compete with statins," he says. "We believe that statins are one of the most successful and important classes of drugs ever invented for lowering LDL-C and reducing cardiovascular disease risk. However, many patients with high LDL-C can't tolerate statin therapy and remain at elevated risk for cardiovascular disease."

Esperion is focusing initially on those who never find a statin they can tolerate, about two million patients in the United States, but in the longer term, it will also focus on the statin-resistant population, about 11 million U.S. patients, who have no good treatment alternative. The company has done well in raising private equity financing through its Phase 2 trials, but Mayleben says public money was essential for its Phase 3 program. It has experienced no great hurdles in clinical trials and expects none ahead. Its confidence may stem partly from having company founder Roger Newton aboard as chairman and CSO. A former R&D head at Warner-Lambert and Pfizer, Newton codiscovered Lipitor. Newton's legacy also proved useful in the company's public offering, according to Mayleben.

"The IPO process was very straightforward — over the span of nine days, Roger and I visited several dozen investors across the U.S. and the EU, many of whom remembered us from the original Esperion and who were keen to support the new Esperion."

VITAL STATISTICS

- Employees: 15
- Headquarters: Plymouth, MI
- Finances/Funding: $140 million total private and public funding (including July 2013 IPO)
- Other partners:
  — Acquired full worldwide rights to ETC-1002 and ESP41091 from Pfizer in 2008 in exchange for 6 percent interest in Esperion.
  — Licensed 4WF, next-generation synthetic HDL therapy, from the Cleveland Clinic Foundation in 2010.

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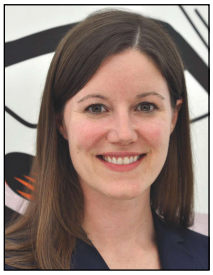

OUTSOURCING INSIGHTS

The Top CROs By Therapeutic Indication Share Strong Regulatory And Productivity Performance

By Kate Hammeke, director of marketing intelligence, Nice Insight

Sponsors often look for a CRO with specific therapeutic experience, including a track record of successfully completed projects. For a sponsor, therapeutic experience inspires confidence that the CRO's project team has familiarity with data points specific to the therapeutic category. While clinical trials are generally conducted the same way — according to the standards established by regulatory authorities — when it comes to detailed data specific to a disease, the metrics used can vary greatly.

In a recent market research study, therapeutic experience (59 percent) topped a list of attributes that influence CRO selection, edging out operational (57 percent) and methodological experience (49 percent), as well as geographic location (37 percent), financial stability (36 percent), risk sharing, (32 percent), and adaptability (27 percent). When asked how many studies need to have been conducted for a sponsor to regard a CRO as "experienced" in a therapeutic category, answers varied widely — the mean response was five studies. Many CROs have already acknowledged the importance of promoting therapeutic experience to potential sponsors, dedicating website space and marketing communications to conveying relevant qualifications by category.

Respondents to Nice Insight's annual pharmaceutical and biotechnology outsourcing survey indicated their companies would engage outsourcing partners for projects across an average of 2.1 therapeutic categories. The most popular areas of focus for outsourced projects are cardiovascular disease (37 percent), oncology (34 percent), and infectious diseases (33 percent). Not surprisingly, the most common therapeutic categories correspond with the leading causes of death worldwide — heart disease, cancers, and infectious diseases.

Big Pharma companies tend to have a higher spread of projects across therapeutic categories (2.8), while emerging pharma companies typically demonstrate a narrower focus, with projects covering an average of 1.2 therapeutic categories. Specialty pharma companies fall in the middle, responding that they plan to outsource projects across an average of 1.6 therapeutic categories. Established (2.1) and emerging (2.2) biotechs showed less variance, with each looking to outsource projects in approximately two therapeutic categories.

Regardless of the type of company you work for, there is a good chance that its drug development pipeline includes compounds in one of the most common therapeutic categories. To help sponsors make an informed decision when selecting a CRO for the project, Nice Insight collects data on CROs, and what follows are some of the results, including the top performers as indicated by peers for each of the leading therapeutic categories.

TOP CARDIOVASCULAR CROs

According to buyers of CRO services, the preferred CROs for cardiovascular projects are Covance, Chiltern, Eurofins, INC Research, and ABC Labs. Covance received the highest overall customer perception (CP) score from respondents outsourcing cardiovascular projects at 78 percent and received "excellent" scores for productivity and regulatory compliance. Chiltern closely followed, also at 78 percent, with an "excellent" score for regulatory compliance. INC Research, with a customer perception (CP) of 76 percent, received an "excellent" score in innovation — reflecting the ability to improve upon a sponsor's in-house capabilities by developing customized solutions — which is likely influenced by the "specialized recruitment and retention strategies" that the company deploys for cardiovascular trials.

The leading CROs for oncology projects based on customer perception were Eurofins and Covance, each with a CP of 77 percent, followed by Charles River Labs and INC Research, both at 75 percent, and Harlan Labs (74 percent). Covance and Eurofins received their strongest scores in productivity and regulatory compliance. Charles River Labs and INC Research had the highest quality scores in the group and likely lost the top rankings due to their low scores in affordability. Harlan Laboratories, while not particularly well-known, is highly regarded for its early development oncology portfolio, including rodent models and diet.

For infectious disease projects, Eurofins — with a customer perception score of 79 percent — along with Covance and Chiltern (77 percent each), were once again among the top five CROs. Quintiles, at 78 percent, landed in second place and received "excellent" scores in three customer perception categories — innovation, productivity, and regulatory compliance. Comprehensive

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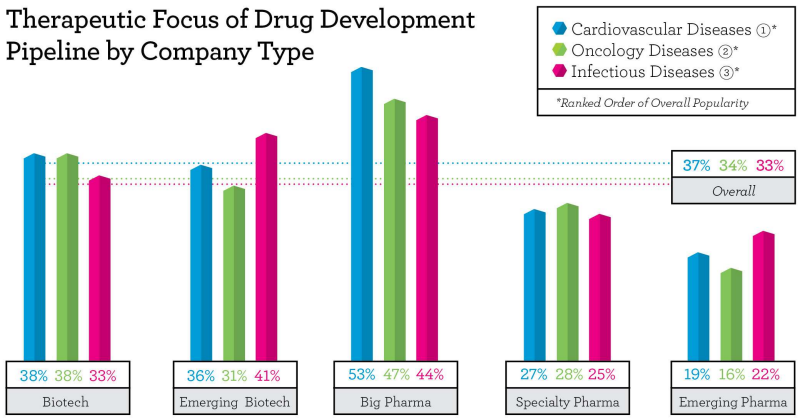
Clinical Development rounds out the top five CROs for infectious disease projects, with the company's strongest scores coming in innovation, followed by regulatory compliance.

After a deeper examination of the strengths specific to the leading CROs by therapeutic category, it has become clear that strong regulatory knowledge is highly valued for facilitating study execution (and later, market entry) across regulatory jurisdictions. Expediting the path to market with inventive methods of increasing productivity — such as rodent model diets or recruiting methods for in-patient clinical research — is another factor.

Therapeutic Focus of Drug Development Pipeline by Company Type



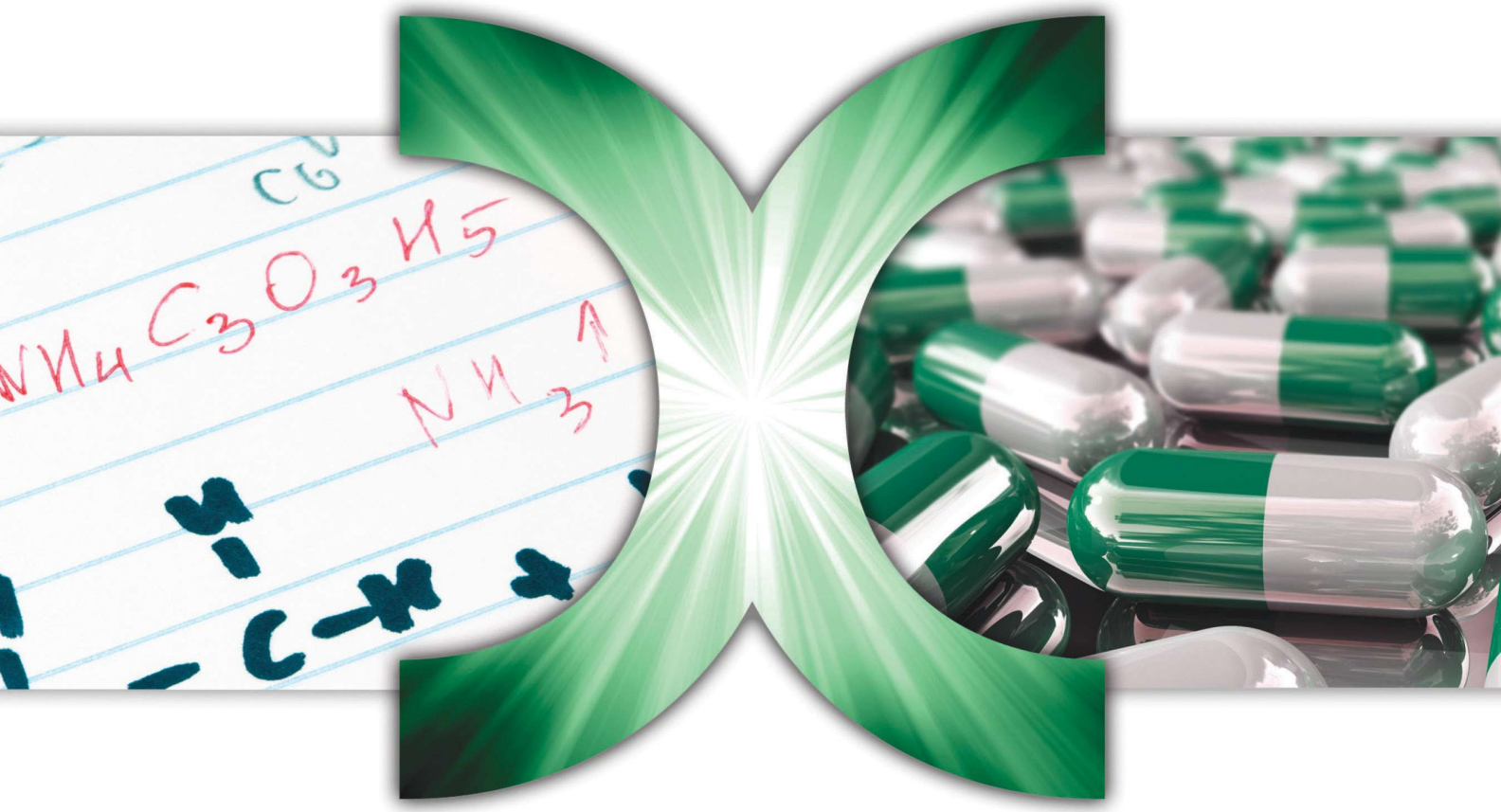
Top CROs for...

Project type	CA score	CP score	Company
Cardiovascular	58%	78%	Covance
	49%	78%	Chiltern
	47%	76%	Eurofins Lancaster Laboratories
	56%	76%	INC Research
	49%	76%	ABC Laboratories
Oncology	40%	77%	Eurofins Lancaster Laboratories
	58%	77%	Covance
	54%	75%	Charles River Laboratories
	45%	75%	INC Research
	40%	74%	Harlan
Infectious Disease	51%	79%	Eurofins Lancaster Laboratories
	54%	78%	Quintiles
	45%	77%	Chiltern
	52%	77%	Covance
	44%	76%	Comprehensive Clinical Development

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 comprises 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.



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BIO INNOVATION NOTES

Innovation In Expression Systems Yields Increased Productivity

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

Technological advances in genetic engineering, particularly expression systems (the genetically modified cells that express desired proteins), process design, and equipment continue to be combined such that the same amount of drug product can be manufactured at a much smaller scale. Today, smaller-scale, less-expensive equipment is permitting more rapid drug development and production in smaller facilities.

This year's *10th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production* continues to show overall increased productivity and efficiency in biomanufacturing. The average expression yield (amount of protein produced in a fixed bioreactor fluid volume), exemplified by mammalian cell culture production of monoclonal antibodies, is now reported to be 2.68 grams/Liter for late-stage clinical supplies manufacturing and 2.29 grams/Liter for commercial-scale manufacturing. These production yields have been increasing since 2008 at an average annual growth rate of 9.8 percent. This almost exclusively involves cell culture using Chinese hamster ovary (CHO) cells. With CHO serving very well and major changes generally avoided in this highly regulated industry, adoption of other and improved expression systems, despite offering further advantages, remains slow.

Because bioprocessing for drug products is generally "locked-down" early in development, the reported clinical supply yields more reflect the current state-of-the-art for new bioprocesses. It must be kept in mind that, at any time, the great majority of commercial-scale manufacturing involves established products with their original bioprocessing usually developed decades ago, with these facilities operating at much lower titres than now reported for new processes.

Only about a decade ago, expression yields of up to 1 gram/Liter were considered truly state-of-the-art. Many older products, including many current blockbuster (≥$1 billion/year sales) monoclonal antibody products, such as those originally developed in the 1980s, were developed with yields of only a few tenths gram/Liter. This generally required multiple≥10,000 L bioreactors operating continuously for commercial manufacture. Many of the largest biopharmaceutical facilities now have excess capacity, with legacy facilities either being taken offline, refurbished, or used to provide CMO services, manufacturing products for other companies.

About 3 grams/L yield could soon become the future reference standard for monoclonal antibody and other mammalian cell-based manufacture, with further steady growth likely. At 3 grams/L, a single-use 2,000 L bioreactor production run can provide ~6,000 g or 6 kg of protein, with even a low-potency, cheaper product providing sales approaching $100 million. If larger amounts of product are needed to support sales, multiple single-use process lines can be run in parallel. For comparison, a yield of 0.6 gram/L would require 10,000 L capacity, e.g. a 10,000 L stainless steel bioreactor to manufacture the same amount of product. Operating at higher yield and lower scale to produce the same amount of product provides savings in many areas, including culture media and other supplies, space, utilities, infrastructure/support, and labor.

Further, during the past decade, most bioprocessing at pre-commercial scales is now being performed using single-use (dispose of after use) plastics-based rather than fixed stainless steel equipment. Our study reports about 2/3 of all new processes are being developed using single-use systems. And as products in the development pipeline manufactured using single-use systems gain approvals, commercial manufacturing will increasingly be performed using single-use systems and at much smaller scales than conventional stainless steel facilities.

Attaining even higher yields in mammalian systems at large scale, such as ≥5 grams/L, is becoming much more attainable. Some CMOs are now offering routine monoclonal antibody scale-up at high yields. For example, the PER.C6 cell line development joint venture of DSM and Crucell (now the Center for Vaccines, Johnson & Johnson Co.) has reported a record level titre of over 30 grams/L harvest for an antibody product. Presuming yields of just 10 grams/L will be attainable in practice at commercial scale in coming years, a 1,000 L bioreactor will be able to match the output of four 2,000 L bioreactors operating at the current state-of-the-art of about 2.5 grams/L or a 10,000 L bioreactor operating at 1 gram/L.

CONTINUOUS PROCESSING IMPROVEMENTS ON THE RISE

Besides improvements in genetic engineering of cell lines and adoption of single-use systems, the industry is seeing rapid adoption of perfusion, using pumps and filters or other methods to increase the concentration of cells and expressed products within bioreactors, with this further increasing productivity. Other improvements contributing to increased expression yields include improved culture media and process design, with both culture media selection and bioprocessing design

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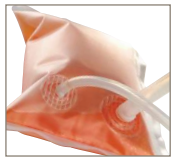

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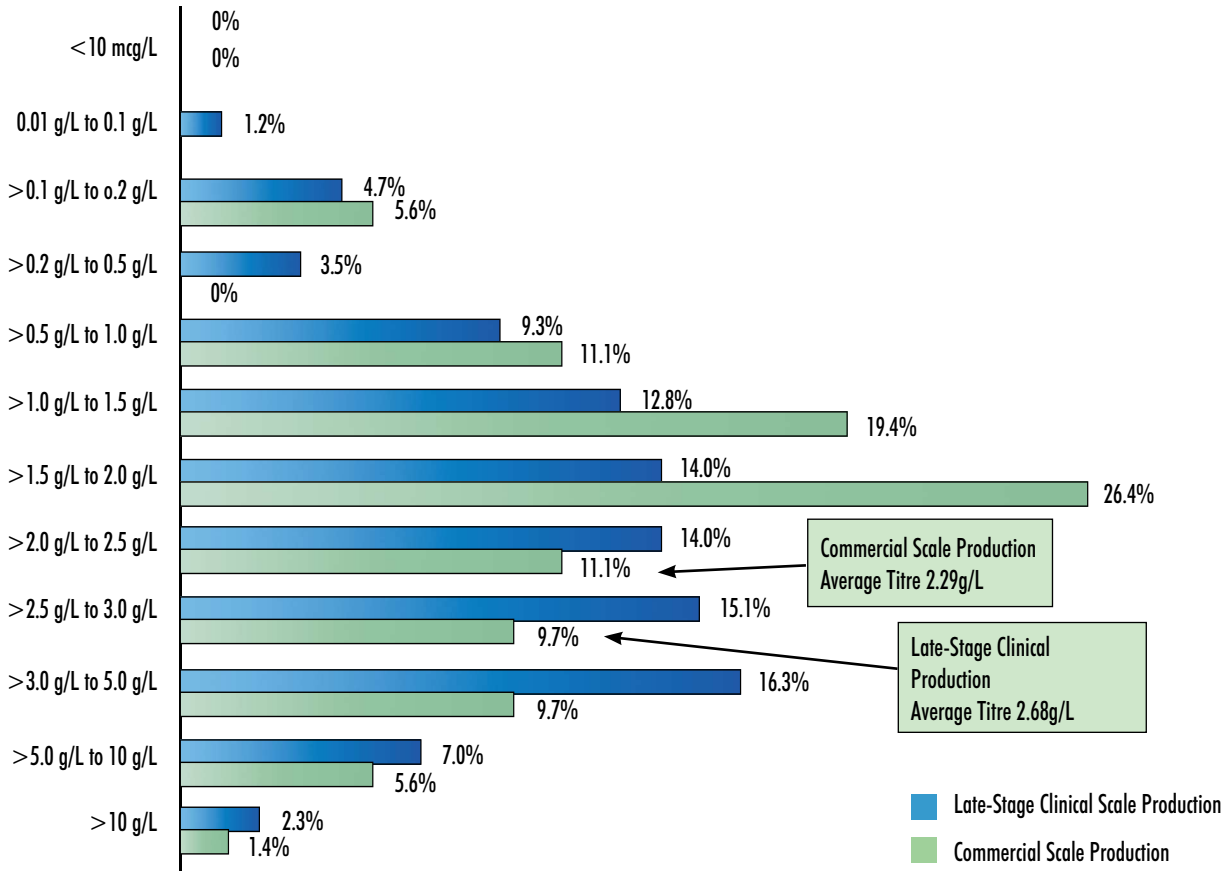
Increases in expression yields, besides reducing costs and making manufacturing simpler, are having other impacts in the biopharmaceutical industry:

- CMOs are now offering commercial monoclonal antibody scale-up services using 500 L, rather than 2,000 L, bioreactors.
- Many companies with large banks of ≥10,000 L bioreactors increasingly have excess capacity.
- Legacy facilities are being decommissioned, refurbished, being used less, and being used to provide CMO services.
- More large biopharmaceutical companies are considering providing CMO services to use this manufacturing capacity.

Ever-improving process yields, particularly when combined with other recent major advances in bioprocessing, such as the adoption of single-use rather than stainless steel systems for manufacture, are providing increasing efficiencies in bioprocessing, dramatically reducing the scale and costs for biopharmaceutical manufacture. Combined with advances in expression systems engineering (such as cell line development, media optimization, and metabolic engineering), we expect to see continued increases in volumetric titres and yields.

Figure 1: 2013 Range Of Titres For Mabs Obtained At Various Production Scales



Survey Methodology: The 2013 Tenth Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production 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.

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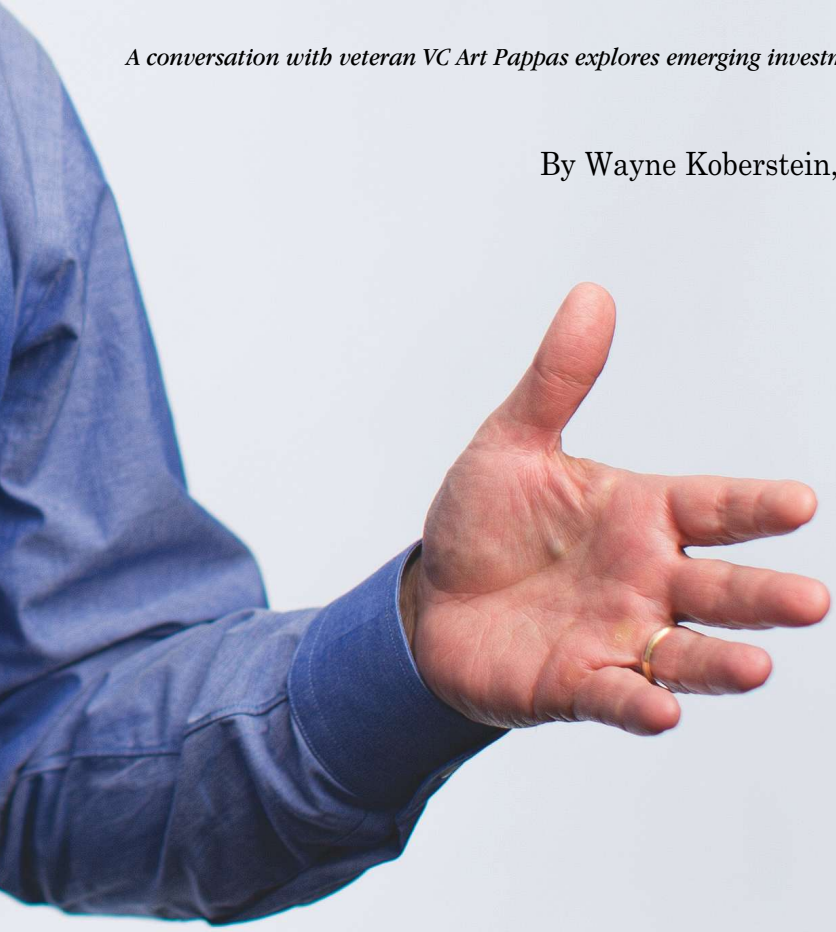
Adaptive Funding: Survival Of The Fittest In The Start-Up Evolution

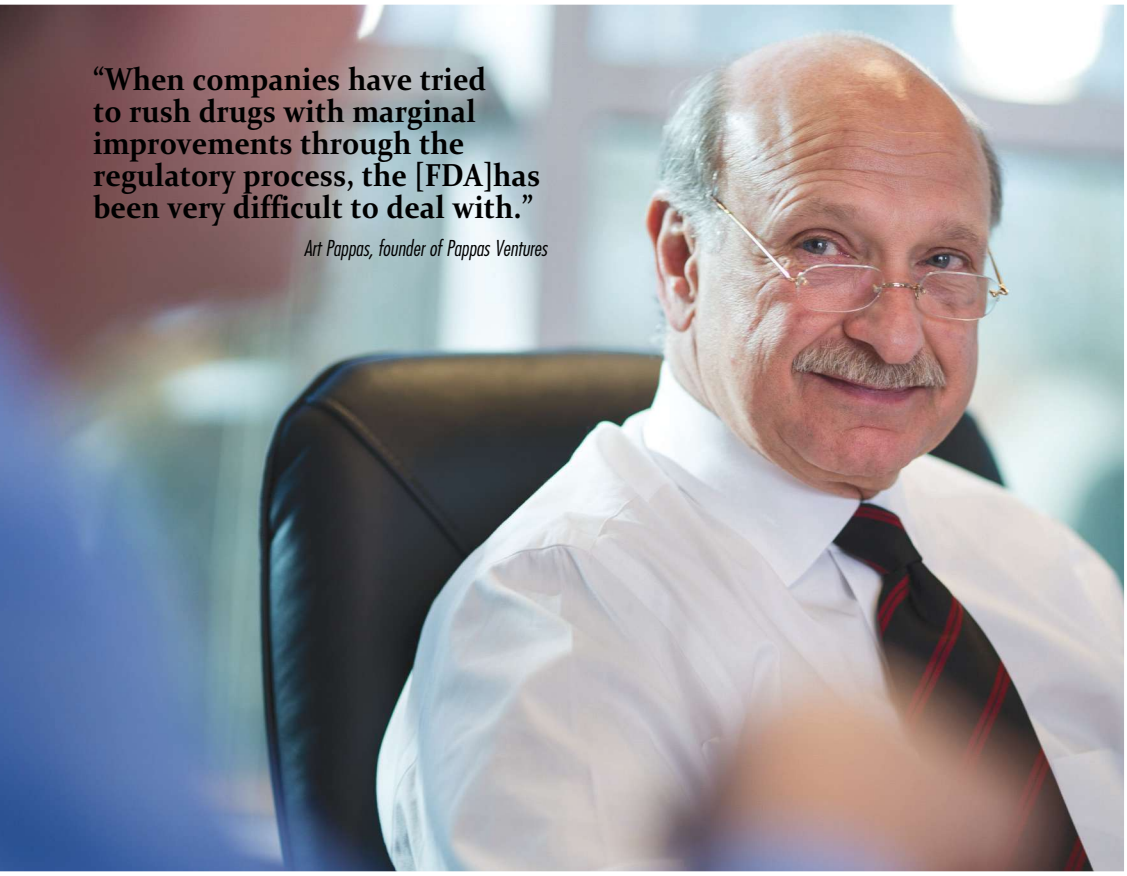
A conversation with veteran VC Art Pappas explores emerging investment options for new life sciences companies.

By Wayne Koberstein, executive editor



Evolution, like democracy, is a crazy system but it's the best one we have for its purpose: adaptation. As living organisms, we have arrived at our present adaptive state with a collection of often wondrous yet imperfect tools of survival. So you can look at the evolutionary progress of life sciences start-ups as either a miracle or an utter mess. But if you focus on the inevitable contribution of natural selection over time, you can mainly and optimistically expect the fittest companies — those that have a solid concept and are prepared to prove it — will survive.

And the present seems to be a good time for optimism, with biotech IPOs in a remarkable boom, as well as new funding pipelines opening up to fill the gap left by venture capital's retreat from early-stage deals. So goes at least part of the story we hear from Art Pappas, founder of Pappas Ventures and a seasoned veteran of life science investment. Pappas sounds primarily upbeat about the emerging options for an industry made largely of start-ups and venture capitalists.



"We've seen an appropriate culling of the industry in the number and size of funds, as well as the number of science projects versus true sustainable enterprises, after a period where excellent investment returns were dampened by poor product performance and regulatory hurdles," Pappas says. "Now we're seeing an unbelievable pipeline of exceptional medical discoveries being developed in a regulatory environment that is much more transparent and predictable for investors, where we can count on survival of the fittest."

Pappas Ventures is not the largest fund in life sciences, but it is one that exemplifies VC survival and success through the perilous times the life sciences sector has been facing. Pappas founded his firm in 1994 to invest solely in biotechnology, biopharmaceuticals, drug delivery, medical devices, and related life science ventures. The firm now manages more than $350 million in capital and claims credit for "launch and/or development" of more than 50 companies, such as Arena, Chimerix, Peninsula, Plexxikon, and Tesaro. Pappas and his partners remain bullish but highly selective in funding early-stage companies and products.

THE STATE OF VENTURE CAPITAL

This is where I'm supposed to tell you how awful the VC climate for biotech has become. But of course it isn't that bad, as the VCs themselves well know. I had read through most of the PwC report on life science deals in Q1 2013 when I spotted it — yes, overall life science VC activity dropped 28 percent in dollars and 23 percent in number of deals from Q1 2012 to Q1 this year. But the human biotechnology sector actually rose 1 percent in the same period. Medical devices also fell as a whole but had some growth in the medical/health products subsector.

And then came the great Q2 boom of 2013, with more than a dozen life sciences companies going public successfully and VCs putting about $1.3 billion more into the sector than they had in the previous quarter. Was this all paper headlines drifting in the prairie wind? Or does the surge in funding relate more to fundamentals — a general healing of the macro economy, the return of "specialist" industry-wise investors, and the de novo participation of a fresh crop of "generalist" investors and funding sources? Pappas simply welcomes all comers.

"The industry itself is in a bit of flux, maybe in a bit of a crisis," says Pappas. "Venture capital, in general, has stimulated the creation and growth of the overall biopharmaceutical and medical device industries, including that of the diagnostics sector. But the performance, particularly over the last 15 years, has been less than impressive for the life science asset class."

Pappas has a credible perspective on shifting times and trends — arguably, a sanguine view you can only obtain through sufficient years and experience. The broader sense of accomplishment tem-

pers how he views investment highs and lows. "Even though the industry is in flux, I don't see it as an overall bad place. Funds have resized themselves so, at least at this juncture, the right amount of capital is there to move some of the new technology and products forward. The limited-partnership investor base has become much more sophisticated and better understands the asset class, as well as the importance of investment in innovation from a societal and an economic perspective."

SURPRISING BONUS? REGULATORY ACCELERATION

A large part of the credit for the sunnier investment climate goes rightfully to the industry's regulators. A spike in product approvals, especially by the FDA, as well as the agency's aggressive use of priority reviews and accelerated approvals, has put the spotlight on novel therapies and diagnostics for unmet medical needs. In many cases, new investors have rushed into the sector without much information to distract them. But the prospect that the high approvals rate will continue has also drawn former funders back to the fold.

Pappas believes the surge of approvals signals more than a change in FDA policy — and that companies have also brought more to the table. "Where there is unmet medical need, the FDA has been the most cooperative, the most transparent, and the most predictable for companies developing new drugs," he says. "But when companies have tried to rush drugs with marginal improvements through the regulatory process, the agency has been very difficult to deal with." He cites oncology as one area where developers of innovative drugs addressing a clear medical need have received strong support from the FDA.

Oncology has also gotten a boost of late from the FDA's cancer czar, Richard Pazdur, whose office had once grown infamous for its multiple refusals to approve new drugs. Pazdur gets little flack these days when he says the new approved therapies are superior to past candidates and NDA (new drug application) submissions have also improved.

Beyond oncology, drugs for treating orphan diseases have been the leading model of the FDA's support for "unmet need" therapies, largely because orphan drugs enjoy a natural base of support and a dedicated regulatory pathway based on need in small populations. Orphan drugs bear a close relationship, and often overlap,

with personalized medicines, which have received some criticism for creating tiny commercial segments while escalating prices to unprecedented heights.

But Pappas perceives a larger value to the personalized medicine strategy. "So-called ultrasegmentation requires the developer to go through the FDA and the payer processes in a way that confirms MoA (mechanism of action) and PoC (proof of concept), usually in a smaller trial with a very targeted base. In time, the discipline of personalized medicine will be seen as a favorable approach to developing medicines for broader areas as well."

Along with the regulatory breakthroughs, Pappas also sees other strengths emerging among young companies and their funders: "The Darwinian element is playing out on a number of different fronts. All of our companies have become more capital-efficient — the whole industry has become more capital-efficient. And the chance to have this kind of constructive dialogue with regulators about very novel and unique medicines, just by definition, has made it easier to speed their progress through review. The FDA has realized it needs to give us better clarity and predictability as we start new trials."

FINDING FUNDS IN ALL THE RIGHT PLACES

Downturns naturally precede turnarounds, and there may be a large cyclical component of the latest upsurge in life science investment, but also perhaps some unique elements. One possible benefit of VC flight from the industry is the creative response of companies that had to look elsewhere for funding support — thus giving rise to new, nontraditional funding mechanisms often customized to each company. Limited, semipublic offerings, biodefense grants, philanthropic funds, and corporate capital groups such as GSK's SR-One have become some of the more widely employed vehicles for filling the funding gap.

According to Pappas, such groups have not only supported small-company innovation, but have done so at only a marginal cost to the pharma companies that support them. "The estimated amount of cash Big Pharma had on its balance sheet in 2003 was about $70 billion; today, it's around $130 billion. If we added up all the corporate VC funds, including their overhead and infrastructure costs, it would be a very small fraction of that cash amount. All of those corporate VC efforts are primarily off balance sheet and clearly an effective business and R&D development approach."

As corporate VC groups have entered the scene and grown in sophistication, another new source of funding has emerged in parallel: venture philanthropy. Not only have the philanthropy groups increased in numbers and size of funds, but they have also enlarged their roles in the entire process of drug dis-

covery and development, Pappas explains. "Venture philanthropy does three things: one, provide funding; two, provide access to patients; and three, provide access to physicians in the disease space. So if you have a drug or treatment approach that no one has pursued before, the philanthropists can be extremely helpful."

Accelerators or incubators have proliferated as a way to support life sciences start-ups and attract companies into local economies. Pappas believes the jury is still out on the question of whether such entities will ultimately make money for investors, but says he is seeing some better quality programs come out that are more capital-efficient. But these days, he believes the most effective industry-boosting action in the United States is happening at the federal level, namely with new NIH programs, DARPA, and most recently the JOBS (Jumpstart Our Business Startups) Act.

"We encourage all of our companies to make sure they're effectively looking at NIH, DARPA, and all similar organizations and programs, particularly if they are not going to use venture dollars. Those programs have been there for a while and do continue, particularly in the major areas, and we advise companies to pursue them as needed."

By some provisions in the JOBS Act, companies below a certain size can forego some disclosure requirements and negotiate with investors confidentially. "The JOBS Act is giving companies an opportunity to tap into the capital markets in a way that we haven't seen in over a decade," Pappas says.

Besides and before the confidential JOBS Act filings, and as an alternative to the traditional S1 IPO, companies have been making use of the cluster of "Form 10" SEC filings to set up reverse mergers, essentially by turning a public company into a shell. An updated Form 10 issued in 2008 allows a new twist on the reverse merger, different from a typical S1 or a JOBS Act filing.

Company investors prepare and file an S1, advising the SEC that the company plans to go public. Then the investors put a small amount of money, say $500,000, into that vehicle and take it public, using primarily a retail base to buy the stock, which creates a tradable security as a pink-sheet listed company. The company then uses the appropriate SEC regulatory process to bring in large institutional investors to hopefully buy the public stock. The SEC will review the S1 again as an already-filed public document.

But Pappas doubts the practice will significantly grow. He has not seen a lot of new Form 10 filings come forward, primarily because the JOBS Act has become so attractive and the absolute costs for the traditional IPO, a JOBS Act IPO, or Form 10 IPO are exactly the same. He believes there may be less interest in the Form 10 route and more movement toward the JOBS Act, and when a company has an especially unique proposition, it should proceed under a standard IPO. Yet he says it is fundamentally important to see these new and various instruments come forward because they are providing attractive alternatives for financing life sciences companies.

Whatever the alternatives, all of them together are unlikely to fill the gap left by VCs since their life science heyday. Despite even the current upsurge, many new companies will still wander into the veritable Valley of Death, often to meet the final fate its moniker implies. But Pappas sees the valley more as a filter than a fatal furnace: "The Valley of Death is not a bad situation to have. It helps sort out the science projects, which may be better done under the purview of the NIH and until they get to the point of true translational medicine, where they can define a plan to effectively pursue mechanism-of-action, proof-of-concept, and a financially sustainable business model."

> "Venture capital, in general, has stimulated the creation and growth of the overall biopharmaceutical and medical device industries, including that of the diagnostics sector. But the performance, particularly over the last 15 years, has been less than impressive for the life science asset class."
>
> *Art Pappas, founder of Pappas Ventures*

SOURCING FUNDS — AND STABILITY

Whether the recent surge in biotech IPOs and VC cash proves to be a lasting boost or transitory bubble for early-stage investment, the full lessons of the past would favor an adaptive funding model. Young, fragile companies need ways to insulate themselves from boom-and-bust cycles by diversifying their funding portfolios to tap sources that don't flood in one season only to vanish with the rains in the next. Even the strongest organism can rapidly perish if it depends entirely on a single element of its environment and the element suddenly disappears. Tiny foragers persist where the dinosaurs fall.

Time is the real commodity purchased with investment money. Time to do the right work — formulate the compound, interrogate the toxicology, prepare to test in people, recruit patients and investigators, and run even the most elementary Phase 1 trial — all the work necessary to attract more capital, a partnership, or an acquisition to advance the drug toward legal sale for use in medical practice.

At a minimum, the young company must survive long enough to prove its concept. To fail proof-of-concept in a fair scientific test is regrettable, but not nearly so much as failing to achieve proof-of-concept because there is insufficient money in the bank to pay for testing it. In such cases, the lost-opportunity costs for the company, the industry, and society remain as unknown as an unresolved tragedy in the true sense.

Menelas Pangalos,
executive VP of innovative medicines, AZ

AstraZeneca Translates "Winning With Science"

From Words To Action

By Wayne Koberstein, executive editor

A majority of the recent press on AstraZeneca has tried to criticize the company over its late-phase failures with once-promising products in development. But in many ways the fates of those products were sealed years ago — long before the large-scale human trials were completed and their results tallied. Yet the choices made now and the company's current moves to reverse its fortunes will neither face their ultimate test nor show their true worth for many years to come. So how do we judge their chances of success before then?

It would be easier if this were the first time AZ attempted an R&D turnaround. Like most of Big Pharma, however, the company had already gone through various reconstructions before its new CEO, Pascal Soriot, arrived in March 2012 — the previous one in 2010 under then R&D chief Martin Mackay and other management since departed. Many of Mackay's moves headed in the same direction as the current push toward clearer therapeutic focus and science-driven portfolios; the strategic mantra, "winning with science" originated with Mackay's reforms. But the new structure under Soriot further simplifies the therapeutic focus and management structure, reinforces an emphasis on tapping scientific expertise, and places major bets-to-win on science-driven models for its research units.

"I am encouraging my scientists to work with new and different partners across sectors, to speed the translation of good science into innovative medicines."

Menelas Pangalos, executive VP of innovative medicines, AZ

Today, three R&D executives report directly to the CEO, with hands-on responsibility for small-molecule and biologics discovery and clinical development. The company's "core" therapy areas, where it focuses the weight of its internal research and business development, include respiratory, inflammation, and autoimmunity; cardiovascular and metabolic disease; and oncology. The company is also engaged in neuroscience and infectious disease research. Menelas Pangalos, executive VP of innovative medicines, is one of the three direct-to-CEO reports, responsible for small-molecule discovery and early-stage (through Phase 2) development. To feed the late-stage pipeline, Pangalos works shoulder-to-shoulder with Bahija Jallal, EVP of AZ's biologics division, MedImmune.

CAN SCIENCE LEAD TO SUCCESS?

The Innovative Medicines organization was already responsible for generating the Phase 2 pipeline in small molecules, but its range has now expanded to include the organization running clinical development through that stage. When Pangalos arrived at the company in 2010, his group conducted an early pipeline assessment, reviewing five years of data on the selection of candidates from preclinical to Phase 2 with the goal of improving the decision making. "One of the key findings was that we had to do a much better job of understanding the basic biology of the target and the mechanism and its role in the disease that we're trying to treat," Pangalos says.

He offers an example. "Historically, a company might decide to go into asthma, with a single compound to capture a larger share of the total population and market — which we now believe is the wrong thing to do. Now we stratify the asthma into, for example, neutrophilic- or eosinophilic- driven disease. We are focusing our programs on the right patient population based on sound science and the population that will best respond to our medicine, for maximum efficacy and the best possible risk/benefit."

The same assessment led the group to identify the areas where it was strongest scientifically, where its approach was innovative, and where it was ahead of the competition, according to Pangalos. Subsequent decisions to narrow AZ's therapeutic-area focus, retaining current areas and dropping others, stemmed from those findings.

"Picking the right molecules, with the right properties for the right patient population" equals an "increased probability of success" in the disease areas where the company is most competitive — in AZ's equation. Pangalos says strong support from the new top management has helped his group put those terms into action.

"Pascal has been pushing the new agenda forward, and it's a continuation of the journey we've been on. One of the core goals of the journey is building our scientific reputation. We have been pushing our organization to focus on deeper scientific understanding of molecular mechanisms, disease pathophysiology, and disease heterogeneity, and our corporate strategy is now perfectly aligned with our scientific focus."

BRIDGE OVER THE LARGE-SMALL MOLECULE DIVIDE

Physical relocation for the sake of co-location will occupy much of AZ's resources for some time to come. Construction of a £330 million ($500 million) R&D center in Cambridge, England, along with other site expansions and closings, has generated most of the headlines around the company's "turnaround." AZ is consolidating its R&D at Cambridge and two other centers in Gaithersburg, MD, and Mölndal near Gothenburg, Sweden.

Plans alone have not satisfied the company's critics who doubt the R&D restructuring, accompanied by thousands of layoffs and expansion in emerging markets, will rescue its pipeline and commercial portfolio. But AZ has momentum in early discovery and development and seems determined to lay the intellectual foundation for a new kind of pharma R&D built on working relationships among its constituents.

At the top level, a critical collaboration crosses the traditional line between biologics and small-molecule science. MedImmune and Pangalos' Innovative Medicines group closely coordinate their discovery and development efforts in many areas and indications.

"Bahija and I are fully dependent on each other for being successful," says Pangalos. "Our therapy area heads all work together; for example, our respective heads of oncology prioritize their projects together across the oncology pipeline. They also think about product combinations wherever combinations maximize the value of the portfolio. Their partnership and synergy differentiates us from some other companies where it might be more difficult for the small-molecule and biologics developers to share priorities."

MedImmune and Pangalos' Innovative Medicines will also be sharing facilities to a greater extent once the Cambridge center is finished. Corporate officers and the commercial team will locate in the R&D center as well, an arrangement intended to expedite decision making but keep science at the top of the agenda, according to Pangalos.

"We'll be surrounding ourselves with scientific excellence from places like the Addenbrooke's Hospital, the MRC Laboratory of Molecular Biology, Cancer Research UK, and the Babraham Institute. There are many top-quality research labs and a vibrant biotech sector there as well, making our whole ecosystem very attractive. Our scientists will be rubbing shoulders with some of the best scientists in Europe, an incredibly exciting proposition for scientific innovation."

By sheer reduction of internal personnel along with associated labs and other infrastructure, weighed against a necessarily ambitious R&D agenda, AZ must obviously rely more on external collaborations for drug discovery and development, mainly with academia and biotech. "I am encouraging my scientists to work with new and different partners across sectors, to speed the translation of good science into innovative medicines," says Pangalos.

To illustrate, he says the NIH announced funding on June 18 for a collaborative program that aims to develop new medicines, matching U.S. academic researchers with previously studied compounds. AZ and other pharma companies partnered with the NIH's National Center for Advancing Translational Sciences (NCATS) by making dozens of their compounds available for

study. "Because of our involvement, AstraZeneca's investigational compounds are now the subject of three separate proposals that will receive funding via NCATS and allow our scientists to work together with some of the top academic research institutions in the United States."

AstraZeneca and MedImmune have multiple iMeds (Innovative Medicines units) that conduct small-molecule and biologics discovery and early development together covering all of the therapeutic areas, with each iMed dedicated to a specific therapy area. Separate from the iMeds, an early clinical development function reports to Pangalos and is accountable for conducting the early clinical trial work on candidate drugs from the iMeds; it also provides a key link between the individual iMeds and late-stage clinical development. A small "emerging innovations" group of scientists and clinicians focus on repositioning AstraZeneca and MedImmune molecules into alternate indications, particularly those outside the core therapy areas, and open innovation opportunities around the world. The group initiated the collaborative drug repurposing efforts with NCATS and the UK-based Medical Research Council.

A NEURAL NETWORK FOR NEUROSCIENCE

Beyond AZ's "core" therapeutic areas in R&D, where it sees the most immediate opportunities, the company has chosen to persist in other areas of "high risk" but potentially with high rewards. For CNS, perhaps the riskiest of spaces historically, the company has adopted an externally based model — closing internal programs and turning to a network of outside partners. The Neuroscience iMed will presumably deal with the risk as independent life sciences companies do — responsible to AZ as its chief "investor," but otherwise operating entrepreneurially and autonomously.

"CNS is high risk because disease understanding is somewhat more limited, trials are particularly expensive and long, and clinical endpoints in some areas are challenging and quite subjective," explains Pangalos. "But research in neuroscience is actually moving rapidly these days, and some high quality academic and biotech groups are working in this space. So we wanted to work in the space in a more collaborative way."

The iMed employs 40 experienced neuroscientists with expertise in biology, chemistry, clinical, toxicology, and all other aspects of neuroscience R&D. In addition to coordinating external partnerships, the unit has access to AZ resources such as its high throughput screening, protein crystallography, and drug safety. It is charged with running research and clinical development of a portfolio using academic, biotech, and CRO networks. "What we want them to do is spend our CNS dollars on projects and innovative science, not bricks, mortar, and infrastructure." (See also "AZ's Neuroscience iMed — Virtual Model for a High-Risk Area.")

EXCITEMENT & EXPECTATION FOR THE EARLY PIPELINE

Even as this article was in preparation, more headlines arrived to

AZ'S NEUROSCIENCE iMED — VIRTUAL MODEL FOR A HIGH-RISK AREA

To gain further insights on AstraZeneca's new Neuroscience Innovative Medicines (iMed) unit, we spoke with John Dunlop, vice president, responsible for the unit's discovery and preclinical portfolio.

HOW IS RUNNING A VIRTUAL RESEARCH GROUP DIFFERENT FROM OPERATING A SIMILAR UNIT INSIDE THE COMPANY?

By externalizing research into a collaborative model, we don't have access to our own neuroscience labs, though we can access other resources within AstraZeneca to help us move our portfolio. We are also free to look for the best opportunities and collaborations that we might find in the outside world. We spent a lot of time developing tools and infrastructure, including IT, that allow us to manage and oversee an external "workshop" of people on our projects.

WHEN YOU GO FROM AN INTERNAL TO AN EXTERNAL MODEL, WHAT HAPPENS TO THE LEGACY THAT YOU HAD FROM THE INTERNAL MODEL?

We built the foundation of the group on a set of projects that came from the legacy organizations in both AstraZeneca and MedImmune. We spent a lot of time with knowledge transfer, and half of our current team came from those organizations. But it was important early on to make sure that we transferred the resources and capabilities of those projects to the now large network of external CRO and academic partners. Then we could supplement the portfolio by both seeking opportunities on the outside as well as thinking about starting additional programs.

WHAT IS AN EXAMPLE OF NEW AREAS THAT THE EXTERNAL APPROACH HAS OPENED UP FOR YOU TO THIS POINT?

We took an asset that was sitting in our portfolio and pursued historically for Alzheimer's disease and found a new indication for it. We looked at the whole totality of the data and found the compound was strongly implicated as a potential target for the treatment of complications of dopamine treatment in Parkinson's disease. So following where the science took us, we moved into an area that traditionally has not been an area of focus for AstraZeneca. Also, as an example of collaboration with the patient community, we are researching this compound in Parkinson's disease via a grant from the Michael J. Fox Foundation.

HOW DOES BEING AN EXTERNAL GROUP AFFECT YOUR WORKING RELATIONSHIP WITH CORPORATE MANAGEMENT?

We have been given quite a significant amount of autonomy, especially in the early-stage portfolio. We have an allocated budget for our group, and we make decisions without too much need to check in with the larger organization on how we allocate those resources. We tend to have a much closer alignment with the larger organization as molecules advance closer to our clinical development, especially in oversight for patient safety. We must also think about how our programs will fit strategically with AstraZeneca.

declare a late-phase setback, disappointing sales results, downgraded S&P rating, and more patent-loss worries for AZ. But the Innovative Medicines unit, in tune with MedImmune, sounds a more optimistic note.

"I see huge opportunities in areas like oncology, with new genetic targets and new ways of stratifying disease in lung, prostate, and breast cancer appearing almost monthly," says Pangalos. "Doing great science and building a pipeline doesn't happen overnight; it's a long journey, and we're on that road. Our pipeline is on the right path, and it will take time to manifest itself in terms of launching molecules into the marketplace and to patients. Having the patience for us to deliver on that vision is important."

As short-term milestones, Pangalos foresees AZ moving the following early-stage development programs into Phase 3:

- Olaparib, a PARP inhibitor in Phase 2 for gBRCAm ovarian cancer, gBRCAm breast cancer, and gastric cancer.
- Selumetinib, an MEK inhibitor in Phase 2 for solid tumors.
- Benralizumab, an anti-IL-5R monoclonal antibody in Phase 2 for asthma/COPD.

"Moving some of those molecules from an early development to Phase 3 development will give people confidence that the direction we're taking is the right one," he says with real excitement. He mentions AZ's recent partnership deal with Moderna, developer of messenger-RNA-based therapies in Boston, and a collaboration with Karolinska Institutet in Stockholm focused on translational research in his cardiovascular metabolic group, as "indicating the direction we're taking the company is really science, science, science. To me, as an R&D leader, it doesn't get better than that."

Science is not faith. Though it requires belief, it is a belief based on the scientific method and placed on investigative principles that, if followed with minimum outside bias, reliably lead to valid conclusions. But "winning with science" does demand a leap of sorts — not in faith so much as in dedication to a higher purpose. When pharma scientists envision the market, and they do, it must be in terms of how well their work ultimately serves the needs of the key players: patients, physicians, and payers. In due time, whether short or long, the world will see how well AstraZeneca navigates its scientific path to victory.

Establishing A Culture Of Brand Protection In Your Organization

By Ron Guido

It has been described as the "Crime of the 21st Century." The growing problems of counterfeiting and intellectual property piracy threaten businesses and consumers in nearly every industry sector and within every country. Fake products deprive legitimate businesses of revenue and undermine consumer confidence in their brand names. Consumers are also adversely affected because they are deceived into buying fake products that don't meet the brand owner's standards and can pose health and safety hazards.

In short, counterfeiting is a big problem for society, as well as for legitimate companies that collectively forfeit hundreds of millions of dollars in sales annually. Reliable statistics on this illicit business don't exist, but the International Chamber of Commerce's Counterfeiting Intelligence Bureau estimates that fakes account for 5 to 7 percent of international trade, or about $650 billion annually. While some observers dispute this estimate, it's hard to argue with U.S. Customs and Border Protection, which reported seizures with MSRP of more than $1.2 billion in counterfeit and pirated goods in fiscal 2012. More alarming is the observation that the value of last year's seizures has grown 450% from five years ago. A few years ago, the World Health Organization issued a gross estimate as to the annual market value of fake prescription medicines in the range of $70 billion to $100 billion, or 8 to 10 percent of all prescribed drug sales.

These fakes come in many forms, from no active ingredient to harmful components to "underpowered" doses that lead to drug-resistant diseases. Whatever form the counterfeiter chooses can be lethal. By definition, medicines are "prescribed" to treat disease, so the absence of clinically proven therapy is tantamount to being life-threatening. In reality, there are no benign counterfeits in the life sciences.

So this problem — some say "epidemic" — elicits two questions for leaders in life sciences businesses.

1. What factors are contributing to the growth and global spread of brand violations?
2. What can organizations do to protect themselves?

Among the many factors which have spawned the growth of illicit commerce (notably counterfeits, trademark infringements, product adulteration, and gray-market diversion), the most enabling are the globalization of the economy and international trade agreements making counterfeit goods easy to hide from under-resourced enforcement agents through free trade zones — including the Internet — and the supportive lack of IP rights protection in many countries.

Many aspects of the counterfeiting problem seem to be beyond the control of legitimate businesses. But one important area over which businesses can exert a large measure of control is the security of their own supply chains. There is virtually no way to prevent a counterfeiter from making fake medicines, but we can build more secure supply networks. Lax security creates opportunities for counterfeit and stolen goods to make their way into the growing network of legitimate production, wholesale, and retail channels. Unfortunately, many businesses do not fully appreciate the bottom-line cost of supply chain insecurity and the adverse impact it has on top-line brand value.

So that brings us to the second question. How can your organization establish a culture and supporting infrastructure to help identify fake goods entering the legitimate supply chain? The short answer is that companies with anticounterfeiting strategies that are based upon a solid understanding of the mechanisms of counterfeit trade, that are strongly supported by senior management, and that include well-defined monitoring and response processes that foster strong collaborations

with external stakeholders are best-positioned to maximize the market value of their goods and services. In doing so, they also preserve, perhaps enhance, brand and company equity.

In establishing such a culture across your company, it is important to begin with a humbling awareness which is counterintuitive to business leaders who pride themselves in knowing their products, customers, competitors, and markets incredibly well. Unfortunately when it comes to counterfeits, even the best "brand protectors" in the industry will be quick to say, *"We don't know what we don't know."* For this reason, it is imperative for ethical and reputable companies to focus on risk assessment, preventive business practices, and immediate response to known incidents with appropriate root-cause analyses. This also implies having well-documented procedures and proper attention to organizational expertise to manage incident reporting, legal and enforcement efforts, and systemwide communications.

In the pharmaceuticals supply industry, it is easy to understand why we suffer from lack of knowledge of the problem. This lack of business intelligence is attributable to four common supply chain realities:

1. The majority of trade occurs "downstream" from company-managed operations where the transparency and control of our goods is limited to information obtained from trading partners and customers.
2. Ownership of goods typically transfers to the intermediary (distributor) or directly to the end customer early in the supply chain. Unless there is a contractual or legal obligation for trading partners to share such detail with the manufacturers, visibility to further transfers is limited to syndicated sources of data.
3. With few exceptions, there is no industrywide network of tracking or tracing products through the supply chain (so-called pedigree, or chain, of custody systems) to record the time, value, and place of product transfers.
4. The quality of the counterfeiters' work has become so sophisticated that the product and/or its packaging is often indistinguishable from the genuine product and can pass through to consumption or administration by a practitioner without detection.

As a result of these conditions, all industry stakeholders must develop and implement monitoring systems to look for and uncover fakes anywhere in the supply chain. But this is no easy task, since the pathways of the counterfeiter are varied, inconsistent, and largely underground.

Due to the inability of business leaders to accurately estimate how counterfeit goods are affecting revenue from traditional internal data systems, we must take a top-down approach from the World Health Organization statistics in order to build a credible "Case For Action" within our scope of operations. There are at least two ways of addressing this need for quantifying the unknown: (1) it is not unreasonable to assume that your high-volume, high-profit brands are being "violated" at a 2 percent to 3 percent rate when combining all illicit trade categories or (2) treat the aggregation of all counterfeiters as being equivalent to a second-tier competitor, taking away some of the natural demand that exists for your products. The latter approach works particularly well among marketers who enjoy staging campaigns to win market share.

There are other qualitative factors that can refine your internal estimate of counterfeits when comparing your company to the industry average (until more reliable business intelligence is obtained):

- Does your company's drug portfolio include any of the highly counterfeited product categories (e.g., lifestyle drugs, antimalarials, or statins)?
- What is your relative market share and price point in specific high-risk categories?
- Do you have effective safeguards currently in place?
- What is your relative penetration and operational presence in emerging markets compared to that in more regulated markets?
- Do you have product security contracts and auditing procedures with your key distributors?
- Can you apply your incident history to determine the degree and scope of your brands which are being targeted by counterfeiters?

The key message though is, regardless of how you sculpt the known data into an assessment of the business opportunity, ANY counterfeit trade of your brands or any sale of a genuine but diverted product that has been mishandled, stored improperly, or allowed to expire places a patient at risk. For this reason, you must maintain a culture of governance that reinforces a "NO TOLERANCE" policy on illicit trade worldwide.

5 KEY ESSENTIALS TO A STRONG COMPANY CULTURE OF INTOLERANCE TO BRAND VIOLATIONS

Preaching a company commitment to anticounterfeiting policies and practices will not stop counterfeit drug trade, but it's a start. In fact, I have prepared five basic ingredients to a strong company culture to reinforce your "no tolerance" message with strategies, actions, processes, metrics, and assessments, all aimed at brand protection and patient safety and all starting with the commitment of the company's C-suite leaders:

1. senior management commitment and accountability
2. cross-functional governance and policy stewardship
3. brand protection functional expertise
4. widely adopted set of supply chain best practices
5. measurement systems and data analytics.

Management Commitment. As in most companywide culture initiatives, it is vital to have the CEO or president address the

company's commitment to thwart the effects of counterfeiters and to demonstrate such commitment through regular and open communications on the topic. Anticounterfeiting measures may not immediately have a positive business case, and for many associates, it is difficult to see the benefits of the effort at all. Support from top management is crucial to signal that the problem must be addressed proactively and that associates who are empowered to implement anticounterfeiting measures are contributing to the wealth of the company. Without *explicit* executive acknowledgement of a strong case for action, typically rooted in consumer safety, brand equity, and business value, brand protection commitments inside the supply chain will become fragmented, ineffective, inconsistent, and financially challenged and will eventually lead to unmitigated risks.

Governance and Policy Stewardship. Because counterfeit trade can engulf virtually every function in the organization, cross-functional oversight and governance of policies, positions, and practices are vital to the effectiveness and sustainability of the company's brand protection efforts. Typically, pharmaceuticals organizations will set policies and procedures pertaining to IP protection through close collaboration among the law department, including trademark and patent attorneys, quality & compliance officers, government affairs, the security department, and business unit heads. This internal governing body, composed of proven leaders, can guide and inform senior executives on strategic brand protection issues, political and regulatory direction, and important events. This standing committee (council) will create and maintain internal policies and mandates pertaining to the broad issues of protecting the supply chain. It is also important for the company to have a consistent "voice" to external partners and the public, relative to its practices. Such a council is invaluable in communicating such positions throughout internal and external communications networks.

Brand Protection Expertise. As a business discipline, brand protection is a nascent function for most organizations. It is important to design, fund, and manage brand protection activities as an operational unit for the purpose of providing subject-matter expertise for the long term. The core mission of the brand protection group is to assess risk, develop and advise on the implementation of counter measures, and develop the tools needed to protect the company and its customers from false versions of its brands.

This group can report organizationally to the commercial units or to supply chain leaders or to the law department. Given the need to implement anticounterfeiting practices and technologies inside the supply chain, it may be best for this group to reside there or at least have liberal access to production operations. Lastly, depending upon the markets served, the brand protection organization might have regionally deployed experts "on the ground" in addition to enterprise-based specialists to support new product launches or legislated anticounterfeiting programs.

Supply Chain Best Practices. Leading organizations in this space refuse to adopt a "victim mentality" when counterfeits surface in the marketplace. Instead they study the causal factors of each incident using available information and assess what, if anything, can be changed inside the company or through affiliated suppliers and commercial partners to prevent the counterfeits getting into the legitimate channels of trade. Such best practices become evolutionary as each incident is a new learning, and every violation can be linked to a pattern of behavior. Best practices then become prescriptive anticounterfeiting guidance documents for widespread implementation across the enterprise. In some cases the recommendation for increased control and security are best implemented as standard operating procedures with appropriate training, validation, and version control. The categories of prime importance for best practice development include distributor compliance, reporting and escalating incidents, market monitoring, employee education (e.g. call center personnel), appropriate use of deterrent or authentication technologies, and managing reverse logistics. These practices should be reviewed periodically by the cross-functional governance committee and the brand protection experts for completeness and feasibility of deployment.

Measurement and Data Analytics. The old management adage, "you achieve what you measure," also applies to brand protection. Despite the fact that information about specific counterfeit activity is sketchy at best, it behooves an organization to track incidents and place a value (lost or recovered revenue) for each violation and for each protective measure. Internal rules can apply to the metrics so that credibility is not challenged if the cause and effect are not clearly stated. In addition to the wins and losses amassed over time, as a measure of brand protection effectiveness, it is important to learn from the aggregation of the data. It is not

unreasonable to catalog forensic information obtained from a cluster of fake goods, to help profile the counterfeiters' actions or perhaps some elements of their supply network. For example, the clandestine nature of drugs sold via the Internet can make triaging incidents a difficult task. However, by looking for patterns of packaging, pricing, graphics, etc., it is possible to determine if one or many cells of illicit producers are involved. Lastly, as mentioned earlier, many aspects of brand protection are counterintuitive to common business logic. Measuring incidents is at the top of the list. In the early phases of establishing a culture to proactively combat counterfeits, an organization will see the number of reported incidents rise simply because the company's search antennae are more active. Here it is important for senior leaders NOT to react negatively to rising reports of illicit trade. You may be observing the tip of the iceberg, whereas before the focus on metrics, your company was merely reporting the "tip of the tip" of the iceberg. Take heart; eventually your new 5-Step Plan will drive incidents down and revenue recovery up.

In summary, a successful organizational commitment to brand protection and supply-chain integrity is no different from any other pursuit of business excellence. It begins with visibility to the case for action from the top of the organization down through the ranks with shared accountability for a "no tolerance" culture. That culture becomes sustainable when the organization understands individual roles and responsibilities needed to help mitigate the risks of counterfeits invading the legitimate supply network and proactively embraces the policies, practices, and technologies needed to deploy a comprehensive and sustainable brand protection program. Your patients will applaud your efforts.

About the Author

Ron Guido is the president of Lifecare Services, LLC, a management consulting firm specializing in healthcare marketing, brand protection, and strategic planning. He has more than 36 years of experience in the healthcare industry and is the former vice president of brand protection at Johnson & Johnson. In that role, he and his team were responsible for global anti-counterfeiting programs and policies.

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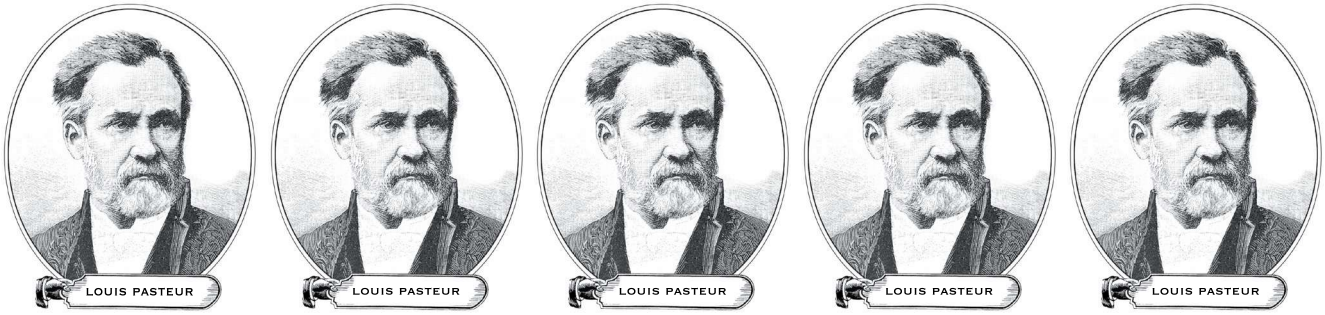

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Pfizer's Hybrid Approach To Implementing Continuous Manufacturing Processes

By Rob Wright, chief editor

When Kevin Nepveux joined Pfizer, his first job out of college was working as a production engineer manufacturing penicillin in one of the company's original plants in Groton, CT. Today, Nepveux is the VP of global technology services within Pfizer Global Supply. "Actually making the product and seeing it go into drums every day was very fulfilling," he states. Being close to where the action is may have been rewarding as a new employee, but as a senior leader he has found it to be even more important to understand how to best improve Pfizer's manufacturing processes. Nepveux sat down with me to share some of his insights about continuous manufacturing (CM) and how Pfizer is deploying continuous and batch processes as a hybrid approach toward improving manufacturing efficiencies.

LIFE SCIENCE LEADER (LSL): DESCRIBE HOW PFIZER WENT ABOUT DEPLOYING CM TECHNOLOGIES.

Kevin Nepveux (KN): The Global Technology Services (GTS) group initially started on these projects back in the late 1990s. The pharmaceutical industry environment was very different from today. The cost pressures were building, but weren't as severe, and our model was still that of the blockbuster. As a result, it was a more receptive time for developing and deploying these technologies than where we are today.

When we started to look at CM technologies, we first looked outside of pharma. A lot of the continuous technology had been developed and deployed in other industries that had experienced cost pressures long before pharma. We weren't necessarily inventing anything new, but applying technologies from other industries to pharmaceuticals, recognizing, of course, that we typically have much tighter specifications and control ranges. The food processing and specialty chemical processing industries were good sources of ideas, as they use similar unit operations. The significant challenge was in adapting some of those technologies to pharma, as these industries have a different regulatory and cost environment and operate in much higher volumes.

We would pick some of the unit operations that were the most broadly used throughout Pfizer that we felt most comfortable making continuous via adapting similar technologies from other industries. These were typically the common unit operations, such as roller compaction within a dry granulation unit operation. The philosophy was, once you get that working for one product, it should be readily applicable to others, though it would usually require some additional customization or development depending upon the product. We would then pick a specific product we thought served as a good example of that unit operation. For the most part, these were usually high-volume, capital-, and labor-intensive products, with a fixed set of unit operations performed in a batch mode — the low-hanging fruit, if you will. We would develop the continuous option at a small laboratory or pilot plant, along with the site that was manufacturing the product to verify that it worked and to uncover the various challenges that would have to be overcome from either an engineering or a technology perspective prior to scaling up. In three or four cases, we built CM commercial-scale setups or

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production lines in those facilities. Two products with different unit operation processes were picked as part of our initial deployments — Lipitor (a wet granulation process) and Geodon (a dry granulation process). We also looked at some of the active pharmaceutical ingredients (API) processes for Lipitor, Lyrica, and Celebrex (which are all blockbuster drugs).

LSL: WHAT WERE SOME OF THE LESSONS LEARNED FROM THESE DEPLOYMENTS?

KN: For starters, the business cases changed over time. It takes some time to adapt and develop these applications. You start in a pilot environment to develop data that convinces you it will work. Then you develop data to convince regulators so they will approve it as an alternate process. These activities take several years to work through. In our case, some of the business cases changed during this time frame. Though the deployments were technically very successful and effective when installed for commercial manufacturing, some of the manufacturing sites are no longer in our network, and the products have gone generic. When we look at the costs to relocate that technology to another site, it really didn't have a good ROI. The cost pressures from generic competition changed the landscape. Today, when we approach a deployment, we do a much more rigorous job of identifying and making sure, up front, it has an enduring business case. We also look for projects that can be rapidly deployed on a number of products. It is difficult to have a project tied to one individual product, because as it moves through its life cycle, and generic competition begins, volumes drop and the cost environment changes. We look for opportunities with broader applicability that can be applied fairly quickly.

"I think one of the best ways to go about implementing CM processes is to develop the analytics in line with the application."

Kevin Nepveux, VP of global technology services, Pfizer Global Supply

Another lesson learned involved analysis. For example, when we did Lipitor and Geodon, we did business cases comparing what we believed the technology would look like in five years, relative to how it was at the time, in terms of production costs, demand, margins, etc. In conducting our analysis, as we were the only manufacturer of the drugs, we used ourselves as the comparator with which to benchmark. Now, when a drug loses exclusivity, you are no longer competing with yourself, but with generic manufacturers, which often have much lower labor and capital costs. As a result, shortly after we had developed and implemented the CM process for these drugs, our analysis was no longer valid because the benchmark had shifted from internal to external.

Pfizer's value proposition hinges on quality and supply assurance. We excel in manufacturing the highest quality products and assuring their supply globally. A lot of the customers have found that not always to be the case with generics. The ability to produce variable quantities of medicines, as well as the ability to ramp up and produce more medicines very quickly, has enabled us to compete effectively in the generic area. While it is challenging to provide both quality and supply assurance while also having the lowest cost, we have found that customers are willing to pay a bit more for the quality and supply assurance we offer.

LSL: WHAT PARTICULAR TYPE OF DATA ARE YOU EVALUATING IN THIS DECISION-MAKING PROCESS?

KN: You are generally looking for a comparison to the baseline for the product or unit operation. We usually have quite a bit of data, because we have been running these unit operations for a long time. The most compelling data is situations where continuous processing can do something significantly better or something that a batch unit operation can't do. One example is the synthesis part of small molecule API. You can do some exothermic reactions or hazardous reactions in a continuous-mode plug-flow reactor that you could not do in a batch reactor for either safety reasons or that the chemistry may be self-limiting. A second way to look at it is if you are going to be incrementally better from either a labor or productivity perspective. Those are still strong business cases, but you have to look beyond just the current situation with that product. You probably need to look at least 5 to 10 years down the road to determine whether the benefit of implementation will still exist or accumulate. In situations where you need additional capacity for a product or a suite of products, and you need to build more capacity, it is important to consider developing continuous processes, as I believe these applications are going to be significantly less capital-intensive, have a smaller footprint, and be more productive than building a large, traditional batch facility. At present, this is not generally the case, since we have excess capacity for most of the traditional unit operations. Where we are finding opportunities is in some of the smaller emerging markets where, either for tactical or political reasons, you are looking to establish a local manufacturing presence.

LSL: WHAT ARE SOME OF THE ADVANTAGES OF CONTINUOUS VERSUS BATCH MANUFACTURING PROCESSES?

KN: In CM you can operate at a steady state, which is optimal for that process or unit operation. Batch, by definition, is a transition from a starting point, through a process, to an ending. There may be a point along the way where it is optimal: a "sweet spot" for that specific process (i.e. a chemical reaction, for-

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mulation process, a cell-growth profile). But because it is in a batch, the sweet spot isn't maintained. With CM you have the possibility of being able to maintain the process at that sweet spot for a long period of time, which can be more effective than batching. However, you need to be concerned with how long it takes you to get to that sweet spot, since there can be quite a lot of auxiliary equipment and processes necessary to maintain the environment around one processing step. That's one of the challenges with a CM process. The other challenge that we have seen concerns linking multiple unit operations together in one CM process. This is the approach the Novartis MIT project has taken with great results. Using creative engineering and sophisticated control systems technology, they were able to match each process step, each unit operation, to the rest of the process to avoid bottlenecks or hold points where inventory might build up. Building in buffers is a technical challenge that can be overcome, but it takes a lot more work on the unit operations and is a potential downside to CM.

One of the big upsides to CM is that you don't have a fixed batch size, so you can make as little or as much as you need. As the market dynamics change, and we try to get into a supply model that is more responsive to the customer demands (especially as we start to look at some of the emerging markets with smaller and variable demands that need to be satisfied very quickly in order to be effective from a business standpoint), CM gives you a lot more flexibility than batch. CM lead times (from purchase of raw materials to delivery of finished products) are typically a fraction of batch lead times — this can substantially reduce inventory carrying costs. Another basic advantage of CM is that you can get a higher throughput on a smaller footprint for less of a capital investment as compared to a batch process.

The other area where CM is really effective is when your process cannot tolerate much variability. In these cases, you can be more consistent and more robust using CM. This is also an advantage when introducing new products, since there is no "scale-up" — you can manufacture development, clinical, and commercial product on the same equipment by running longer.

> "As the market dynamics change, and we try to get into a supply model that is more responsive to the customer demands, continuous manufacturing gives you a lot more flexibility than batch."
>
> Kevin Nepveux, VP of global technology services, Pfizer Global Supply

LSL: WHAT ABOUT A HYBRID MANUFACTURING PROCESS THAT UTILIZES THE BEST OF BOTH BATCH AND CONTINUOUS AS A MEANS OF IMPROVING EFFICIENCIES AND MANAGING BOTTLENECKS?

KN: That is what we've evolved to. I don't know that this was an intentional, planned evolution, but it's where we are now. We have evaluated CM for most unit operations that we execute in both large and small molecule areas of pharmaceutical manufacturing. There are some unit operations that are really effective and carry a very strong business case. As the business case justifies it, we are deploying CM for those products or for multiple products for that unit operation within our manufacturing network.

As of yet, we don't have any situations that are true end-to-end continuous whereby you start with a raw material on one end and finish with a final drug product on the other with zero interruptions. We term our manufacturing approach as being a hybrid, which utilizes some elements of batch and continuous. We may have one unit operation or one step in a four- or five-step process that is continuous, or maybe a couple that are back-to-back, but there will also be some batch processes or batch steps within that process. The hybrid approach has proven effective for us, especially when you have one unit operation that might be the real bottleneck in a process. For example, tablet coating is a bottleneck, and can be a very long process in a batch mode. It is often the rate-limiting step for a drug product manufacturing operation. We have looked at and deployed platforms of continuous coating in those situations, which can de-bottleneck a process and allow your granulation and tableting, which is in front, and your packaging, which is in back, to be better utilized overall. Another example in the small molecule API area is crystallization, which can be a variable process. This variability can result in changes to physical properties of your API, which in turn can cause you problems in filtration, drying, and formulation. There are some cases where we've looked at continuous crystallization as a way to get more consistent physical properties, which improves other components of the manufacturing process.

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LSL: WHAT ARE SOME OF THE CHALLENGES TO IMPLEMENTING CM GIVEN THE ABSENCE OF FDA REGULATORY GUIDANCE?

KN: There are two issues. One is how big is a lot size, and how do you define that with CM. I think there is some good guidance that has been developed here. The other issue involves the use of online analytics to monitor and control your process. These are not the traditional, single-loop feedback control systems (i.e. controlling temperature or pressure on a reactor). They require much higher-level control strategies, and understanding those is a challenge. These provide more data than that of a batch environment (i.e. doing military-standard sampling and testing for release). When you gather more data, you are going to see more variability than when working with a smaller sample size.

Now, the variability was always there; you just weren't picking it up in the sampling technique you were using. That has been somewhat of a challenge — to talk about how you manage this much larger data set, and what is acceptable in terms of adequately controlling your process. This is a learning process for both the manufacturers and the regulators. We have found the FDA to be relatively open and cooperative to the manufacturing approaches we want to take at Pfizer. Some of the new approaches should improve overall robustness of manufacturing processes over time. In many cases, multiproduct CM platforms will make it easier to respond to surges in demand, allowing companies to better manage drug shortage situations.

I think one of the best ways to go about implementing CM processes is to develop the analytics in line with the application. Once we get to the point where we are satisfied with a control strategy, it's really good to be open and suggest it to the regulators as part of the data exchange around the technology. Engage the regulatory agencies as early as you are comfortable, sharing with them where you are going. You need to suggest and propose the appropriate control strategy around that technology to the regulators, because you are the experts.

LSL: WHAT ARE SOME OF THE IMPORTANT CONSIDERATIONS FOR CREATING CONTROL STRATEGIES FOR HYBRID MANUFACTURING?

KN: Quite often, a lot of the data you've been capturing all along for other reasons can really be helpful in monitoring the health of your total manufacturing process. That's where you start to get into some of the more subtle and less obvious relationships that can give you information on your process. This is a big challenge, because you have so much information now that you've got to be careful in terms of how you use it versus what is actually needed specifically for process control.

Take tablet coating, for example. Occasionally, we would have coatings that were uneven, which might result in having to reprocess or reject a batch that wasn't cosmetically acceptable, even though the active and the tablet were fine. For years we have been striving to get better control of the inherent challenges with tablet coating. To that end, we placed some better technology to monitor temperature in the tablet coater. We found that we were collecting a lot of other data, like motor speed on the drum of the coater, flow rate of the coating solution going in, air flow rate and temperature, as well as the routine types of monitoring metrics. We then conducted a fairly sophisticated analysis that provided a "fingerprint" of the tablet-coating process. This allowed us to watch for trends and anticipate flaws before they showed up in the physical product.

LSL: WHAT ARE SOME OF THE METRICS EMPLOYED TO DETERMINE HYBRID MANUFACTURING AS BEING EFFECTIVE?

KN: You can evaluate those traditional measures — quality, yield, productivity, labor costs, etc. — as a straight comparison. Certainly, we do see improvements in those unit operations that can benefit significantly from CM. From an expense perspective or in an ongoing cost per unit, you'll typically see a lower cost for continuous than you would for batch. But if you've got a batch facility that is largely depreciated, and you've got to build a new CM facility, you need to compare capital and operating costs in your analysis. The other thing we noticed is that the processing costs are typically incremental. You need high volume so that you're multiplying by a big number of units to realize value. This is something to pay close attention to as a product approaches the end of its life cycle. Generic incursion can drop volumes, substantially reducing the total benefit.

LSL: ANY PLEASANT SURPRISES FROM IMPLEMENTATION OF CM PROCESSES?

KN: Yes, we have seen some examples. I can't go into detail on the products, but they were typically in situations where you could actually do something a different way with continuous than you could with batch. I'll use an example of a chemical process step where you have an exothermic reaction that you couldn't do in batch because it was unsafe to have that much material in a reactor generating that much heat. Because you couldn't control it safely, you had to use different chemistry. In a flow reactor, because you're dealing with microscopic amounts of the material, even though the heat is generated, you can remove it much more effectively. Because you are using a small amount of material, there's not as much of a risk. We've had a couple of cases that have produced substantial ROI compared to a batch process.

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The Importance Of Investment And R&D In The Health Of Life Sciences

By Mark Howard And Jodie Dennis

The AIM (formerly the Alternative Investment Market) IPO market has seen a number of significant listings recently in the life sciences sphere. Notably, the market appears to be strong for companies providing clinical services or medical devices, with a wide range of such companies coming to market in the last 12 months, including Clinigen Group (clinical trials supply and specialty pharmaceuticals) and Venn Life Sciences Holdings (consulting and clinical trial provision).

For companies involved in drug discovery, the market remains challenging. But there are signs of interest from certain institutional investors in this part of the sector too, and the successful floatation of Retroscreen Virology Group's shares on the AIM market demonstrates a willingness to invest in businesses carrying out quality R&D, albeit in this case counter-balanced by a novel clinical services business. Retroscreen is a virology healthcare business that provides preclinical analytical services and clinical services to large pharmaceutical and biotech companies. Last year it successfully raised £15 million ($23.5 million) from an AIM IPO to fund its R&D and working capital requirements.

In April 2013, the London Stock Exchange welcomed Electrical Geodesic, Inc. (EGI), a U.S.-based medical device company, to AIM. EGI made a strong debut, raising the £8 million ($12.5 million) before expenses on admission.

EGI's successful floatation is not surprising, given the company's measured evolution, both in operational and financing terms, prior to coming to market. EGI has steadily advanced and developed its core technology over the last 20 years and has obtained regulatory clearance in the U.S., EU, and from a number of other major international regulatory bodies. EGI has an established revenue stream with around 500 customers internationally.

EGI and almost all recent IPOs in the United Kingdom demonstrate that companies with a strong pathway to profit are seeing a lot of interest from institutional investors. Investors are also interested in strong management teams that have a proven track record of bringing life sciences companies to market and providing them with a profitable exit. For example, David Evans, chairman of Healthcare Investment Opportunities (which was admitted to AIM in April), has been part of a number of successful management teams in this area, including Venn.

ALTERNATIVE SOURCES OF R&D FUNDING

Companies that are very early in their development are unlikely to be suitable investments for institutional investors. However, as Venn and Retroscreen (previously backed by private equity houses Calculus Capital and Aquarius Equity, respectively) have shown, there are other sources of finance available to fund the earlier part of the life cycle. In addition to private equity/venture capital, alternative providers of finance, such as national development funds and mentoring initiatives (for example, Government's Biomedical Catalyst and the Growth Accelerator) and regional development funds, such as the Thames Valley EIS Fund, can be invaluable alternatives for early-stage, next-generation businesses. This is especially true in the context of an economy where traditional providers of debt finance remain relatively cautious.

Companies early in their life cycle also may benefit from partnering relationships with universities, charities, or large corporations. Such partnerships can help smaller companies plug the funding gap and provide access to R&D expertise and services critical to their long-term success.

For those companies with established revenue streams, access to a public market, whether this is AIM or the main market, can offer many advantages. Recent admissions on AIM have raised

from a relatively modest £8 million ($12.5 million) (EGI) to a very healthy £50 million ($78.3 million)(Clinigen), providing these companies with crucial funds for further development. The secondary fundraising market also has been buoyant, with more than £2.5 billion ($3.9 billion) and £4.1 billion ($6.4 billion) being raised in 2012 through secondary issues on AIM and the main market, respectively. In addition to access to capital, companies benefit from enhanced status and public profile, the ability to incentivize employees through share-option schemes, a transactional currency in the form of their listed shares, and a profitable exit option for investors (e.g. at Clinigen, the existing shareholders achieved a significant sell-down, receiving aggregate consideration of over £40 million [$62.6 million]).

In March 2013, the LSE (London Stock Exchange) launched a new high-growth segment of the main market. The new platform is aimed predominantly at addressing the needs of fast-growing European technology companies with a view to providing such companies with a transitional route to the UKLA's (U.K. Listing Authority) official list. This opens up an exciting new platform for companies in the life sciences arena that are looking for access to capital as a stepping stone to the main market.

The public markets are looking more positive for life sciences companies with strong underlying fundamentals, strong management teams and profits, or a clear pathway to them. Meanwhile, policy initiatives such as the Biomedical Catalyst mean better support is being made available at the other end of the life cycle. Both factors bode well for the future of the sector and R&D.

About the Authors

Jodie Dennis is an associate at Charles Russell LLP. Jodie advises a wide variety of clients, including listed PLCs and large, privately owned corporates. As well as providing general company law advice, Jodie advises on a range of transactions, including mergers and acquisitions (including takeovers), equity capital markets (including IPOs and secondary fundraisings), and private equity investments.

Mark Howard is a partner at Charles Russell LLP. He advises on primary and secondary listings (on AIM and the main market), public takeovers, private M&A, VC/PE investments, joint ventures, restructurings, and distressed asset sales. His sector focus includes companies in the life sciences sector.

Taking It Public: To IPO Or Not To IPO

By Suzanne Elvidge, contributing editor

Once seen as the primary exit strategy for a young biotech company in a booming economy, the IPO (initial public offering) became an impossible dream for many as the economy began to slide. The window is now cautiously opening, and biotechs are starting to take advantage. However, are IPOs still the best route for everyone, and are there any alternatives?

WHERE ARE WE NOW?

The late 1990s saw a boom in IPOs, but the numbers plummeted dramatically in the recession of the early 2000s and the global financial crisis starting in 2007. This climate made many investors very wary of risk.

"During the financial downturn, generally investors were looking for lower-risk investment targets, meaning that we saw a fall off in biotech IPOs in 2008. However, there were still some biotech specialists that continued to invest in later-stage deals," says Glen Giovannetti, global life science sector leader at Ernst & Young. "Mature private companies that have more advanced pipelines, preferably with Phase 2 data, or are developing products that will address critical unmet needs, have 'stories' that are easier to sell to investors. It's also possible to place earlier-stage companies if they have a truly differentiated technology."

There are now signs that the battered biotech IPO market is coming back to life again. This year has seen a rapid increase in the number of offerings, with a queue of companies waiting in the wings. "It's currently the best IPO market in a decade in the United States," says Giovannetti. "Through July 2013, there have been 28 pure biotech IPOs in the United States, compared with 21 combined over the past two years."

Examples of companies that have successfully floated so far this year include bluebird bio, backed by Third Rock Ventures; Cardio3 BioSciences, a Belgian cell therapy company; Chimerix, which has a focus on antivirals and an agreement with Merck; Enanta Pharmaceuticals, with a promising hepatitis C therapeutic; diagnostics company LipoScience; and KaloBios, a San Francisco company looking into antibody therapy.

There's also a robust pipeline, with 10 or so biotech companies waiting to go through registration. These include immunotherapy company Heat Biologics, which is working in the infectious disease and cancer arena; Intrexon, backed by biotech entrepreneur Randal Kirk; and OncoMed, a cancer company with alliances to Bayer and GSK.

"Investors are seeing that large biotech companies are performing particularly well, which creates a cascading effect, raising the values of smaller companies and increasing the appetite for IPOs," says Giovannetti. "Big Pharma companies have also been buying out smaller biotechs at more attractive valuations, which reinforces the good feeling in the market."

ARE IPOs FOR EVERYONE?

IPOs offer investors an exit option, but can undervalue the business, are costly, and have an inherent risk of failure. As an example, in October 2009, Omeros Corp. was the first development-stage pure biotech company to go public since February 2008. According to the Burrill report, its initial share price was $10, which fell 13 percent on the first day of trading, and 44.3 percent by the month end. This performance may have soured the market for biotech IPOs for a period, but both the market and the company itself fortunately appear to have bounced back.

When considering an IPO, decisions about the financial future of the company are critical, and should be discussed from the outset. This includes balancing the need for funding with the long-term impact on the company — for example, partnering may be a cost-effective route to financing, but means sharing intellectual property. Listing as a public company also affects how the company is run; this needs to be taken into account.

"There is a big difference between managing a public company compared with a private company, because of the regulatory requirements, so the right management needs to be in place," says Giovannetti. "For example, a public company CEO will need to spend a lot of time on investor relations, particularly if follow-up funding is needed, pulling focus away from R&D and other management activities."

WHAT'S THE ALTERNATIVE?

Before deciding on an IPO, it's important to think about the purpose of the funding, and

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the most cost-effective route to find that funding. Alternatives to IPOs include private investors, bank loans, providing services for a fee, applying for government or private disease foundation grants, and partnering. Another alternative is "royalty financing" for products in very late-stage clinical development or on the market, where companies give up certain rights related to intellectual property in return for royalties and milestone payments.

Australia has seen opportunities in raising capital from high-net-worth individuals, as Simon James, a partner with Audit and Assurance, Corporate Advisory, HLB Mann Judd, explains: "There has been a shift in the 'wealth market,' with high-net-worth people and the bigger banks looking to move away from investment in stocks and property toward a more diversified investment portfolio. This is fragmented money, but overall is a source of a lot of funding."

Partnering with a distributor rather than spending money creating a sales force offers an alternative to an IPO. It can also add value to the company and its offering by bringing in expertise.

"Going to a specialist, for example for marketing, production, sales, and other parts of the supply chain, can be quicker and cheaper. It also can be quite powerful," says James.

Companies that want to list but don't want to go through the complex and time-consuming process can list "by the back door." This involves buying a business that is already listed.

"This option doesn't have the buzz that goes with an IPO, but it is cheaper, and can inherit tax losses, which is good. However, it can also carry with it legal liabilities and the reputation of a failed company, which is not so good," says James.

PUTTING IT INTO PRACTICE

KaloBios Pharmaceuticals, a U.S.-based company with a focus on monoclonal antibodies for seriously ill patients with difficult-to-treat diseases, completed an IPO in February 2013, raising $70 million. The company's route to financing began with just over $100 million in five private rounds, followed by $15 million of venture debt financing, but it needed more to move projects into Phase 2 and beyond. After weighing the alternatives for further funding, KaloBios decided to begin the process of an IPO around the second quarter of 2012.

"We felt that the IPO was the right decision to raise money to fund our programs," says Jeffrey Cooper, CFO, KaloBios Pharmaceuticals. "While we raised a significant amount of money over the years prior to our IPO, we felt that the market was tapped out for further private funding."

The JOBS (Jumpstart Our Business Startups) Act, which came into law in April 2012, has helped small companies like KaloBios by allowing them to talk to investors before the formal IPO road show.

"These 'testing the waters' meetings helped us educate potential investors, because our story with three programs in the pipeline is somewhat complex," says Cooper. "The JOBS act has also reduced our reporting requirements, which made the whole process easier."

A WORD TO THE WISE

IPOs tend to go in cycles of highs and lows, and it's always difficult to predict what's around the corner, including whether the IPO window will stay open, or close, or whether the market, currently buoyed up by the availability of secondary financing and now IPO financing, will remain upbeat. For companies that have decided to go down the IPO route, there are a few words of advice:

- Take time preparing, and look at all the options.
- Don't go public too early — create value first.
- Use money to move toward a data inflection point, such as results from a Phase 2 trial.
- Ideally, plan to reach the inflection point within six months, and no later than one year, of the IPO.
- Have answers ready for investors' questions, such as:
  - What is the scientific and clinical risk? How compelling is the data, and how much risk will there be moving from Phase 2 to Phase 3?
  - What is the commercial risk? Will the drug be reimbursed, and are there likely to be any other obstacles to adoption?

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How Cloud-Based Tools Can Help With FDA Compliance

By Sunil Gupta

These days, enforcing FDA compliance and mentoring new team members are more challenging than ever, thanks to a workforce that is more remote, international, and diverse. Additionally, today's Internet technology is more global, sophisticated, and secure. With these changes, pharmaceutical companies need to adapt to grow and ride the cost-conscious trend just to survive. Cloud-based tools, such as wikis, offer a paradigm shift in project management, FDA compliance requirements, and job aids for mentoring new employees.

With the lack of face-to-face interactions, more emphasis is placed on Internet technology to help automate and standardize repetitive tasks. For example, project management tools, such as Projecis, capture and communicate important milestones and deliverable details. By using a cloud-based project management application, that important data is always available and automatically backed up. It's those types of benefits that often empower small biotech companies, for example, to outsource their IT infrastructure to gain powerful computing platforms at a minimum cost. As an extension, some vendors also offer cloud-based EDC systems to help automate the collection and "cleaning" of clinical data. In the pharmaceutical industry, practical applications of project management tools include tracking clinical data issues or issues related to validating datasets or summary tables.

For CROs with a global workforce, having an intuitive, centralized data-management analysis system helps to increase user compliance. This is important to track access and updates to clinical data and statistical programs that summarize results. With a centralized system, these validation issue trails can be tracked for QA or FDA auditing purposes. For pivotal clinical studies with large lab datasets, for example, there is an extra advantage of using cloud computing. For example, with advanced signal detection and hypothesis generation, high-speed computers are ideal to optimize repeated tasks on large amounts of data. From an exploratory point of view, this opens new opportunities for comprehensive analysis of any drug-to-drug interaction within any combination of subgroup or stratification.

USE WIKIs TO CREATE DYNAMIC SOPs

Building an online, customized wiki system (without being a webmaster) to support SOPs (standard operating procedures) in statistical programming development and validation is another example of how you can use the cloud. Wikis can be designed to access just-in-time information based on user-defined topic categories. Instead of static SOPs, today's SOPs need to be "alive" and build on lessons learned from FDA submissions. By having access to frequently asked questions and cross-referenced indexes, team members are more empowered to find solutions for similar clinical study-related questions. Ideally, with a user-friendly wiki, statistical programmers and statisticians should be able to look up technical answers to the correct programming syntax with a few mouse clicks. Wikis are the equivalent to docstoc.com, being a repository of knowledge for the pharmaceutical industry.

Wikis also greatly reduce time spent on "reinventing the wheel" and allow statistical programmers to focus on more challenging and complex summary tables and analysis. By having immediate access to best practices resources and references on the Internet for lab conversion and normal ranges, team members can have greater confidence to complete typical tasks in an expected time frame. When senior programmers add insights to a lab data analysis checklist, they create more meaningful instructions. Essentially, this process, over time, builds an online knowledge base that can be harvested by anyone on the clinical or management teams for tracking the progress of the study.

Wikis are also ideal for accessing and


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maintaining links to CDISC (Clinical Data Interchange Standards Consortium) standards. Instead of downloading CDISC guides to the local server, for example, it is better to reference the CDISC website that contains links to the most current CDISC guide versions. This process becomes more vital to ensure that all clinical team members access the most current version of CDISC. In addition, by categorizing and organizing CDISC references, smarter companies guide employees to standardize the process. With SDTM (Study Data Tabulation Model) and ADaM (Analysis Data Model) dataset requirements, having access to downloadable CDISC files and free cloud-based tools will help leverage industrywide resources. Examples of free cloud-based tools to help create and validate SDTM and ADaM datasets include CDISC Express and OpenCDISC. Through time and experience, new statistical programming tips, techniques, and knowledge can be added to the wiki system for future reference. Typically, individuals save several websites as their favorites. But with wikis, teams have a method to store and search hundreds of websites for better utilization of Internet resources.

In addition, wikis are great for saving images of study diagrams, process flowcharts, graphs, and summary tables. Including images with the appropriate text and hyperlinks, for example, can help reinforce the understanding of complex clinical study designs.

ENSURE FDA COMPLIANCE FOR TRAINING

Effective wiki systems not only increase productivity of FDA submissions, but also help ensure FDA compliance on training requirements. Automatic email alerts and monthly newsletters remind team members of new training topics and schedules for completion. As with typical LMS (learning management system) applications, cloud-based tools can keep track of training compliance records for each employee. Managers have administration rights to view and ensure 100 percent compliance for their departments. In addition, managers can establish a mentoring program using job aids to better align senior programmers with junior programmers. By assigning junior programmers with reading tasks about proven technical techniques, for example, senior programmers can have higher expectations with minimum supervision. In this environment, junior programmers benefit from both worlds — formal and informal on-the-job training.

These are a few examples of innovative ways cloud-based tools have enabled pharmaceutical companies and CROs to better manage clinical studies and still provide high-quality deliverables for FDA submissions. Smarter organizations are making it easier for their workers to access the best cloud-based tools.

For the pharmaceutical industry, this extends to providing online statistical programming e-guides, training, and support for any technical issues. Online e-guides provide concise and numerous programming examples, templates, and brief text that solve real-world programming challenges. Monthly, live, online training sessions encourage more sharing of tips and current questions and answers. Previous online training sessions can be recorded and cataloged for new team members to view. With these cloud-based tools, technology and shared resources are better leveraged for more just-in-time response and minimum expense. Finally, it is important to point out that cloud-based tools can support groups as small as 3 to as large as 300 team members without requiring a dedicated staff to maintain application tools.

About the Author

Sunil Gupta is the founder of www.SASSavvy.com and senior SAS/CDISC consultant at Gupta Programming. He has expertise in training, automating, standardizing, and validating clinical data, analysis, and reporting for FDA submissions.

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How I Can Steal Your Competitive Secrets

By Jonathan Snyder

Pharma companies, looking to capitalize on the global demand for their products, pour billions into R&D *hoping* to develop the key ingredients needed to solve, or at least reduce, mass population killers. The demand is enormous, the rewards are enormous, and as a result, this market is fertile ground for the theft of trade secrets.

As a leader in your industry, your primary goal is to find cures to some of the world's most menacing medical issues; however, a close second goal is to drive revenue. As an intelligence and espionage professional, whether you are my target or the "nest" I am trying to protect, my goal is to penetrate your corporate risk management and security infrastructure to either steal or "test penetrate" your protected data or personnel. How would I accomplish my goal? There are many common methods to steal your competitive secrets.

The first and foremost method in this rapidly evolving digital age is the penetration of your technology. At a recent security seminar presented by Nova Southeastern University and the FBI Miami Division, the chief information officer for one of the world's renowned IT security leaders, RSA, stated, "The new focus of technology security professionals is to quickly identify and mitigate network intrusions — not prevent intrusions."

Today we know that even the most robust IT security devices cannot prevent all the sophisticated and overwhelming data-intrusion attempts. The goal is to identify the electronic thieves quickly, eliminate their presence, assess the damage, and attempt to harden the penetration points. A scary fact is that the average electronic spy has spent 34 days inside a network before the penetration is even detected. Putting this statistic in context, imagine a criminal being inside of your home for a month monitoring everything you are doing while going undetected!

Several other ways to steal your secrets traverse various areas of the organized crime realm. A highly simplistic yet powerful tool is the phenomenon known as "dumpster diving." Most organizations literally dump their proprietary secrets into their corporate trash bins without regard to who is waiting to score big on a critical formula, investment report, or interoffice memo that will identify who is critical to the research. All of this info provides key insights for spies to develop an attack plan to acquire secrets.

A parallel thought to the dumpster dive concept is the identification of key employees and their home residences. Monitoring their homes, where most people put their guard down, is another step in the process of stealing secrets. The average person becomes complacent with corporate security initiatives while working at home. In fact, company security policies are difficult, if not impossible, to impose on an employee's home turf. As an example, most homes have wireless routers installed, which all have included security, but most people only know to password protect the actual wireless broadcast. What they fail to password protect is the manufacturer's standard "admin" login Internet protocol. What this does is provide espionage agents the ability to bypass the wireless security protocols and gain access to all home computer systems. Examples also relate to the trash put out in the regular bins by the homeowners; they would never think of someone purposely looking for their company secrets in their home trash.

THE SECURITY RISKS OF CLINICAL TRIAL MEETINGS

Another successful way to penetrate an organization's proprietary info is to track its numerous clinical trial meetings and the panelists involved in those meetings. As someone who has provided security and counter-intelligence services to many organizations globally, including pharma, I have witnessed scientific leaders who

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were very nonchalant about protecting data secrets. Simply stated, foreign soil is a hotbed for data theft. Penetration of hotel rooms, listening devices planted into meeting rooms, and the infamous "honey trap" (i.e. using sexual exploitation to get what you want) are all methods of espionage that seem to work with endless success. The adversary who has targeted your organization thrives on organizational and vendor tendencies to be complacent and naïve. The goal of espionage agents is to remain undetected, which results in their best work. The more complacent or arrogant the target, the better chances of theft success.

A simple example of an environment at risk for a security breach is a hotel meeting room with the window curtains wide open. Such places provide corporate spies an opportunity to steal your secrets with the proper surveillance equipment. Simply closing the meeting room curtains can usually prevent laser surveillance equipment from picking up the conversations of the proprietary clinical study findings. Basically, if the curtains absorb the sound waves, spies cannot collect the sound bites.

If I were trying to gather intelligence on your company, it would be my goal to track your data and people. But sometimes it is challenging and exciting to, as we say in the industry, physically "work the room." For example, most hotel uniforms for food and beverage personnel are generic and easily bought at a local uniform supply. I have been able to penetrate many meeting rooms with covert listening devices and pin-hole photographic equipment to "take out the trash," or plant electronic bugs inside the room while the meeting is in progress. An even better opportunity is when the participants break for lunch and leave the room dirty. If I time it right, and I usually do, I can be in and out before the regular staff knows I was even there. Even if a hotel employee or participant seems curious as to whether I belong in the area, 99.9 percent of the time the curiosity never manifests into action on their part. My presence usually goes without further investigation.

Meeting planners are usually the easiest to penetrate, as they are spending the better part of their time appeasing the scientific attendees by catering to their every whim, rather than paying attention to who may be entering the room to clean up. Frequently, I run into laptops that are left on with critical data, and are easily stolen if the data seems to be a "big hit" worth the potential of being caught. As well, charts and graphs with formulas and attendee names and organizations are easily purged from the environment and go unnoticed.

FOREIGN MANUFACTURING SITES ARE VULNERABLE

If we haven't discussed enough means and methods, there are definitely more to address. Depending on the resources I have at my disposal, foreign manufacturing environments are great places to steal secrets. They say in Kazakhstan, you can buy a fully automatic AK-47 rifle from a 10-year-old child for a pack of cigarettes. Fortunately for spies, the value of integrity and loyalty in most foreign environments is a commodity that is traded easily.

Penetrating foreign workforces to build a pipeline of information is easier than trying to raise an American teenager in the Twitter era. While foreign manufacturing has its benefits, most secrets are stolen from sources derived from developing-country environments. There is no level of security that can be put in place that can fully stop the collection efforts by espionage professionals working within foreign territories.

A creative alternative to directly stealing is to allow targets to self-implicate through their personal integrity choices. For example, considering that most conventions are attended by professional executive types, it is quite clear that an unspoken world of illegal sex trade has probably infiltrated some of your organizational personnel, prospective employees, or vendors — the statistics simply do not lie! You may ask, "How does the sex trade affect our secrets?" Probably the oldest trick in the tradecraft book is to compromise a target through the "honey trap." The potential for enormous damage to both professional and personal life is usually enough for most targets to secretly cooperate to reveal secrets. The benefits of this typically yield a long-term "asset" (insider threat) to assist in stealing more secrets when needed.

At its darkest point, espionage has led to severe cases of kidnapping, torture, and even sometimes the murder of critical participants. The FBI says, "On average, 3 percent of all U.S. domestic terrorist events involves the assassination of executives." The data is not particularly reflective of the pharmaceutical industry; however, the information does cause concern that such tragic incidents are possible — especially in such an aggressive world of economic crisis and prowess.

One thing is for sure, there is absolutely no way to fully remove the possibility of theft of your corporate secrets. Utilizing the same Secret Service methodology for protecting the president of the United States of America, the goal is to "harden" the target as much as feasibly possible and become unpredictable to your adversaries — all for the goal of discouraging most from engaging in a targeted campaign of espionage-laden activities.

About the Author

Jonathan Snyder, CGC, CHS, is a 20-year veteran of the security and intelligence community and serves as the president and CEO of Argus International Risk Services, Inc., a global provider of security, intelligence/counter-intelligence, specialized training, and risk management solutions to the Fortune 500, federal agencies, and the Department of Defense.

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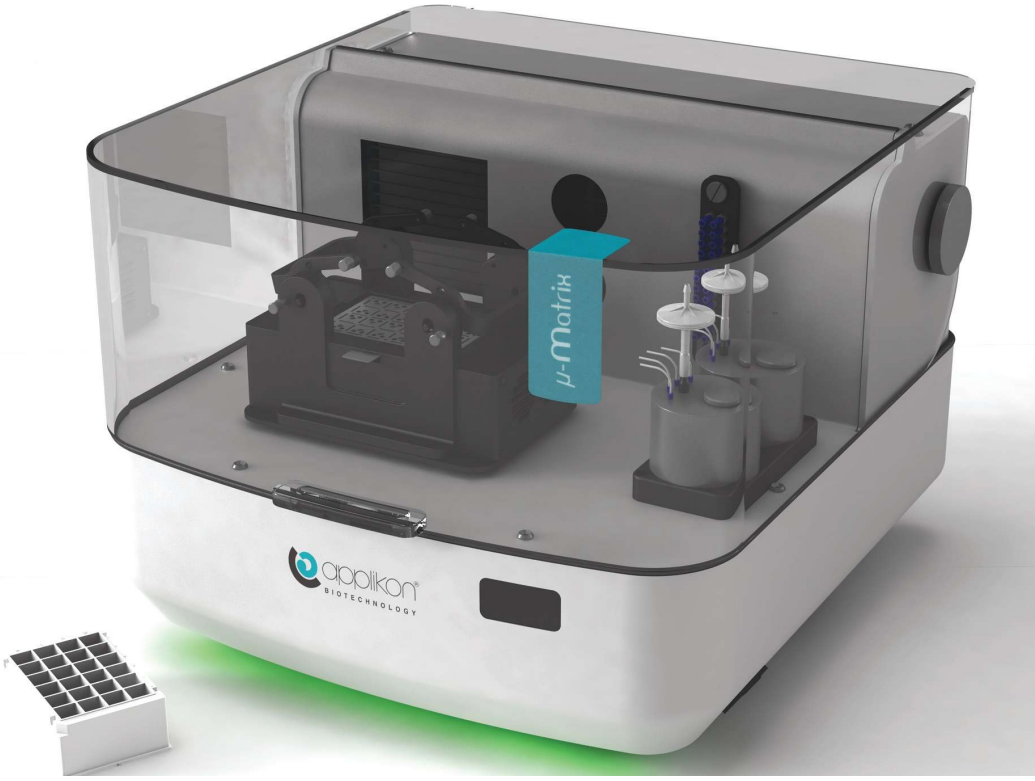

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Global Business Update

Looking Into Biopharma IP Protection In China

By Suzanne Elvidge, contributing editor

China is an attractive pharmaceutical market because of its large and aging population, increasing urbanization, and growing affluence. It is also an appealing location for drug R&D and manufacturing, as labor costs are still lower than Europe and the United States. However, some companies are reluctant to work in this region because, along with India, China has had a less-than-perfect history for intellectual property protection, with a reputation for reverse engineering drugs to provide cheap copies.

This is reflected by China's late entry into the international intellectual property (IP) arena. China's trademark law took effect in 1983 and its patent law in 1985, and the country became a member of the World Intellectual Property Organization in 1985. In 1986, China put legislation into place that defined IP rights in basic civil law, affirming a citizen's right of authorship (copyright) for the first time. China became a signatory to the World Trade Organization's Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) in 2001, which requires members to regulate intellectual property.

CONCERN NUMBER ONE: GAINING IP PROTECTION IN CHINA IS VERY COMPLICATED

Many companies are worried that creating patents in China is a long or complicated process. However, this hasn't been the experience of Nick Ede, Ph.D., executive director at the Australian drug delivery company Imugene. In May 2013, the Chinese State Intellectual Property Office granted a patent for Imugene's drug delivery technology, Linguet, for the delivery of bisphosphonates to prevent the loss of bone mass in osteoporosis and multiple myeloma.

"I've found the experience incredibly efficient. Chinese examiners move through the process quite rapidly," says Ede. "Usually, the first report will be issued about six to nine months from requesting examination and the patent office will follow up on responses filed by applicants within about two to three months. Because of this, it's important to have all your ducks in a row before you get started."

When creating IP protection in China, it's a good idea to use a two-pronged approach. For example, a patent on biotech products or processes does ensure protection but can reveal some of the technology. Adding a second layer of protection by ensuring that the cell line is a closely guarded trade secret ensures that while competitors may be able to reproduce the process, they may not be able to produce the product itself in as pure a form, or with as good a yield.

"It's important to combine both physical and legal protection," says Jiwen Chen, a U.S.-based attorney educated and practicing in both China and the United States, and specializing in global IP protection, including Asia. "And the forms of these will depend on the industry sector. For example, chemicals can include a tracking compound that can be traced."

CONCERN NUMBER TWO: CHINESE PARTNERS IGNORE IP LAWS AND STEAL TRADE SECRETS

China has a historical reputation for not applying IP laws and misappropriating trade secrets. According to the Office of the United States Trade Representative (USTR), enforcing IP rights in China is still a challenge, but the country is making major efforts in legal reform, including revised laws and guidelines. As Ede comments, "I've been doing business with Chinese life sciences companies for 10 years, and in my experience, they are extremely respectful of your IP and in-house knowledge under confidentiality."

However, this unfortunately isn't representative of all liaisons in China. In a 2013 survey from the American Chamber of Commerce, 26 percent of respondents reported having experienced the breach or theft of data and/or trade secrets from their operations in China.

Chinese authorities can treat trade-secret violations as commercial disputes rather than as infringements of the law, resulting in lower rates of prosecutions. Going to court over trade-secret violations may just alert rivals that there is a secret there to be protected. Because of this, prevention is better than cure.

"Companies need to have good internal procedures in place to keep trade secrets confidential, and need to be able to show that they have taken reasonable precautions," says Benjamin Liu, assis-

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CONCERN NUMBER THREE: CHINESE AUTHORITIES FAVOR DOMESTIC OVER FOREIGN COMPANIES

The USTR has raised concerns that Chinese agencies may put pressure on rights holders to transfer IP from overseas to Chinese domestic companies. Some local courts may also lean toward domestic businesses.

"Some judges may be protective of local companies," says Chen. "However, in major cities, the judges are more likely to be better-trained and less-influenced. It's important to show that you have taken reasonable precautions, and have good internal procedures to keep information confidential."

Another concern is that overseas partners won't be able to protect or even control the IP for inventions made while working in China. But as Robert Wenslow, VP of business development at Crystal Pharmatech, explains, a master service agreement should ensure that the rights and titles to all inventions are owned and controlled by the company.

CONCERN NUMBER FOUR: THERE'S NO POINT PURSUING BREACHES

Companies considering moving into China may be put off by the concern that no action will be taken over IP infringements. This is, however, one of the areas where things are improving. Litigation is becoming more common. In 2011, China filed more patent lawsuits and patent applications than the United States, and this is an increasing trend, according to Chen.

According to the USTR, rights holders have reported increases in enforcement against counterfeiting of trademarks, both via administrative and criminal routes. This is supported by the American Chamber of Commerce survey in 2013, where 47 percent of participants responded that China's enforcement of IP has improved over the last year, and 63 percent of companies that had brought infringements to court in China in 2012 were somewhat or very satisfied.

Companies that believe their IP has been breached have three different approaches — administrative, judicial, and criminal. Depending on the approach taken, the offending companies may have to pay civil damages based on the loss incurred, with injunctions to stop infringements, or may face criminal penalties. In contrast to the process in the United States, there is little or no exchange of evidence before going into court in China. It is important, however, to remember that the statute of limitations for most IP litigation is short, only two years, and that payments for damages are likely to be low.

"In the United States, companies send a warning letter if they believe there has been a threat to their IP. It's a different approach in China. Here, a warning letter can simply alert the infringers that they have been detected, giving them time to destroy any evidence," says Chen. To prevent this, it's essential to get a preliminary injunction to protect the evidence, and then show up on-site with backup from the police or other government agencies."

A WORD TO THE WISE

Companies need to integrate IP strategies and security precautions into their business strategies from the beginning, and take China's culture and legal system into account, for example, by hiring people who understand the laws in both countries. Companies working in China are advised to put a web of measures into place to prevent IP problems from occurring in the first place, starting with a solid contract.

"Contracts need to be unambiguous — they should include specifics like ownership rights and damages, and any agreement should be more than just a handshake," says Liu.

Security is key in IP protection, and companies from outside China need to ensure that their potential Chinese partners have effective protection in place. One of the next steps is to ask about security policies and carry out due diligence, according to Wenslow. "If a company is serious, it will have safeguards in place. You need to be confident that your Chinese partner will pursue any offenders."

Forms of physical security for the labs can include fingerprint access and CCTV in laboratories; banning use of USB drives; creating secure routes to transfer information, such as virtual data rooms; and encryption of all digital files. Companies can choose to keep information in different locations, or even only use less-critical technologies when working in China.

"Companies that install these measures in existing or new labs put themselves in a better position to serve their customers," says Wenslow.

Agreements with staff are also key to keeping information confidential. Employees' contracts should include a clause stating that any intellectual property violations will result in immediate termination of employment and prosecution under law.

"If you have concerns about your IP in China, then a good starting point would be to draw up a nondisclosure agreement in both English and Chinese to be executed and sealed," says Ede.

Relationships are always important, though, as Ede explains: "In any form of business, relationship building is critical. I would recommend that if you have partners overseas, you jump on a plane and try to have as much face-to-face time with them as possible," says Ede.

SO, IS IT WORTH IT?

Is it worth going through the process to create IP protection in China? Ede seems to think so. "In my opinion, it's not difficult to apply for a Chinese patent. In terms of our product Linguet, it was important to be a player in a large market like China because it is one of the biggest users of pharma drugs worldwide," says Ede.

As Chen sums up, "Take precautions — but remember that if you don't go to China, your competitor might!"

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Should Your Outsourcing Model Be Functional, Full-Service, Or A Hybrid FSP?

Clinical outsourcing is constantly changing as drug companies seek new ways of working faster, leaner, and to higher standards. This is causing sponsors to reexamine their outsourcing options, consider different models, and challenge traditional approaches.

Traditional outsourcing models are familiar. Full-service models outsource all (or most) functions of an entire project, typically including trial conduct, oversight, data collection, analysis, and reporting. Functional outsourcing (FSP) models outsource an entire function across a portfolio of projects, such as clinical monitoring, data management, or statistics.

More recently, "strategic partnerships" have emerged. These partnerships evolved traditional, full-service models from a tactical, project-focused arrangement, to a relationship and volume-driven approach focused on a drug development portfolio. CROs are invited to take more ownership and risk and are rewarded with higher revenue and greater flexibility in their approach. Many in the industry believed that such partnership models would lead to the demise of functional outsourcing, with the Pfizer move from FSP to strategic outsourcing signaling the beginning of the end for the FSP model.

However, functional outsourcing is enjoying a resurgence in popularity as both an option within strategic partnership arrangements and as a viable option to full-service strategic models. Indeed, there is visible movement toward hybrid FSP models which seek to take the best of both full-service and functional models with a view to building custom solutions on a sponsor-specific basis.

WHAT DETERMINES A SUITABLE OUTSOURCING MODEL FOR YOUR ORGANIZATION?

Functional models tend to appeal to companies that wish to retain a high degree of control over project delivery, while full-service models have appealed to companies that need access to expertise, technology, and leadership.

In fact, the drive to control progress and ensure effective oversight has led many companies to build duplicate internal organizations to oversee the activities of CROs deploying traditional full-service models. When outsourcers agree on outcomes-based measures of success, require significant external support and expertise on key therapeutic areas of regulatory advice, and have a trusted CRO partner, then full-service outsourcing (tactical or strategic partnerships) makes sense. CROs are experts at managing and delivering projects, particularly when they are given the flexibility and autonomy to be innovative, thereby utilizing their internal resources optimally.

But when control and oversight are imperative for the sponsor, internal access to expertise is already available, systems and processes are already in place, and the sponsor seeks a lower-cost solution, functional models can provide the level of resourcing flexibility and efficiency that can best suit the outsourcer. The sponsor can create an extension of its own organization, maintaining control of project management, technology, and all processes related to the trial. A well-functioning FSP operates as a natural extension of the sponsor — the arms and legs, where the heart and mind reside within the sponsor's organization, thereby eliminating duplication. Scale of portfolio of work will also influence model choice. It likely does not work for either the sponsor or CRO to create functional models (where efficiency comes from scale) for a single outsourced project. Traditional wisdom tended to treat these models as binary, implying (with some exceptions) that clients were FSPs or full-service outsourcers. But increasingly the norms of these models are being challenged.

Colin Stanley

Colin Stanley is president of DOCS. He has over 14 years of experience working in the CRO industry. He joined ICON as a project manager in 2001 and has since held a range of positions of increasing responsibility.

A HYBRID FSP APPROACH

Both models outlined have advantages. But what if a sponsor's requirements are not quite as simplistic or binary? Recent discussions point to a growing wish to utilize the best of both worlds. Some clients want the control, transparency, and flexibility of a functional model, but they also want access to SOPs, technology, and the expertise of a full-service model. They want to pare down costs to reflect a lean, resourcing-focused solution, but they are prepared to layer in the costs associated with technology, process input, and thought leadership. They seek the scalability of FSP combined with the focus of traditional full-service models.

The critical success factor is in the design and support of the hybrid FSP solution. This design requires a solid global CRO infrastructure and a background in FSP delivery. It may also require significant customization. FSPs act as an extension of the sponsor's organization, so no two FSPs are exactly alike.

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Mitigate Risk With Package Quality

In the life sciences industry, quality is the drumbeat for profitability. Most quality initiatives are passive and driven by organizational jargon. How about real progressive change for once? Package testing and container closure integrity are cornerstones for quality. Without a quality package, there is no product. In fact, a bad package is a serious liability. Product that may be assumed good will fall short of end-use requirements, will be exposed to contaminants, and is a common cause for regulatory action. When developing new products, clarity around package quality control can better define the process requirements and set the stage for successful product launch and profitability throughout the product life cycle.

Now more than ever, innovative package designs are being used to differentiate and simplify pharmaceutical product delivery and end use. With new designs come new challenges to validate package stability and performance. A product development team must understand very clearly what level of package failure is critical to the quality of the product over the duration of the product's shelf life. Key questions to ask include, "At what point does my package stop working?" "At what point does my barrier fail to fulfill its purpose?"

When assuring package quality, you must understand what quality actually means for your package system and product. Quality is often defined as whether or not the package has maintained a sterile barrier or has been breached.

Answer these two guiding questions when defining package quality for your specific application. (1) What is critical to the quality of the product? (2) What is critical to the package and delivery system that may affect the quality of the product? For a parenteral closure system it can be quite simple — leaks below 10 micrometers in diameter still pose a significant risk to product sterility. For medical devices the answer is far more complex. A balance of risk assessment and best-available technology usually prevails when defining quality.

FOLLOW THE DMAIC PROCESS FOR QUALITY

In following the Six Sigma DMAIC process, once quality is defined (D), it should be measured (M). Measurement can be subdivided into categories: subjective/objective, qualitative/quantitative, continuous/discrete/attribute data. The life sciences industry is experiencing a significant shift away from the qualitative methods requiring human intervention. Quantitative and more automated test solutions are taking over as quality control solutions due to the reliability and accuracy of information. In today's market where we battle to find the smallest microbes and assure the sterility of product at the highest confidence levels, the answers lie in accurate and precise quantitative data.

Sensory technologies continue to improve. New test-method designs are continuing to evolve, finding ways to challenge similar quality standards but with better precision and accuracy. A method that may have been implemented a decade ago with mediocre success may have matured in capability and reduced in capital cost. Technologies are now available that can pinpoint the location of micron-size defects on parenteral vials and prefilled syringes nondestructively.

Analysis (A) is used every time an audit occurs, by internal QA or external regulatory agency. During an FDA audit, handing over accurate quantitative assessments of the package and delivery system is far more powerful than a clipboard with handwritten notes and a signature. Quantitative data will provide the manufacturing team a high level of confidence when managing quality deviations or when defending the quality standards by which they stand.

Invest the time to define quality, and then investigate different quantitative and objective measures of quality. Improving (I) the process involves having the right technologies that are focused on measuring the quality of the package and the product. Today's sensory technologies increase sampling capabilities, and quantitative methods improve access to data mining and analysis.

Control (C), the final stage of the DMAIC process, relies on the foundation of the first two steps. If you invest the time to define quality (D), you understand what you need to measure. If you implement an objective quantitative measure of quality (M), you will eventually achieve an optimal state of quality control.

Oliver Stauffer

Oliver Stauffer is VP/COO of PTI Packaging Technologies & Inspection. Prior to joining PTI in 2005 he worked for several years in analytical and R&D laboratories. His expertise and focus has primarily been new sensory technologies and test method development specific to package testing.

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Cultivate The "I Trust You" Style of Management

John Baldoni

Don't make me think about it!

That was some advice an executive I know shared with one of his direct reports. The executive was not being flippant; he was letting his junior colleague know that he wanted him to come with well-thought-out plans of action. He was delegating decision making to his subordinate and wanted this individual to pick up the ball and run with it.

Such advice is the opposite of micro-management, call it "I trust you" management, and it is something that all executives need to instill in their people. Otherwise, executives get bogged down in too much detail and essentially manage beneath their level. When that happens, why do you need a subordinate if you are doing the thinking and the doing?

Pascal wrote, "Man's greatness lies in his power of thought." So how can you cultivate the "I trust you" management style? Here are some guidelines.

Spade the ground. Not all subordinates are ready to think and do on their own. They need to be competent in their job first and foremost. They also have to be seasoned enough to know how the organization works, specifically what the boss likes and dislikes. They must also know the culture and respect the values of the organization.

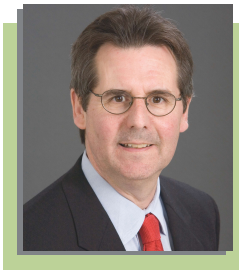
Set clear expectations. Make it known that thinking for oneself involves more "what" than "how." Give subordinates the freedom to experiment and to come up with their own way of doing it. Let them be creative in their approach.

Keep in the loop, not out of it. Execution requires the boss' involvement, if only to be kept informed. Let people know you will be checking, not because you distrust them but because you want to know how things are going. This is especially critical when situations change and the scope of a job or task shifts.

Insist on a debriefing session. Holding a "lessons learned" meeting after the first couple of assignments is important. Let the direct reports share what they experienced and how they would do things differently — if at all — the next time. Feel free to chime in and share your observations, too. Consider such events as "teachable moments."

There are limitations to this advice. If a subordinate does all the thinking and acting, then why keep the boss? Executives in charge need to focus on big-picture topics, and that is where they need to apply time and reflection, as well as energy and enthusiasm.

From the subordinate's point of view, thinking for your boss is essential to influencing upward. It is an opportunity to share your ideas as well as to develop ways to execute them. Individuals who capitalize on this make themselves ready for greater levels of responsibility. And that's good for the individual and the boss!



John Baldoni is an internationally recognized leadership development consultant, executive coach, author, and speaker. In 2010, Top Leadership Gurus named John one of the world's top 25 leadership experts. John's newest book is *12 Steps to Power Presence: How to Assert Your Authority to Lead*. www.johnbaldoni.com.

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