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John Maraganore, Ph.D., CEO
Alnylam Pharmaceuticals

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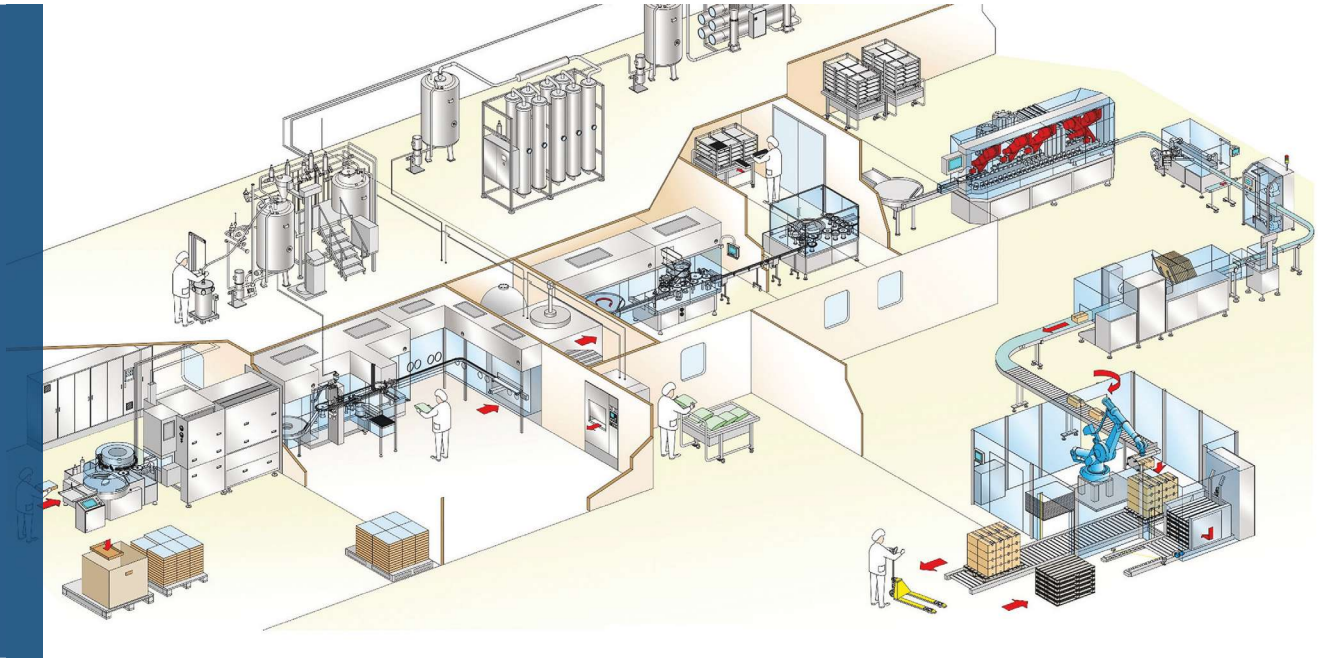

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24 FEATURE: ALNYLAM

"Partnerships are critical to any new company getting started. However, if you end up giving away a scope of rights that might be a significant proportion of the future of your company — that becomes the most dilutive form of capital there is," says Alnylam CEO John Maraganore, Ph.D.

May 2013

DEPARTMENTS

CORRECTION: In the April issue, the author of "New Approaches To Vaccine Manufacturing" on page 70 should have been Olivier Loelliot, not as given.

Welcome to *Life Science Leader*

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MAY 2013

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EDITOR'S NOTE

Thanks For Being Part Of Our Success

In February I received a book in the mail with this personalized note written on the inside cover, "2/23/13 To Rob, Thanks for being part of my success. Fred." The book, *Reinvent – A Leader's Playbook For Serial Success*, by Fred Hassan, was mailed to me by the author. Last month at the 2013 Pharmaceutical Research and Manufacturers of America's (PhRMA) annual meeting in San Diego, I had the opportunity to return the favor and thank Fred for being part of *Life Science Leader's* success. Fred was featured in our April 2011 issue, and a few months later we asked him for a favor — could he connect us with Carrie Cox, a former member of his leadership team at Schering-Plough who had since become the CEO of Humacyte? He obliged, and we were able to feature Carrie on the cover of our June 2011 issue along with Maxine Gowen, CEO of Trevena. Over the years, we have periodically reached out to Fred, and he has graciously helped us — never once asking what's in it for him. Given that he was already helping us, I thought it only appropriate to invite him to become a member of our editorial advisory board. I am pleased to announce that he has accepted. We are thrilled to have Fred's wealth of wisdom and experience as an asset to guide *Life Science Leader* to new heights.

One of Fred's messages is to be authentic. I think this is an important point. Since the establishment of *Life Science Leader's* editorial advisory board, I have called on members to provide answers to reader-submitted questions for what has become a very popular monthly feature — "Ask The Board" (page 8). Editorial advisory board members have graciously complied, and I have called on them to connect me with other key opinion leaders, participate in roundtable articles, and help me create questions for interviews and panels/discussions I moderate. Not long ago I received a letter from one of our board members, Carol Nacy, Ph.D., the CEO of Sequella. In her letter, she wrote, "I don't say this often, or at all to any scientific journal I work with, but I can say to you that it is a pleasure to be on the editorial advisory board of *Life Science Leader*." Another editorial advisory board member, Mitch Katz, Ph.D., executive director for Purdue Pharma, stated in a letter dated Jan. 28, 2013, "I attribute the quality of the magazine to your outreach and your efforts to get out into the field to learn about topics relevant to and across the pharmaceutical industry." John Hubbard, Ph.D, SVP worldwide development operations for Pfizer, stated in a letter last year, "Thank you for your efforts to provide us with an excellent magazine." Ron Cohen, M.D., is the CEO of Acorda Therapeutics and a recent addition to our editorial advisory board. In a letter this past February, Ron wrote, "I am pleased to join the editorial board of *Life Science Leader* and look forward to contributing content that will appear beside the high-quality articles that regularly appear in each issue."

Let me be clear — the pleasure is *all mine*. The chief editor gets a lot of credit, which is really the result of being surrounded by an engaged editorial advisory board, a talented staff of contributing editors, exceptional publishers, and you, our readers. Thanks for being a part of our success.

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CHIEF EDITOR'S BLOG

Want to find out what's on the mind of our Chief Editor, Rob Wright? Check out his blog on our website where he writes about a variety of topics such as recent shows attended, conversations with industry experts, and irritating business buzzwords. And don't forget about your opportunity to pick the brains of our editorial board. Send your questions for our monthly "Ask the Board" section to atb@lifescienceconnect.com.

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ASK THE BOARD

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

Q: What is your opinion on the biosimilars provision within the ACA?

The Biologics Price Competition and Innovation Act, which is part of the Patient Protection and Affordable Care Act (ACA), created a pathway for the approval of biosimilars that will help ensure the U.S. biotech community's continued development of innovative lifesaving therapies and cures while encouraging competition to lower costs and expand patient access. BIO strongly supported passage of this provision and will continue to work with the FDA to implement it in a way that will ensure patient safety, recognize scientific differences between drugs and biologics, maintain the physician-patient relationship, and preserve incentives for innovation. The final regulatory structure for biosimilars must include mechanisms to allow for robust postmarketing data collection and evaluation along with unique trade and nonproprietary names, so that safety issues can be recognized quickly and patient risk can be limited.

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: Why do you believe U.S. pharma manufacturing facilities have been slow to adopt blow-fill-seal (BFS) technology?

Beyond validation, stability studies, equipment changes, and the comfort of many years of experience with glass containers, there are other technical barriers to overcome to enable the change to BFS. For instance, the inability to inspect the final product for defects, the potential for product/container interactions (product engineered for storage in glass may need to be re-engineered for storage in plastic), and extractables, leachables, and potential particle shedding are additional considerations for delivering a safe product to the patient. So far, these obstacles have been too significant for an appropriately conservative industry to overcome as the current approach for sterile injectables is safe and effective. Yet, when someone does develop a path to this technology for sterile injectable products, they will benefit from a significant cost savings in every dose they make.

James Robinson
Robinson is the VP for vaccine and biologics technical operations for Merck. He supports the manufacturing strategy, process development, technical transfer, approval, and production of Merck's vaccines and biologicals.

Q: Why do we need mixed-mode chromatography media?

Mixed-mode resins take advantage of two types of interactions simultaneously, such as ion exchange and hydrophobic interaction, ion exchange and metal affinity, and so on. A single mixed-mode resin step might in theory, therefore, replace two chromatographic steps in a process. Alternatively, the novel mixed-mode ligands also can provide for new selectivities during purification. Both can lead to reduced purification costs. The use of mixed-mode resins is increasing because, as different types of proteins begin to enter the development pipeline, new selectivities are required to tackle purification challenges. This is especially true with nonplatform IgG-based drugs (i.e. diabodies, minibodies, etc.), other immune-based therapies (IgMs), and other recombinant proteins. Working with mixed-mode resins is straightforward if one understands the forces at play. Users must know that each mixed-mode resin is different. For best results in terms of purification performance and especially for process robustness, one must screen several resins to find the best choice for the challenge at hand.

Mark Snyder, Ph.D.
Snyder is manager of the process R&D applications group in the Process Chromatography Division of Bio-Rad Laboratories. He spent five years at Scios (then California Biotechnology) followed by four years as manager of process development at XOMA.

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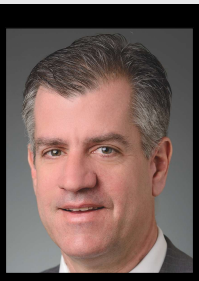
The 340B Discount Program Is In Dire Need Of Reform

How does a program created to assist low-income, uninsured patients with their drug costs become a boondoggle worth millions of dollars to well-financed university hospitals that serve few indigent or uninsured patients? That's what a congressional investigation led by Senator Chuck Grassley (R-IA), ranking member of the Judiciary Committee, wants to know.

Senator Grassley discovered that, last year, under the so-called "340B program," Duke University Hospital was able to pocket a $48.3 million profit from outpatient drugs it sold to primarily privately insured patients. Two-thirds of Duke's patients are privately insured, and only 5% are uninsured. Yet Duke received statutorily mandated discounts on all the outpatient drugs it provided to all of its patients regardless of whether they were insured or not. In other words, it then sells those drugs to insured patients at a substantial markup. Interestingly, Duke provided just $35 million in charity care —- or substantially less than the revenue it amassed under the 340B program, even though it is characterized as a nonprofit and exempt from taxes.



John McManus, The McManus Group

Duke University hospital's exploitation of the 340B program is not an isolated incident. It represents the norm. And it is perfectly legal, though clearly not at all appropriate.

A little more than two decades ago, Congress enacted a program called 340B to require pharmaceutical manufacturers to provide discounted drugs to "safety-net" public health clinics serving uninsured and low-income patients and certain not-for-profit, disproportionate share hospitals (DSHs). Ironically, the DSH formula doesn't measure charity care but instead measures how many Medicaid- and Medicare-insured in-patients the hospital treats. Manufacturers are required to provide discounts equal to the Medicaid rebate to these qualified entities. These discounts vary across products but average about 45%, and for some products they are so substantial that the hospital actually acquires the drug for a penny!

For years the program garnered little attention, but its recent explosive growth has sparked congressional interest. A Government Accountability Office (GAO) report issued in 2011 found that the Health Resources Service Administration (HRSA), which administers the program, provided little oversight. GAO discovered that HRSA had never performed an audit, relied on self-policing by 340B participants, and failed to periodically confirm eligibility for all covered entities or even inquire whether they have a system in place to prevent diversion.

With the help of private vendors seeking to exploit the price delta between the statutorily mandated discount prices and market prices of expensive new chemotherapy drugs, the 340B program exploded in the last half of the last decade. Indeed, between 2005 and 2011, the number of qualified entities tripled from 591 to 1,673, and the number of hospital sites quadrupled. Today, about one-third of all hospitals participate.

Healthcare reform will result in even greater expansion of the program because the number of Medicaid patients a hospital serves is a key criterion for triggering 340B eligibility. As health reform is projected to increase Medicaid enrollment by about 50%, the number of hospitals that can qualify for 340B status will multiply. This raises a curious question: If healthcare reform produces more insured patients, shouldn't a program intended to assist the uninsured shrink commensurately, not grow commensurately?

In addition, hospitals and other entities that had already received the 340B designation also benefited from an unrelated negotiation in the bill. When the pharmaceutical industry agreed to a 53% hike of the minimum Medicaid rebate to help finance health reform (increasing it from 15.1% to 23.1%), 340B hospitals enjoyed a windfall in steeper discounts because those discounts are tied to the size of the Medicaid rebate.

CONTRACT PHARMACIES = BIG PROBLEM

But a more troubling development in the 340B program has been the proliferation of "contract pharmacies" that service 340B hospitals. In the early 1990s HRSA only allowed for a single contract pharmacy for clinics that didn't have their own pharmacy services. Then, in 2010 HRSA issued guidance to permit covered 340B entities to provide drugs through an unlimited number of contract pharmacies with no geographic proximity requirement. GAO found that by July 2011, there were 7,000 contract pharmacy arrangements and an unknown (i.e. substantially greater) number of contract pharmacies. This sent contract pharmacy volume skyrocketing from $75 million in 2010 to $436 million in 2011 and projections heading for $3.6 billion in 2016. Large chain-drug pharmacies are now actively sharing in the "spread" of profits with

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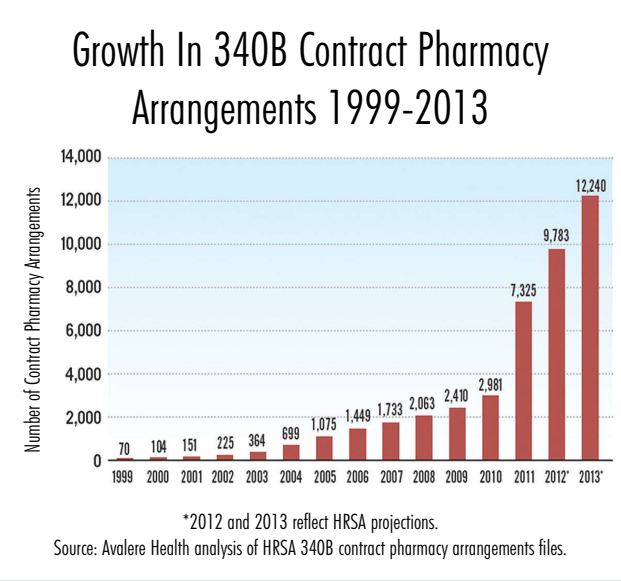
340B hospitals between the prices they sell the drugs to patients and the discounts they obtain from the program.

In addition, 340B hospitals have stretched the definition of "patient." GAO expressed concern that many 340B hospitals were determining individuals eligible for 340B discounts who were only loosely affiliated with the institution and not actually receiving care there. Certain 340B hospitals have even argued that their own employees should qualify as eligible patients.

It should be no surprise that the Berkeley Research Group, which conducted an in-depth analysis of the program, projects drug purchases under the 340B program will double from $6 billion in 2010 to $12 billion in 2016, and the estimated discounts will escalate from $2.2 billion to $4.4 billion in the same period. Keep in mind: The discounts were just $1 billion in 2005.



*2012 and 2013 reflect HRSA projections.
Source: Avalere Health analysis of HRSA 340B contract pharmacy arrangements files.

Of course, program expansion of this magnitude will have substantial economic and policy ramifications. Community oncology clinics are finding it increasingly challenging to compete with 340B hospitals and their multiple contract pharmacies. This is particularly troubling, because as documented in Steven Brill's insightful *Time* magazine piece, "Why Medical Bills are Killing Us," hospitals have already consolidated market share in many communities, allowing them to demand huge markups from commercial insurers. The 340B program exacerbates this consolidation and anticompetitive behavior.

Certain Medicare Advantage plans now require their patients to obtain their prescriptions at select 340B hospitals that may require hours of driving even though community clinics are available in their area. Nondiscrimination rules under the 340B program prohibit manufacturers from withholding product from 340B entities, and their stockpiling of product has often resulted in drug shortages to community clinics.

WHAT SHOULD BE DONE?

First, greater transparency is required. The 340B hospitals and other participants should be required to disclose the extent of the discounts they receive and what patients (privately insured, Medicare beneficiaries, and the uninsured) are receiving those drugs. The disclosure should include whether the discounts were passed on to the consumer and how hospitals are using the resources they've garnered ostensibly to assist poor and uninsured patients. Senator Grassley's investigation is just the tip of the iceberg.

Second, Congress should return the program to its original intent. Discounts should not flow to all patients of eligible 340B entities. Rather, the discounts should flow to the patients who need assistance —- the poor and uninsured who receive care at those entities. There simply is no justifiable policy argument for a government program that enables hospitals to produce massive profits on the backs of Medicare beneficiaries for care financed by the taxpayers and our seniors.

This will require real inventory management by hospitals to parse discounted drugs for eligible patients from market-priced drugs for those with healthcare coverage. It will also require greater accountability of 340B hospitals. But if they are going to claim they are nonprofit and forgo paying taxes because they service the community, Congress should ensure that the indigent uninsured patients in the community actually benefit from this drug-discount program.

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.

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By Wayne Koberstein

Immune Pharmaceuticals

A midmerger study of perseverance and survival in a tough life sciences world

SNAPSHOT

Immune Pharmaceuticals is a renewed and broader company as the result of its merger with EpiCept, which is working its way toward a shareholder vote. The merger arose as the answer to EpiCept's financial struggles and to Immune's need for a wider portfolio of products to balance its ambitious development program for its main compound, bertilimumab. Licensed from iCo Therapeutics soon after Immune's founding in 2010, bertilimumab could prove to be one of the industry's most versatile drugs, if the extensive lineup of clinical trials pans out. Immune is targeting indications for bertilimumab in cancer, ulcerative colitis, asthma, and other inflammatory diseases. Its antibody-conjugate NanomAbs platform is in preclinical development for cancer. EpiCept's pipeline, including "vascular disruptive agents" and a cancer-related pain medication, AmiKet (amitriptyline/ketamine), give Immune a wider window into oncology.

Daniel Teper, CEO

LATEST UPDATES

- Received approval from Israel Ministry of Health to initiate Phase 2 trial with bertilimumab in ulcerative colitis (March 2013).
- Closing of EpiCept merger and related financing expected for June 2013.

WHAT'S AT STAKE

One apparently unique aspect of the initially Israel-based Immune Pharmaceuticals is that it started as a business rather than a research arm. Its model is based on in-licensing and product development rather than internal discovery and development. Its entire portfolio reflects that model. "Immune's strategy is to build a biopharmaceutical company with critical mass in a capital-efficient way — in a shorter time frame and with an improved risk/reward for investors," says CEO Daniel Teper. He says Immune's total burn since its inception in 2010 is only $8 million, including nonequity financing and cost of acquisitions. But its history, including the recent merger with EpiCept, also illustrates the sometimes complex maneuvers entrepreneurial life sciences companies must take to survive and grow.

Struggles and higher aims for the companies on both sides of the merger made the union all the more essential. Most publicly, EpiCept had suffered through a stalled regulatory review in the United States of a product already approved in Europe. Its cancer drug Ceplene (histamine dihydrochloride), cleared by the EMEA in 2008 for acute myeloid leukemia (AML) remission maintenance, ran into a crisis at the FDA following post-approval trial failures by Avastin and other products; without notice, the agency decided it would accept only overall survival (OS), not progression-free survival (PFS) data for cancer drug approvals. Trial endpoints for Ceplene were PFS, not OS. Licensed to Swedish Meda Pharmaceuticals, Ceplene's Euro sales stagnated. EpiCept's market cap fell, and it faced difficulty raising money. Similarly, Immune wanted to boost its money-raising capability, chiefly in the United States, as well as its pipeline. EpiCept offered a way to both ends, and thus the needs and strengths of the two companies were complementary.

"The rationale for the EpiCept merger is faster access to U.S. public capital markets through a merger between two operational companies, allowing for up-listing to a U.S. national and more liquid market such as NASDAQ or NYSE," says Teper. Such funds will be essential to fuel Immune's ambitious development programs for bertilimumab, the NanomAbs platform, and EpiCept's contributions, including the chemo-related pain drug AmiKet.

It is always fascinating to capture a view of a company in mid-merger — admittedly, a big part of Immune's appeal at this point. But the larger lessons go beyond finding a complementary merger partner and speak to the survival of the life sciences species. Creativity and innovation in this industry are not confined to science. Immune's product acquisition model may actually make more sense than starting a new business from the laboratory bench. Sometimes a company may have a better shot at success when the business starts first with a therapeutic focus, then finds the science.

VITAL STATISTICS

- Employees: 14
- Headquarters: Herzliya-Pituach, Israel, and New York
- Finances: over $5 million in equity financing (high net worth individuals and family offices); $1 million in U.S. and Israeli grants; signed definitive agreement on Nov. 8, 2012, to merge with EpiCept (NASDAQ Nordic, OTC QX: EPCT)
- Research partnership funding: Hebrew University of Jerusalem: Immune is funding up to $1.8 million of research over several years on Antibody Nanoparticle Conjugates (NanomAbs).

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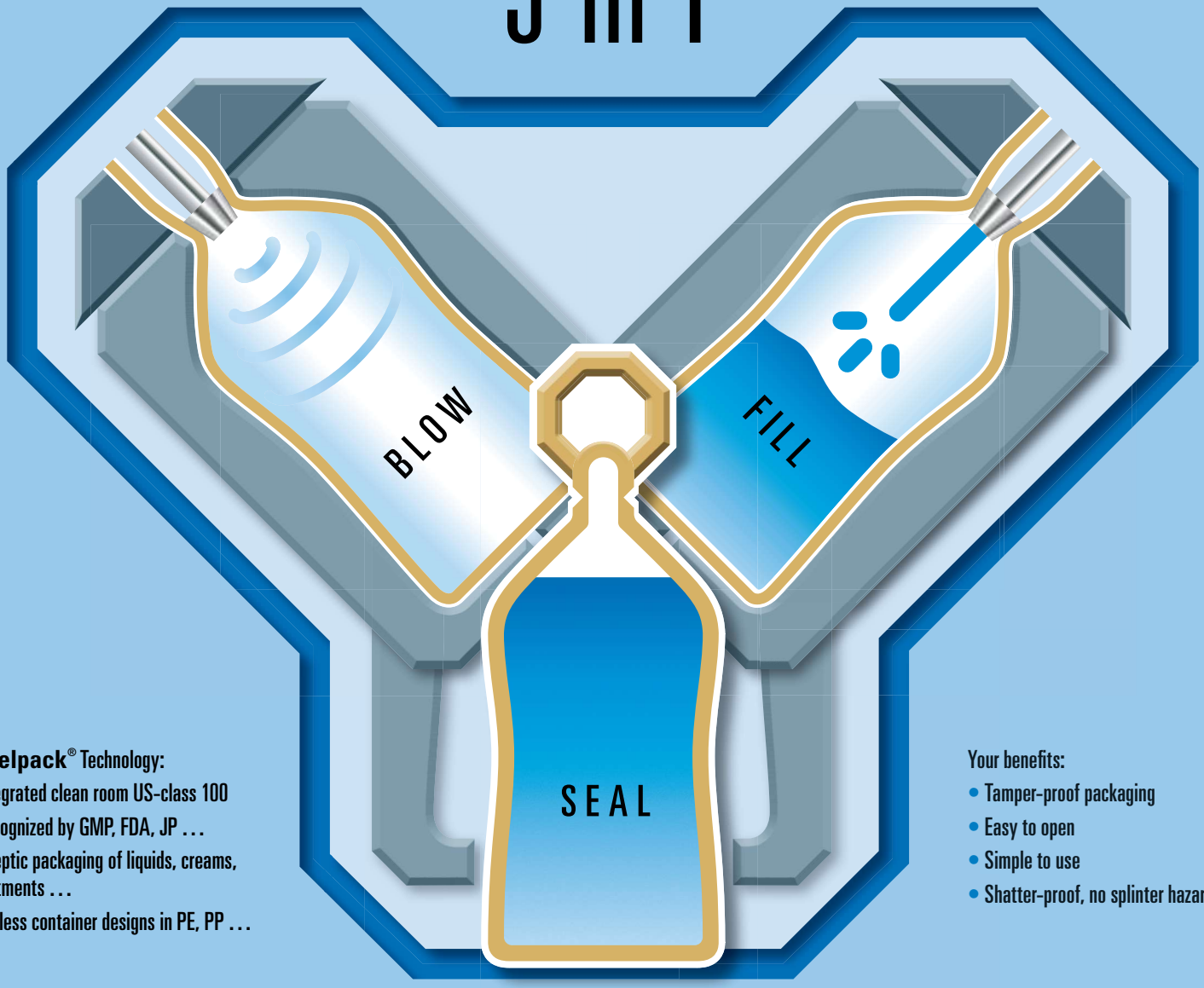

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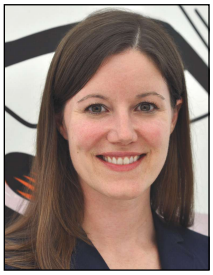

OUTSOURCING INSIGHTS

Increased Demand For Vaccines Will Continue To Benefit CMOs

By Kate Hammeke, director of marketing intelligence, Nice Insight

At a time of year when flu season is usually winding down, news of a new form of bird flu has emanated from China. The strain was identified as H7N9, which had not been found in humans before. However, it took the lives of two Shanghai residents in late March. Initially, H7N9 was thought to be a low-pathogenic strain that was not easily transmitted between humans. But an expert from WHO has now expressed concern that the strain does show signs of mammalian adaptation. This news reminds us all too painfully of the recent swine flu pandemic, which killed 284,500 people in 2009 according to the Centers for Disease Control and that the possibility of a global pandemic is real.

This news came after a particularly rough flu season, where increased demand for the flu vaccine created spot shortages across the United States. According to industry research released by Kalorama Information, the vaccine market has grown from $5.7 billion 10 years ago to exceed $27 billion currently. Increased global demand for the influenza vaccine has contributed significantly to this growth because the vaccine does not offer long-term immunity and must therefore be administered annually.

Each year, infectious disease monitoring organizations worldwide coordinate with vaccine manufacturers, fill/finish suppliers, distributors, and healthcare practitioners to try to ensure the parameters are in place to meet demand. The large market for the influenza vaccine brings two key vaccine production issues to the forefront — time-to-market and cost.

VACCINE CONTRACT MANUFACTURING MARKET GROWING

Improving time-to-market and reducing costs consistently rank among the top three reasons behind decisions to outsource work to a CMO (alongside improved quality). While vaccine production has historically been retained in-house for quality control and regulatory reasons, the evolving nature of outsourcing — from an ad hoc basis to more long-term partnerships — means it is highly likely we will see growth in outsourced vaccine manufacturing. Current predictions estimate the vaccine contract manufacturing market will reach $620 million by 2015.

In reviewing the data from Nice Insight's pharmaceutical and biotechnology outsourcing survey, we looked at how CMOs offering vaccine manufacturing scored on productivity as it relates to improved time to market and affordability, since decreasing manufacturing costs can positively impact product price. Two companies scored in the top five for both productivity and affordability — GSK Biopharmaceuticals (76% and 71%) and OSO BioPharmaceuticals (75% and 71%).

The remaining CMOs to rank in the top five for productivity were Fujifilm Diosynth Biotechnologies (80%) — the only company to receive an "excellent" score in productivity — Althea Technologies (78%), and BioReliance (75%). For affordability, Cytovance Biologics (73%), Cook Pharmica (71%), and IDT Biologika (71%) joined GSK Biopharmaceuticals and OSO Bio in the top five providers. It is important to note that GSK Biopharmaceuticals was the only company to rank in the top five for quality in addition to productivity and affordability. However, the companies that ranked highest in productivity and affordability tended to score above the benchmark in quality, meaning these businesses still performed above average among their competitors.

Interestingly, there were no strong patterns across the 20 CMOs included in this analysis. Twelve different companies comprise the top-five lists for each of the six outsourcing drivers, with only one company scoring among the top five across all six categories — GSK Biopharmaceuticals. As such, finding the right CMO for a specific project will vary depending on factors specific to the vaccine.

In the case of the influenza vaccine, improved time-to-market and affordability are key to reaching a large population on an annual basis. Another benefit of CMOs adding vaccine production is increased capacity, which will reduce the potential for vaccine shortages, including those caused by the need to shift production of seasonal flu vaccines to the manufacture of vaccines for new threats like the H7N9 bird flu.

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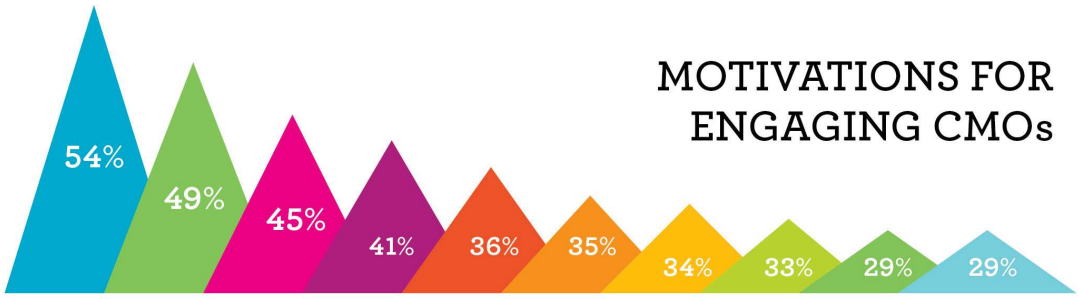

Top 5 Companies in Quality

76%	GlaxoSmithKline Biopharmaceuticals
75%	Novasep
75%	CMC Biologics
74%	Paragon Bioservices
74%	Catalent Pharma Solutions

Top 5 Companies in Productivity

80%	Fujifilm Diosynth Biotechnologies
78%	Althea Technologies
76%	GlaxoSmithKline Biopharmaceuticals
75%	OSO BioPharmaceuticals Manufacturing
75%	BioReliance

Top 5 Companies in Affordability

73%	Cytovance Biologics
71%	GlaxoSmithKline Biopharmaceuticals
71%	OSO BioPharmaceuticals Manufacturing
71%	Cook Pharmica
71%	IDT Biologika

Survey Methodology: The Nice Insight Pharmaceutical and Biotechnology Survey is deployed to outsourcing-facing pharmaceutical and biotechnology executives on an annual basis. The 2012 sample size is 10,036 respondents. The survey is composed of 500+ questions and randomly presents ~30 questions to each respondent in order to collect baseline information with respect to customer awareness and customer perceptions on 170 companies that service the drug development cycle. More than 800 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 about 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

Disposable-Sensor Innovation Needed

Even basic sensing technology is in demand.

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

New single-use technologies are seeing greater adoption beyond preclinical and clinical applications and into commercial-scale manufacturing. As biomanufacturers attempt to keep up with the steady increase in expression yields and improve the management of their processes, more — and better — sensors and control equipment are being demanded. The need for single-use bioprocessing sensors and probes is increasing, as process monitoring and automation pushes their adoption. Comparatively few of these single-use products are currently available, and there are often issues regarding utility, standardization, and connectivity. Even aspects like ports and how to pass disposable sensors through bioreactors and bag liners need improvement.

In our 10th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production, we measured current interest and prior trends in disposable probes and sensors. When we asked global biomanufacturers to identify the areas where they are demanding new product development (in all bioprocessing), nearly 40% in 2013 indicated probes and sensors. In fact, disposable probes and sensors are the second-most in-demand innovation behind disposable bags and connectors.

When we break down the responses, we find that disposable probes and sensors are much more desired this year by biotherapeutic developers (41.3%) than CMOs (27.8%). On a regional basis, U.S. respondents have become more interested in innovation in this area (46.5% this year vs. 41.3% last year), while Europeans are slightly less interested (31.4% this year). Respondents from other countries around the world, who last year displayed limited desire for innovation in disposable probes and sensors, are catching up this year, up 10% points to 26.1%. This could be another indication of developing countries' need for bioproduction using single-use technologies.

DIGGING DEEPER: SIMPLE SENSORS ARE MOST CRITICAL

To look further into the need for improved single-use sensors, we asked respondents to identify which, out of a list of 12, they would like to see introduced or improved. We found that the most critically needed device is for measuring pH in single-use applications, noted by 71% of respondents. A majority of respondents also indicated that they are seeking innovation in dissolved oxygen (61%) and cell density (52%) sensors.

Interest in innovation was fairly high across much of the list of sensors we provided. About 4 in 10 respondents indicated that they would like to see the introduction or improvement of the following sensors: CO^2, glucose, in-line titer, cell viability, temperature, and conductivity. Although growing rapidly, relatively fewer users of TOC and flow sensors showed interest in greater innovation.

Looking at trends on a year-over-year basis, we see that interest in assays overall is growing at a rapid clip. Of the 12 sensors we identified, 9 saw increases in demand this year. CO^2 topped the list in terms of growth in interest, 47% this year, up from 38% last year. The most notable increases include:

- CO^2
- temperature
- UV
- TOC
- flow

It's worthwhile to note that some of the biggest gains came for sensors that were low on the list last year. With at least 50% of respondents already clamoring for sensors such as pH and dissolved oxygen, increased interest for such products are likely to be more muted. But the jumps for those on the lower rungs suggests that demand for improved sensors is broad, and innovations in a number of these might find ready markets.

WHAT'S NEXT FOR DISPOSABLES IN BIOMANUFACTURING

Measuring and monitoring production processes is critical in biomanufacturing. Today, however, many of the common devices used to manufacture biologics in stainless-steel, fixed facilities do not always translate well into single-use systems. The need to avoid product contact and reduce the risk of product contamination is critical to designing a fully disposable operation.

We do see indications that the industry's suppliers and innovators are investing in research to improve versions of

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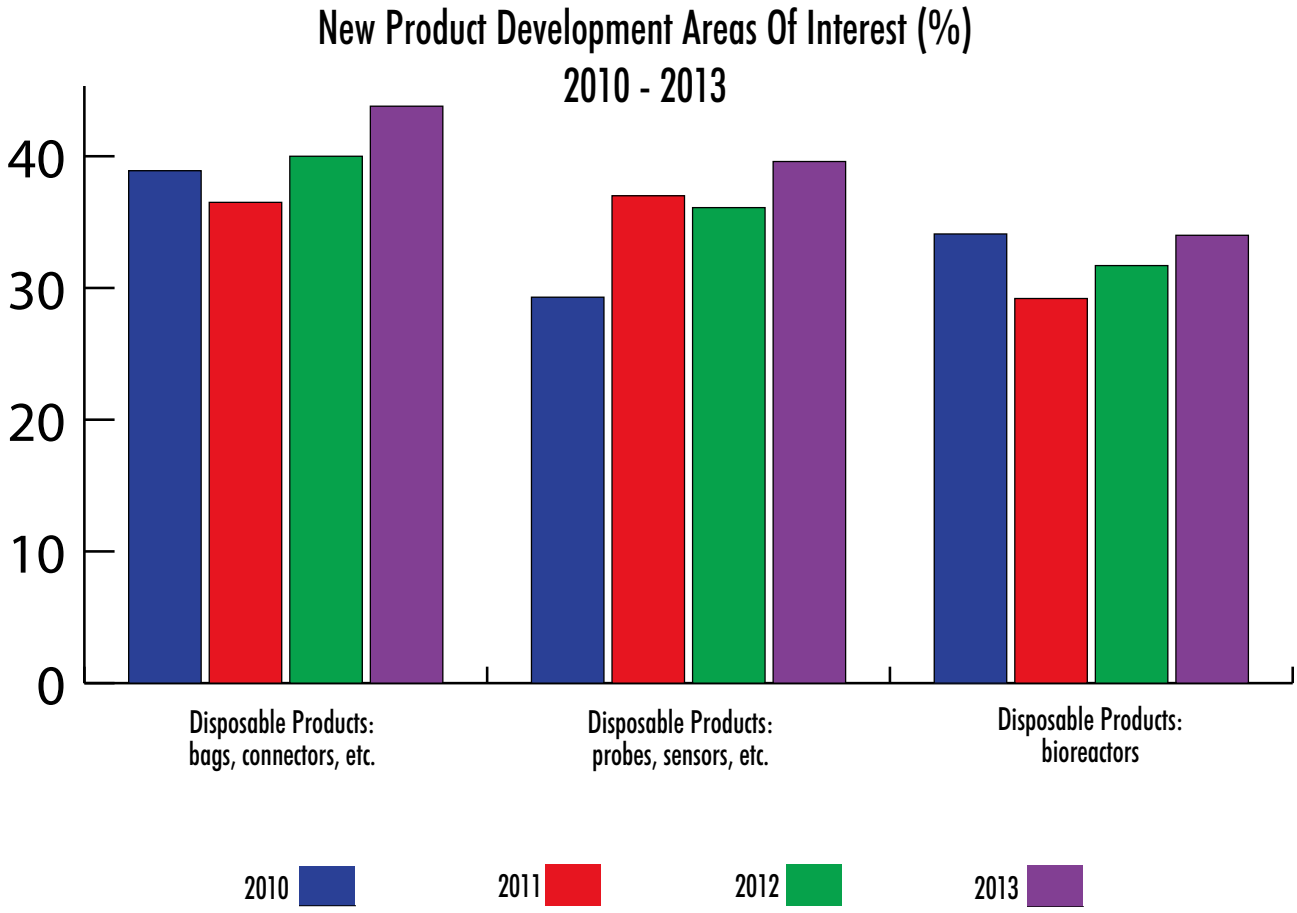
sensors and assay devices. Separately in our report, when we asked vendors what new technologies or new product development areas they are working on, around one in five suppliers indicated sensors and probes to be an area of focus for their new product R&D. While that may appear to be a fairly small proportion, it was roughly in the top quintile of responses among the long list of areas that were evaluated. As the industry matures, we can expect to see several suppliers introducing technologies such as single-use sensors and mixers to differentiate themselves from the competition.

It is indeed possible that the next step for increased use of disposables in biomanufacturing will concern implementation of disposable sensors (such as UV detectors and pH and DO [dissolved oxygen] probes), rather than disposable containers, filters, and chromatography columns.



Survey Methodology: The 2013 10th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production is an evaluation by BioPlan Associates, Inc. that yields a composite view of and trend analysis from 300 to 400 responsible individuals at biopharmaceutical manufacturers and CMOs in 29 countries. The respondents also include more than 185 direct suppliers of materials, services, and equipment to this industry. Each year the study covers issues including new product needs, facility budget changes, current capacity, future capacity constraints, expansions, use of disposables, trends and budgets in disposables, trends in downstream purification, quality management and control, hiring, 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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John Maraganore, Ph.D., CEO, Alnylam Pharmaceuticals

Navigating Alnylam To The Brink Of A Big Breakthrough

By Rob Wright, chief editor

A natural process cells use to silence the activity of specific genes, ribonucleic acid interference (RNAi), was first discovered in 1998. Soon after, the race by investigators to understand RNAi's role in normal and diseased cells began with a focus on how to harness the mechanism for use in medical therapies. From 2002 to 2005, a number of RNAi biotechnology start-ups popped up to try to capitalize on the potentially disruptive technology, including Alnylam Pharmaceuticals, which still retains its original name, as well as its first and only CEO, John Maraganore, Ph.D. A 25-year industry veteran, Maraganore has witnessed the initial buzz surrounding RNAi that resulted in Big Pharma jumping into the fray to the tune of $2.5 to $3.5 billion U.S. through partnering and acquisition. He has also observed the subsequent exodus (e.g. Roche) when the technology failed to deliver the quick wins for which Big Pharma was hoping. Throughout it all, he has stayed the course believing in the science of RNAi and Alnylam's ability to deliver on results. Maraganore shares his approach of taking Alnylam from a small start-up, navigating the turbulent waters created by patent cliff chaos and economic turmoil to position the company toward being on the brink of a big breakthrough.

FROM RECRUITED TO RECRUITER

In 2002 Maraganore was happily employed at Millennium Pharmaceuticals. Though not actively seeking a job, let alone the position as CEO of a biotech start-up, he was all ears when he got a call from a renowned MIT professor who wanted to share some insight on a little project on which he was working. The MIT professor just so happens to be Nobel Laureate Phillip Sharp, Ph.D., whom Maraganore had worked closely with when he was at Biogen Idec, and the "little project" was Alnylam Pharmaceuticals. "He told me a little bit about Alnylam, and I just got the bug," he explains. "At the time, Alnylam was really just a concept, an understanding that RNAi could ultimately lead to a whole new class of medicines." In December of that same year, after doing his due diligence on the science, meeting the venture capitalists involved, and discussing with some close advisors, Maraganore joined Alnylam as the CEO. At the time, the company was no more than six employees, with about $17.5 million in the bank. "There were no labs up and running, though a space had been identified and leased."

As a new CEO of a biotech start-up, Maraganore quickly learned the importance of being able to wear multiple hats. Alnylam needed labs so it could begin moving forward on scientific activities. But more importantly, it needed people — scientists to be specific. "I spent incredible amounts of time in those early days on recruiting and building the initial team of scientists," he shares. To begin the process of building the Alnylam team, Maraganore relied on his passion for meeting and spending time with people. "I drive my assistant crazy, because if anybody even reasonably credible sends me an email, I'll follow up with them," he states. "I just really enjoy talking to people." Maraganore believes this to be one of the most important things you can do as a leader, because it allows you to build and keep a network of top talent. "As you mentor and counsel individuals throughout their career development, not only does it ultimately enrich your skillset, it creates a network for you to be able to ultimately find talent for different roles within your company," he affirms. When it came to building the Alnylam team, Maraganore started with the rich substrate of people within his own network who were reachable. In addition, many people contacted the company, excited by the science and the company's transformative vision for targeting previously "undruggable" targets with RNAi. The combination proved to be a powerful mix in the early days of building the Alnylam team. Of course, there were challenges in recruiting, particularly for the company's chief scientific officer, as the bar was incredibly high for a person with the needed leadership skills of a very special company.

By the end of 2003, the Alnylam team had grown to nearly 20 employees. Today it consists of about 130 people engaged in six active clinical development programs, one of

which is on the brink of going into Phase 3 clinical trials. In addition to being Alnylam's number-one recruiter and team builder, Maraganore found two other skills which he acquired through mentorship, to come in rather handy, and rather quickly — his ability to create strategic business partnerships, as well as secure nondilutive capital (see sidebar below).

SCIENCE DRIVES EXCITEMENT

Barely a month into his position as Alnylam's CEO, Maraganore received a phone call from Stephen Friend, an SVP at Merck. Well known in the field of genome analysis, Friend explained Merck was interested in partnering with Alnylam on RNAi. Maraganore had been involved in doing partnerships from both the buy side (in-licenser) and sell side (out-licenser). From his experience, it is very infrequent for the sell side (Alnylam) to be contacted proactively by the buy side (Merck). "Usually, when you're on the sell side, you're pounding the pavement, meeting with people, introducing your technology to companies," he explains. "You're not usually receiving cold calls from senior people at pharma companies who want to work with you." Maraganore took this as a good sign, especially considering the newness of Alnylam. After the initial call, Maraganore and a small Alnylam team visited Merck to discuss the structure of a partnership. As always, there were ups and downs during the course of the negotiations. Maraganore also needed to get internal alignment with his board, as a company's first partnership can often set the stage for future business development activities. After that initial call, it took nine months to ink the deal with signatures.

The phone call from Friend led to Alnylam establishing two partnerships with Merck, the first being consummated in 2003 and what Maraganore described as being a starter deal. Maraganore believes Merck's interest was driven by the excitement surrounding RNAi science. For example, a January 2003 *Science* article named RNAi as the breakthrough of the year, and a February article in *Forbes* proclaimed RNAi as a brand new way to make drugs. Seeing the value of the buzz which was being created by RNAi, Maraganore made an interesting decision, choosing to adopt an open innovation platform, a term which had only recently been coined by Henry Chesbrough in his book, *Open Innovation: The New Imperative for Creating and Profiting from Technology*. "The lesson we learned is science drives enthusiasm and excitement, because people can see how science can translate into transformative new approaches for medicine," he states. "We decided to be very open about our science and to actively publish our scientific results as we achieved them." Maraganore admits the decision was not easy and involved a strong internal debate around the distinct possibility that by publishing the science they could be enabling the competition. This was weighed against the choice of keeping the science confidential and a trade secret. At the end, the decision was made around the dining room table at Maraganore's home, where a small group of Alnylam's senior leaders were meeting for the company's first "off-site." "The consequence of keeping our science private was that people wouldn't really appreciate the quality of the work we were doing, and the only way to really communicate science is through peer-reviewed papers," he explains. The decision, though risky, paid off with multiple deals.

SHARING SCIENCE PROVES PROFITABLE

In 2004 Alnylam scientists published a paper in *Nature* which showed for the first time that RNAi can be achieved in an animal. It was the first time any in vivo evidence for RNAi was proven in an animal. "That paper led to Novartis doing a deal with us in 2005," Maraganore says. The Novartis deal was Alnylam's first substantial transaction, with $65 million up front and significant R&D funding. The deal also resulted in a "rather heated" internal discussion. Specifically, the company's board was concerned that Novartis was

4 TIPS FOR SECURING FUNDING

Some people say Alnylam's CEO, John Maraganore, Ph.D., makes the process of securing funding look easy. He doesn't feel that way, though. "It is incredibly hard, and it takes a significant commitment level," he states. "You have to be prepared to go through the ups and downs, be persistent, consistently passionate, and committed." If you want to secure funding so your team can focus on the science, here are some of Maraganore's tips on how to do so. "Number one, be incredibly straightforward and transparent with investors, regardless of where your capital is coming from," he recommends. "There's really no room for BS. You've just got to lay it on the table and be very clear with people on what the opportunity is." In addition to having and being able to articulate your company's vision, Maraganore feels you need to be open about the things that are working, as well as the areas in which knowledge gaps still exist. "This gives people a clear sense of where the limitations might be going forward."

His second tip is to remember that at some level you are always raising money. "You've always got to keep your eye out for the capital needs of the company, because it takes a lot of capital to build one of these companies," he exclaims. Maraganore refers to great companies like Genentech and Biogen Idec, where each cost between $1 billion to $2 billion and took 10 to 20 years before they were profitable. Thus far, Alnylam has raised about $1.3 billion, with a large amount of money from pharma, a small amount from the venture capitalists, and the balance from the public equity markets. "Be focused on raising capital for when you need it," he suggests. "Raise capital when you have built a lot of value, not when things are tough and at a low point." Maraganore's third tip is to always be dilution-sensitive and, with partnerships, to make sure you are giving fair value to your partners without giving away the company's future. Be willing to start small. Also, be willing to walk away. "We had a discussion with another pharmaceutical company in 2003 before we did the Merck deal," he explains. "They wanted to have an exclusive relationship with Alnylam for a five-year period that would have kept us 'off the market' for any other deals. We felt the cost of entry for an exclusive partnership was at least $100 million. The other company was only willing to go up to $70 million. So we walked away from the deal."

Finally, Maraganore reminds you to be sure you are rewarding your existing shareholders. "If you cannot let your existing shareholders make a lot of money, they won't invest in you again," he says. "You have to be focused on making your investors successful if you're going to raise money."

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"We decided to be very open about our science and to actively publish our scientific results as we achieved them."

John Maraganore, Ph.D., CEO, Alnylam Pharmaceuticals

potentially getting too broad a scope of rights and that the agreement structure could limit future business development activities. "We did have to do some soul searching to make sure the structure of the Novartis relationship would be economically beneficial to Novartis without being detrimental to the long-term growth of Alnylam," he says. The partnership turned out to be a great opportunity for the biotech company, providing nondilutive funding and allowing Alnylam, at this point a publicly traded company, to build its underlying technology without having to go back to the capital markets frequently to raise money.

The company went on to strike numerous lucrative deals without giving away its technology (e.g. Roche $331 million up front, Takeda $150 million up front), as well as establish partnerships with Medtronic, Cubist, Kyowa Hakko Kirin, GSK, Biogen Idec, Monsanto, Genzyme, and The Medicines Company.

If you are interested in creating partnerships, Maraganore has some insight as to how to go about it. First, he recommends choosing committed partners that are going to work well with you and your scientific team. Second, have strong senior-level relationships with those partners. "In other words, know people at the senior-most levels of those companies, and develop a relationship with them that builds a foundation of trust between the two companies," he affirms. For example, in order for the Roche deal to happen, a critical meeting was held at Roche Chairman Franz Humer's New York City condo, where Maraganore and Humer agreed to the final terms and also committed to complete the deal within 30 days . In terms of structuring the partnership, he recommends finding the right balance that gives significant value for the pharma company's economic investment while retaining the freedom to continue building your own business. "Partnerships are critical to any new company getting started," he asserts. "However, if you end up giving away a scope of rights that might be a significant proportion of the future of your company — that becomes the most dilutive form of capital there is. You didn't form a partnership, but rather, you just sold your company," he warns. "Don't be afraid to go small initially when getting started," he advises. "But be prepared and ready to think big when the time is right."

The time sure seems right for Alnylam. Though the buzz around RNAi has gone through peaks and troughs, Maraganore believes the science of RNAi hasn't changed, and Alnylam's commitment to it has never wavered. What has evolved, however, is the understanding of where RNAi can work (e.g. the liver). "In some ways, our current strategy with RNAi therapeutics is like finding a bullet in the wall and painting a target around it," he concludes. The company's product strategy is called "Alnylam 5x15," where the company is focused on RNAi therapeutics for genetically validated targets — often orphan diseases — and where the company aims to have five such programs in clinical development, including in late stages, by the end of 2015. With a number of compounds advancing in clinical trials and one about to start Phase 3, the next two years should prove if Alnylam and RNAi can create a breakthrough of the billion-dollar variety.

COMPETITOR BUYOUT PROVES PIVOTAL FOR ALNYLAM AND RNAi

In 2006, Merck paid a 102% premium when it agreed to purchase Sirna Therapeutics for $1.1 billion. At the time, Sirna was a small biotech firm developing drugs based on RNAi. Despite the fact that just one month earlier RNAi technology was the focal point for the Nobel Prize in medicine, John Maraganore feels the decision was driven in part by Alnylam's 2005 deal with Novartis and another *Nature* paper Alnylam scientists published in 2006 showing that RNAi works in nonhuman primates. "Merck felt the larger deal with Novartis could ultimately limit their access to RNAi opportunities," he states. According to Maraganore, Merck's decision to purchase Sirna Therapeutics turned out to be one of the best things to happen to Alnylam because it did two things. "One is it took what, at the time, was our only real competitor off the market," he affirms. "Two, it completely reset valuation expectations for our technology. It was an amazingly good thing for the field of RNAi, as well as Alnylam." Maraganore believes the Merck acquisition of Sirna played a pivotal role in getting companies like Roche interested in doing something with Alnylam in RNAi. "If Novartis was doing something big, and Merck was doing something big, Roche appropriately reasoned they wanted to be a player in this space as well," he concludes.

Alnylam's 2007 deal with Roche included $331 million up front, and potential future milestones and royalties. This furthered interest in the RNAi field and continued the domino effect for Alnylam deal making. For example, in 2008 the company formed a partnership with Takeda which involved $100 million in up-front cash, $50 million in near-term technology transfer, as well as $171 million in milestones, along with royalties for each product codeveloped. These deals proved pivotal to sustaining Alnylam through the lean times created by the start of the 2008 economic crisis and the R&D budget cutting – including their RNAi efforts - by Big Pharma in 2010.

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Positioning Your Pharma Business To Reach 2020 And Beyond

By Dr. Steve Arlington

The pharmaceutical and life sciences industry is on the cusp of a golden era of renewed productivity and prosperity. Major scientific and technological advances, coupled with socio-demographic changes, increasing demand for medicines, and improved conditions in global trade, will renew pharma's fortunes and deliver dramatic improvements in patient care. Yet, pharma's future has never looked more challenging. Emerging issues, including residual effects of the financial crisis, healthcare reform, new cost constraints, and rising customer expectations, have added new pressures that make pharma's future success uncertain.

Pharmaceutical companies can prosper in the next decade if they are willing to make tough decisions in three areas:

Rising customer expectations: The commercial environment is becoming more difficult, as healthcare payers impose new cost constraints on providers and analyze the value medicines offer much more carefully. Like patients, payers want new therapies that are clinically and economically better than the existing alternatives, together with hard, real-world outcomes data to back any claims about a medicine's superiority.

Pruning the pipeline: Most of the products that will be launched in coming years are already in the pipeline but are not aligned with medical needs and demand or rising expectations from payers, providers, and patients. There is a crucial need for the industry to rebalance expenditures and invest more in the early part of the R&D process to improve productivity that will deliver returns on investment.

Breaking down cultural barriers: The management culture on which the industry depends is the same one it traditionally has relied on. New entrants to the market and new technology are beginning to disrupt the status quo, and pharmaceutical companies can expect an even more demanding commercial environment going forward. Pharma companies in the future will be more collaborative, and the industry's top figures are likely to be mavericks who have the vision and courage to break the mold.

Many of the conditions that will have an impact on what happens to companies in the next decade are already in place. Most, if not all, of the products that will be launched by then already exist or are in development. Similarly, many of the senior executives who will be at the helm have been earmarked for high office or are already in place. Yet, there are a number of tactics companies can pursue now to increase their chances of prosperity over the next decade and thereafter.

MAXIMIZE THE MOLECULE

Mature markets are becoming more difficult places in which to prosper because payers there are demanding better outcomes as a precondition for paying for new medicines. The message they are sending is clear: They want more value for their money, they are measuring the value they get more rigorously, and they are not prepared to pay for medicines that produce only incremental improvements in outcomes.

Pharmaceutical companies have a choice: Either offer more value without charging more or prove that they can remove costs from another part of the healthcare system to justify premium pricing. Outcomes are the new currency. In essence, if there is no outcome, then there is no income.

In mature markets, there is enormous opportunity for the pharmaceutical industry to help payers save money and for providers to deliver better quality care for less money. Roughly 85% of global health spending currently goes to healthcare services delivered by physicians, hospitals, and other providers, and less than 15% goes to medicines. But, by demonstrating that medicine can reduce spending on costly medical services and procedures, PwC estimates that pharma's share of healthcare expenditures could rise to 20% by 2020.

SERVE THE GROWTH MARKETS PROFITABLY

Expenditures on medicines are rising faster in the growth economies than elsewhere, but serving these markets can be very difficult since they are fragmented. As such, the industry cannot rely on the same strategies for making a profit as in mature countries. Global growth strategies should shift from a one-size-fits-all, mass-market approach to a targeted specialty approach in which pharma companies pick the right spots for targeted

populations — those where they can add value. Some organizations have responded by creating new business models, not just new products and services, that use innovation-driven or market-driven approaches, depending on the distinct needs of the market.

COLLABORATE AND CAPITALIZE ON NEW SCIENCES

R&D productivity has remained static for 15 years and is at an all-time low. In the decade prior to 2011, the FDA approved 308 new molecular entities and biologics. Given the amount invested in R&D each year during the same period, that means the annual average cost per approved molecule ranged from $2.3 billion to $4.9 billion. And, there is no sign of these costs coming down. This trend is not sustainable.

Yet there are changes the industry can make to tackle the productivity problem. The industry should rebalance its expenditure and invest more in the early part of the R&D process for productivity improvements that will deliver returns on R&D investment. For example, whole-genome sequencing is critical; it allows scientists to identify new regions for research and to validate or eliminate mechanisms in human populations before subjecting drug candidates to costly, lengthy clinical trials.

Companies also should become more selective about the therapeutic areas they cover and bolster their expertise by hiring or collaborating with the leaders in their chosen fields of research. Executives generally recognize the merits of "open innovation," but cultural obstacles, such as fear of sharing intellectual property and unnecessarily individualistic business processes, still serve to discourage collaboration.

In addition, it is important for companies to devise a clear path to clinical proof of concept for all compounds entering development and to test them in humans as early in the process as possible, using the best tools for selecting subjects. Biomarkers have a significant contribution to make here by narrowing the subset of patients on whom a molecule should be tested, thus exposing defects more rapidly.

MANAGE THE PORTFOLIO MORE RIGOROUSLY

Managerial factors also play a role in pharma's low R&D productivity, and one of the biggest factors is poor decision making. Attrition rates in late-stage clinical trials have climbed steeply over the past two decades, possibly the result of overlapping activity between companies with similar compounds in the pipeline.

This could be because many companies cannot yet manage the relationship between risk and value very effectively. To improve their risk/value management, they can prune their portfolios to focus on the

compounds with the greatest probability of success. In doing so, they should draw on all the information at their disposal. Most companies still focus on technical rather than commercial risks, for example, and few companies consult payers to determine the potential value of new medicines.

Pharma companies also should aim to build balanced portfolios. Many companies concentrate on the molecules with the highest potential revenues and underestimate the risks because they rely too heavily on the opinions of the researchers involved. A better approach is to combine a few speculative compounds with some "bread-and-butter" products that will generate a steady income. It also is essential to appoint an independent committee of senior executives to monitor the portfolio and compare it with those of the company's rivals.

CHANGE THE CULTURE

Despite the seismic shifts of the past few decades, the organizational culture at many pharma companies has changed very little. Many are still operating within a management approach that prevailed 20 years ago, when the blockbuster model reigned. But pharma's business model has altered almost beyond recognition, and the focus is on creating specialist medicines that require a culture that fosters open innovation and collaboration to address the needs of the 21st century.

Cultural transformation will require change in the mindset at the top. That is gradually changing, as younger executives, eager to embrace new ways of doing business, come to the fore. Some of the changes include hiring executives from other industries to give the company access to new ideas and methods and eliminate roadblocks; create autonomous R&D teams that are given a specific challenge, budget, and time frame on which to deliver; and implement a measurement and reward system that combines financial and non-financial metrics, such as motivation and commitment. That system also should be flexible enough to measure different kinds of innovation. But, it is equally important to promote a "fail early, fail cheaply" mindset by providing incentives for quickly terminating weak candidates.

About the Author

Steve Arlington, Ph.D., is PwC's global pharmaceutical and life sciences advisory leader. Based in London, he specializes in the areas of strategy, discovery research, new product and process development, boardroom strategy, and transformation.

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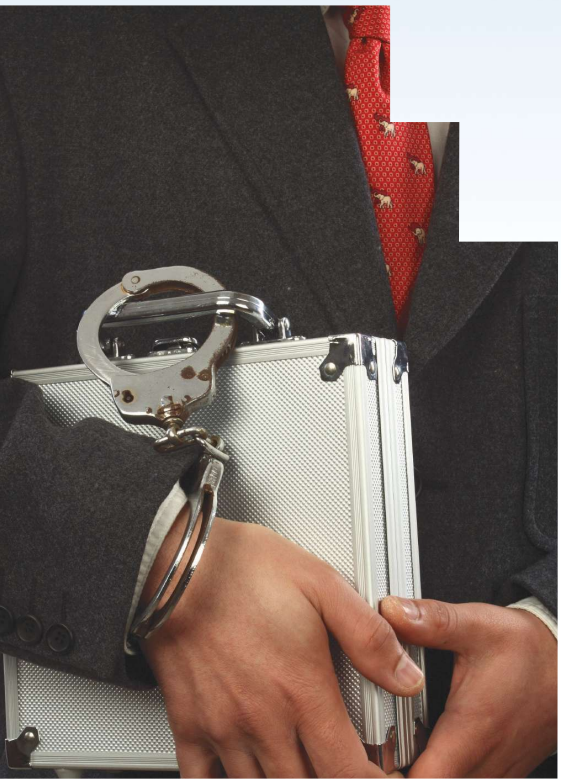

Protecting Trade Secrets And Customer Relationships In Life Sciences

By Marguerite Walsh

"We are going to aggressively protect our intellectual property. Our single greatest asset is the innovation and the ingenuity and creativity of the American people. It is essential to our prosperity and it will only become more so in this century."

— President Barack Obama, February 2013

The Obama administration recently announced a strategic initiative designed to mitigate the theft of United States trade secrets. The administration's multipronged approach encompasses: (1) sustained diplomatic efforts with trading partners to discourage theft of trade secrets, (2) encouraging U.S. businesses to implement best practices to minimize risk, (3) enhancing domestic law enforcement operations, (4) improving domestic legislation, and (5) education and outreach to the public and key stakeholders.

Clearly, the administration's focus on minimizing the risk of theft of trade secrets recognizes the reality that businesses have faced for decades, made even more challenging by a difficult economic climate, increasingly sophisticated technology, and greater numbers of disaffected employees. Nowhere are these factors more prevalent than in the highly competitive life sciences industry. According to a 2009 study, nearly 60% of employees who quit or were discharged acknowledged taking proprietary data from their employers.

At the same time, companies facing these pressures are more anxious than ever to do whatever they reasonably can to avoid the loss of key employees and valuable information. These issues, however, are complex in any industry, and the workloads already facing human resource, compliance, and legal departments in the highly-regulated life sciences industry are overwhelming. It is difficult enough, for instance, to address satisfactorily all the legal, regulatory, and other considerations involved in successfully bringing a new drug to market. Proactively undertaking a thorough review of the processes and programs in place to minimize the risk of losing confidential information often needs to take a back seat to solving the emergent and critical problems that arise every day. Too many companies, including those in the biotech, pharmaceutical, and related fields, find themselves in a state of indecision and paralysis — which is precisely the wrong approach. Instead of trying to tackle the entire problem in one fell swoop, companies would be well served by being mindful of the basics of protecting their proprietary information, key relationships, and personnel. This article provides some practical suggestions about how to do so.

BE FAMILIAR WITH APPLICABLE AGREEMENTS AND THE LEGAL LANDSCAPE

Many companies have no consistent approach to postemployment restrictions, particularly in situations involving mergers, acquisitions, and restructuring — all of which, of course, are common in the life sciences industry. Two key individuals performing virtually the same functions and having essentially the same potential to inflict competitive harm may be subject to two entirely different sets of restrictions, depending on the language of their agreements. Two agreements that are almost identical in post-employment restrictions may be vastly different in enforceability, depending on whether certain technical requirements (like consideration) have been met. Moreover, in some instances, even in sophisticated companies, it is difficult to find the relevant agreements due to ad hoc filing systems that have sprung up as the company has grown.

In addition to the practical difficulties faced by companies in the seemingly simple (but in truth very complicated) process of managing their agreements, it is also a challenge to keep up with the various legal developments that occur in this area, which of course are largely governed by state law. This is especially true in highly regulated industries such as biotech and pharmaceuticals, where the immedi-

ate focus often needs to be on the ever-evolving universe of legislation and regulations that directly impact the company's ability to get the medication, device, or test out the door and available to the public. While for purposes of this article it is not possible to discuss in detail the various legal developments of the past few years, at least two trends are clear: (1) courts are becoming more attentive to the "technical" aspects of agreements containing postemployment restrictions, such as consideration, assignability, and the like, particularly as the traditional "time and geography" boundaries become more blurred, and (2) given the realities of a truly global workplace, courts are taking a more nuanced approach to the "time and geography" analysis. The takeaway is that companies should be more careful than ever about ensuring that the "technical" elements needed to render an agreement enforceable have been met — which, notably, have nothing whatsoever to do with the scope of the actual restrictions. Companies should also be careful about the traditional "kitchen-sink" approach of including every possible restriction in an agreement, to the broadest extent possible, in the hope that a court will find at least something enforceable in the mix; this is by no means guaranteed, if it ever was.

PERFORM AN AUDIT OF YOUR CONFIDENTIAL INFORMATION AND TRADE SECRETS

Companies faced with potential misappropriation of sensitive information by departing employees often address the situation in an unfocused (and therefore risky) manner because they cannot articulate concisely what is, and is not, considered proprietary. There is a tendency to categorize nearly every bit of information as proprietary when, in fact, that is not the case. This hurts credibility when the time comes to articulate to a factfinder (who, of course, knows nothing firsthand about the company) what actually is at stake, or its critical importance.

Companies are well-served by conducting regular audits to identify and update the information that is considered protectable. As noted above, however, this undertaking is often impossible to accomplish due to limited resources and other, more immediate needs. This body of information may include not only technical/R&D information, but also production/process, cost/pricing, quality control, financial, and customer/client information. Those employees having the most relevant knowledge of the information in question should be consulted so that they can provide the best business explanation in real time (i.e. before the information heads out the door) as to

why protection is warranted. Then, companies should institute (if they have not already) procedures whereby they can reasonably quickly identify and gather those categories of information within their various business units that are proprietary. At a minimum, companies should focus on the types of information and/or business lines where the risk is greatest. Certainly, misappropriation of proprietary information about a potential new drug or device could be devastating, so it is difficult to quarrel with a decision to start there.

Further, while technological advances create greater challenges than ever before to a company's information security efforts, courts are still quite interested in the "tried-and-true" steps in place to restrict access. Any litigator who regularly handles these cases would much rather head into court on behalf of a victimized company with a strong list of preventive measures taken, no matter how mundane they may seem. These may include: stamping and labeling (including electronically) documents that are considered confidential, the use of security cameras, using sign-in logs at company facilities, preventing visitors from wandering unescorted through company premises, shredding or otherwise destroying copies of proprietary information, maintaining physical barriers to access when appropriate, using and updating proper password protection, using appropriate monitoring software, including a policy in the handbook concerning access to confidential information, including in job descriptions relevant provisions for employees who have access to proprietary information, and using nondisclosure agreements. Life sciences companies tend to be among the leaders in these sorts of protocols, but it is advisable to re-examine and update them regularly.

Finally, do not underestimate the value of the exit interview and the practice of sending reminder letters to departing employees as to their postemployment restrictions after they leave.

UNDERSTAND THE CHALLENGES OF THE "BRING YOUR OWN DEVICE" MOVEMENT

Thanks to the blurred (and in some cases eradicated) lines between work and nonwork activities, companies face new challenges relating to the use of personal devices for both work and nonwork purposes (i.e. bring your own device, or BYOD). Protecting confidential information becomes even more difficult in this context. Simply firing an employee who is found to have stored confidential company information on such a device is not necessarily the answer. In fact, a recent study by the Poneman Institute shows that companies are often unaware whether and what kind of data might be leaving their networks via nonsecure mobile devices.

While the BYOD movement could form the basis of a much lengthier treatise, ultimately the question is one of balance. Many companies already sanction dual-usage devices, so the question becomes one of finding the best mix of practices to address the realities of the work situation and the need to maintain confidentiality. Considerations to keep in mind are: possible company ownership of the device, greater emphasis on confidentiality agreements and related training, attention to the ramification of the use of cloud-based storage, strong enforcement of policies relating to reporting requirements for lost or stolen devices, and the use of MDM (mobile device management) software that allows companies to remotely manage and configure many aspects of dual-use devices.

> Companies would be well-served by being mindful of the basics of protecting their proprietary information, key relationships, and personnel.

ESTABLISH AND MAINTAIN A CULTURE OF PROTECTION

The most effective step a company can take to guard against the theft of its trade secrets and proprietary information has little or nothing to do with the law. Rather, it all starts with company culture. Employees know when they are simply being talked at, with no commitment behind the words. Conversely, when they work hard as a team to help create a breakthrough drug that could save millions of lives, they need to understand that their efforts are worthy of protection. When they get the message that the company will back them up when that work is threatened, their trust level grows. Moreover, a company needs to practice what it preaches on both sides of the equation — not only in protecting its own legitimate interests but in being mindful of its competitors' legitimate interests when hiring from those competitors.

About the Author

Marguerite Walsh is a shareholder in the Philadelphia office of Littler Mendelson, P.C., an employment and labor law firm representing management. She focuses her practice on representing companies in matters involving protection of intellectual capital and customer relationships, including trade secrets and post-employment restrictions.

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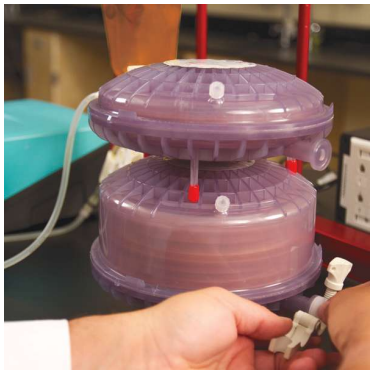

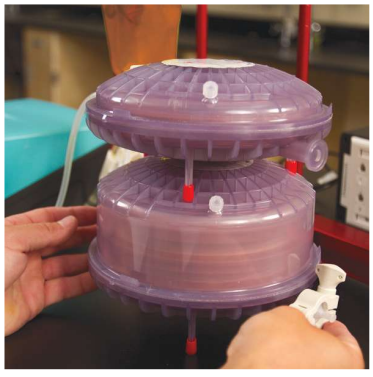

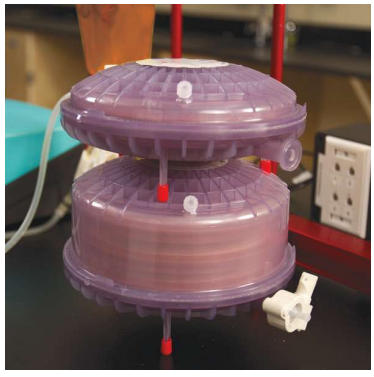

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Save Time And Money By Leveraging Pharma Shipping Regulations

By Gail Dutton, contributing editor

When it comes to logistics, the life sciences industry may be too cautious, using dangerous goods labeling and other restrictive classification requirements unnecessarily. "Things are slipping through the cracks, and life sciences shippers are losing efficiency," says Jay Johnson, regulatory compliance manager for Inmark and chairman of the Dangerous Goods Advisory Council.

The problem often is that shippers don't understand the fine points of the regulations' exceptions and exemptions that can be used without sacrificing quality.

REGULATIONS MAKE "HAZARDOUS MATERIALS" "NONHAZARDOUS" IN TRANSPORTATION

"By knowing the regulations, you may not have to comply with all of the requirements when shipping dangerous goods," Johnson says. "A nonregulated substance labeled with a radioactive isotope or shipped in a flammable liquid is considered a dangerous good for transport. However, infectious-substance regulations allow category A and B pathogenic materials to be shipped with up to 30 ml of flammable, corrosive, and miscellaneous materials in the tube with the pathogen without noting them. That's one of the few examples where you can ignore subsidiary risks."

When cell samples from a Pap smear, in contrast, are shipped in vials containing flammable liquid, the vials must be declared a flammable. "Once the lab draws the samples, capturing the potentially infectious biologic, the cells can be returned to the lab as a category B substance without recognizing the flammable liquid still present. The packaging must comply with the regulations, but only the marking has changed." The benefit, Johnson says, is that some labs report speedier delivery of biologic-substance, category B items than of flammable liquids, even when shipped as a "dangerous goods in excepted quantity."

Shipping departments often depend upon MSDSs (material safety data sheets) to determine whether a substance must be shipped as a dangerous good. However, an MSDS may not include the information shippers need to make that determination. Using an MSDS to determine hazard, for example, could cause a substance containing minor amounts of phosphoric acid to ship as if it is 100% phosphoric acid. "An MSDS may be written to an active ingredient, but transportation should be based on the actual formulation," Johnson says.

The new IATA (International Air Transport Association) dangerous goods regulations, effective January 1, 2013, clarified the requirements for shipping formaldehyde. Solutions composed of less than 10% formaldehyde are not regulated as "dangerous goods," while solutions containing greater than 10% and less than 25% formaldehyde must be shipped as "aviation regulated liquids."

USE THE NEW *DE MINIMIS* EXCEPTION

The changes to the dangerous goods regulations include a new *de minimis* exception, contained within CFR Title 49 part 173.4b and in the international regulations. "The pharmaceutical industry will be one of the main users of this new *de minimis* regulation because of the thousands of samples shipped globally," says Richard Lattimer, health, safety, and environmental compliance assurance consultant for Eli Lilly and Company. "Before the *de minimis* regulations, there was no minimum amount of hazardous material that was considered unworthy of regulation."

The new *de minimis* exception allows certain types of hazardous materials, including division 6.1 toxins, to be shipped as nonregulated goods if the volume of the inner receptacle is less than 1 ml or weighs less than 1 gram, the package contains no more than 100 ml or 100 grams, and

the packaging can withstand a 1.8 meter drop and a compression test.

"These substances may be uncharacterized components in compound libraries, for example, and thus lack LD50 [i.e. the amount of a material, given all at once, which causes the death of 50% of a group of test animals] data needed for proper classification," Johnson elaborates. "Before January, the most restrictive classification of packing group 1 toxins (which some airlines won't accept) was used to transport these items. Now they can be shipped as unregulated substances."

Nonetheless, "It's a good idea to put '*De Minimis* Quantities — Not Restricted' on the paperwork," adds Dave Murphy, VP and director of sales for the Americas at QuickSTAT, a global clinical trials logistics provider.

ORM-D GOES AWAY BUT NEW LIMITED-QUANTITY REGULATIONS EXPAND

The recent planned removal of ORM-D (other regulated materials — domestic) includes expanding the limited-quantity (LTD QTY) exception for dangerous goods shipped domestically. "The new limited-quantity regulations give the power of ORM-D to all domestic limited-quantity shipments by ground. ORM-D only works domestically," Johnson stresses, and neither air nor ocean shipping is included. With the new limited-quantity exception, packing group 3 flammables, for example, now can ship up to 1.3 gallons per bottle in a 30 kg container with virtually no other requirements except a marking," Johnson explains. "This reduces paperwork and special packaging needs." Increased use of the LTD QTY exception could lower shipping costs substantially — "from thousands to hundreds of dollars per shipment — if customers would accept slightly longer shipping times for ground transport," Johnson speculates.

> "Dry ice must be declared a dangerous good when used to refrigerate a dangerous good, but not when used to refrigerate a nondangerous good."
>
> Dave Murphy, VP and director of sales for the Americas, QuickSTAT

UNDERSTAND THE NEW NET QUANTITY DEFINITION

The IATA rules that went into effect January 1 also changed the definition of "net quantity" so that it refers to the weight or volume of the dangerous goods in the package, as described by their proper shipping name. "To ship a fire extinguisher, shippers must list the weight of the extinguisher, not the weight of the gas inside the extinguisher. To ship frozen blood, net volume includes the blood and the dry ice, but not the weight of the carton or other packing materials," Murphy explains.

SHIPPING SPECS AND STABILITY DATA DIFFER

The disconnect between product stability data and shipping specifications causes millions of products to be discarded each year, Johnson says. Stability data may support storage at ambient temperature for 48 hours, while shipping specifications mandate temperatures of 2° to 8°C. Johnson recommends adding stability data to shipping documents then monitoring product temperature. "There's confusion around when temperature control is needed."

In the rush to keep things cool, shippers forget that items also can become too

cold. Johnson gives an example from several years ago regarding a human heart shipped internationally for transplant with instructions to re-ice it at a specific airport. Airport workers, accustomed to dry-ice, used that. The heart was ruined. "Phase change occurs at 0°C, so packages specifying 2° to 8°C must be packed with enough gel pack to keep them cool without freezing. A gel pack frozen to -20°C could spike the temperature too low for products in the 2° to 8°C range," Johnson cautions.

As Murphy adds, "Dry ice must be declared a dangerous good when used to refrigerate a dangerous good, but not when used to refrigerate a nondangerous good. Quantities above 2.5 kg must be declared on the airline air bill and must ride as cargo. In contrast, dry vapor shippers, which use liquid nitrogen, are not considered dangerous goods."

COLLABORATE WITH CARRIERS

Murphy says that, ultimately, the integrity of the shipment is far more important than the speed of shipping. He recommends sending all the documentation — including the commercial invoice, dangerous goods classification, and import or export permits — to the logistics provider for review before the product is packed. Dangerous goods should receive particular attention to ensure the shipper isn't over or under declaring the danger, so that the shipment can move safely and expeditiously.

Close collaboration coupled with a document review before the item is shipped can reduce the number of shipments rejected by carriers and, therefore, speed door-to-door transit. "In the past year or two," Johnson says, "the FAA gained the authority to demand a list of all dangerous goods shippers whose packages failed inspection within the past six months." This implies that shippers appearing frequently on that list may be flagged for special attention. Additionally, the FAA now may open non-compliant dangerous goods.

Murphy also advises shippers to always use current forms. "The change between versions of forms may not be dramatic and, to the inexperienced eye, the forms may look alike. But, it only takes a subtle change to disrupt a shipment."

The airlines have their own rules regarding what they will accept, and logistics providers know those rules. "Individual airlines won't reduce IATA regulations, but may require more," Murphy says. Dry ice is an example. "So, when reviewing documentation, we also look at flights to ensure that the carrier we choose won't deviate from IATA rules."

Ports of entry matter, too. "It's good to evaluate the conditions of ports of origin, transit, and final destination," says Verónica Rocio Piñón, global logistics consultant for Eli Lilly and Company. "Some countries have lower standards of infrastructure that don't always provide ideal storage conditions. Therefore, robust packaging is vital to protect the product until it is released from customs to its final destination."

In addition to infrastructure, also ascertain that ports have the necessary inspectors to minimize delays. In the U.S., this may include customs, FDA, the Department of Agriculture, and even the Department of Fish and Wildlife for some cell cultures, Murphy adds.

Overprotective shippers err on the side of caution. But shipments can be equally safe when shippers use the regulatory exceptions and exemptions applicable to their shipment, thereby saving time and money by reducing the paperwork and the number of reviews needed to move shipments throughout the world. Companies need a deep understanding of the rules and exceptions governing their shipments, either in-house or through their logistics provider.

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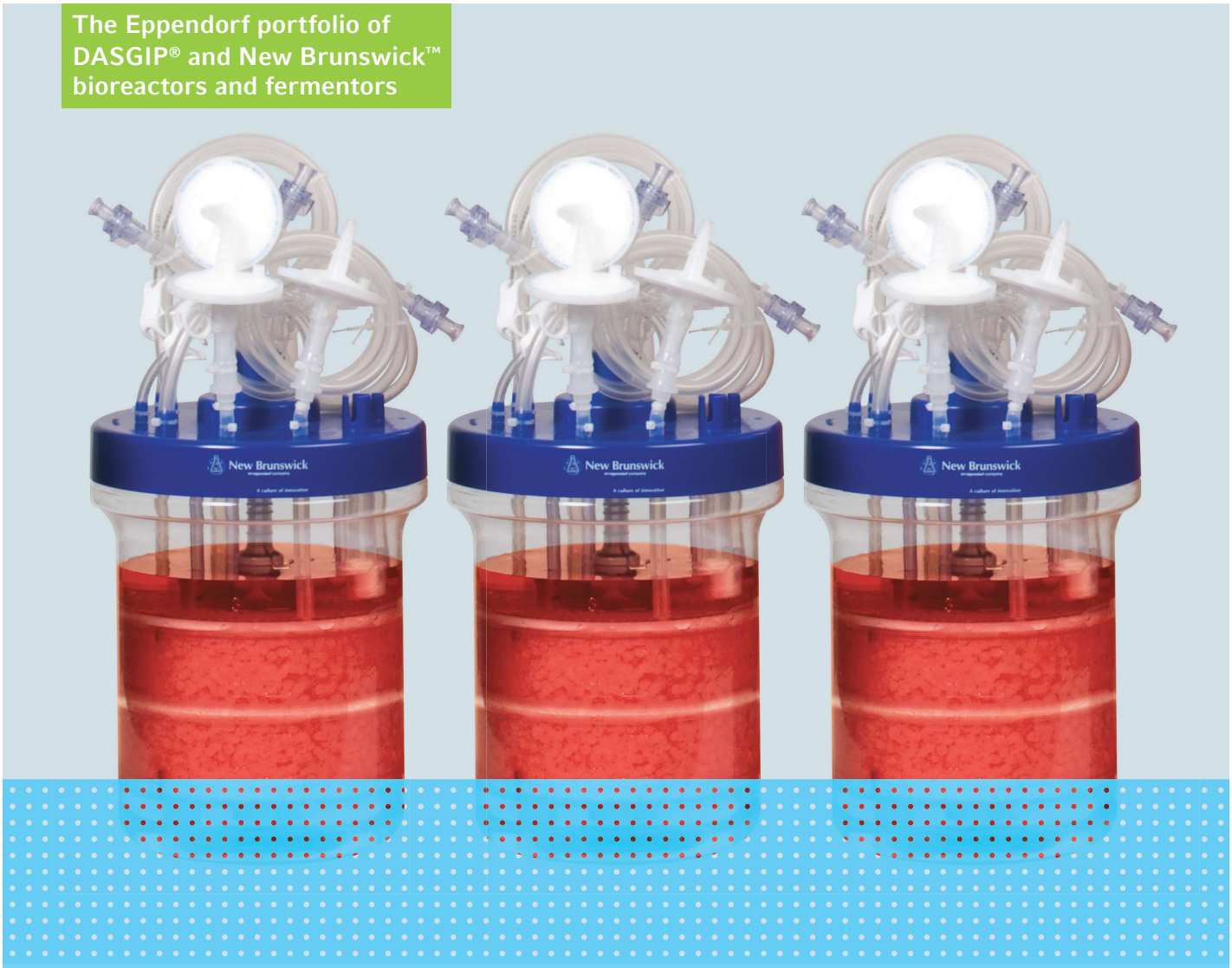

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When Does A Supplier Become A Partner?

Shared risk and responsibility, more than size and capabilities, qualify suppliers for partner status.

By Wayne Koberstein, executive editor

Nobody wants to be a supplier these days; everyone wants to be a partner. It has become conventional wisdom that vendors only want your money, but partners want to succeed along with you. Come on, isn't that what it comes down to? I'm working on the theory that plain language will unblock a discussion usually stalled by polite avoidance and euphemistic businessspeak.

Actually, I am not that skeptical of the partnering concept as applied to CMOs, CROs or other entities that supply goods and services to pharma, biotech, medical device, and other life science developers. In fact, it grows ever more difficult to draw a clean line between companies that deserve the term partner and "mere" suppliers. When a drug-delivery maker teams with a drug company to reformulate and reconfigure a compound into a new product with superior attributes, is it only supplying a technology or taking part in a strategic alliance? But, ever the doubter (though I hope a healthy one), I keep thinking the industry's use of "partner" is often indiscriminate and sometimes harmfully inappropriate. Beware of any term used universally as a marketing device by even the smallest vendor of widgets. Just doing business with a developer doesn't make you a partner.

Technically speaking, a supplier is a business that cannot exist on its own. If you took away all the companies discovering and developing new products, how many CMOs or CROs would there be? Of course, the editor's answer would be none, considering the word "contract" lies behind both acronyms. As long as the work is on contract, it is not partnering in the literal sense. Yet, if you relax the definition into a practical model, you start to see real differences between contractors who simply supply things and those who share their lives, fortunes, and sacred honor with their "clients."

DEFINING A TRUE PARTNER

Partner status must be earned. Applying — or claiming — the honorific, without good justification, devalues it. So what defines a true partner? Largely, it is a combination of what the organization brings to the table and how much of that it actually shares with the other party. Hidden agendas, procedures, consequences, and quality issues do not a partner make.

One test of partnership is what happens when the nominal supplier gets in trouble with regulators. By "when," I mean before, during, and after a problem event such as a warning letter. Does the letter catch the client off guard? Was the client aware of recent inspections and any problems that arose? Is there a mechanism or interface by which the contractor and client share information and data on a frequent, ongoing basis — or are the contractor's operations a black box from which the goods and services mysteriously emerge?

Another test can only be described with the word "sophistication." Is the contractor thinking and operating at the same level of informed, strategic management as its client? Do the two parties share an equally refined view of the world — the social, political, and commercial environment that shapes their common fate? Picture yourself as a pharmaceutical executive walking into your CRO and discussing the pricing situation in Korea. Will people immediately jump in with knowledgeable comments and a sense of what's at stake, or do you see nothing but blank stares. If it's the former, you may have a partner; if the latter, it's a supplier, pure and simple.

Not that there's anything wrong with that! (A nod to *Seinfeld* fans.) It is actually quite okay to be a supplier. The world needs suppliers. It is a legitimate and honorable role. But here's the rub: don't claim to be one thing if you're really another. You may set up expectations that you cannot meet and thus ruin what could have been a perfectly satisfactory business arrangement when you fail to deliver your end of the "partnership."

ARE SUPPLIERS REALLY ONE-STOP SHOPS?

These days, the word for CMOs and CROs on this issue is generally good. At a recent industry meeting, R&D leaders from innovator companies of all sizes appeared to agree that the large manufacturing and research contractors had grown into such global, multifaceted, and sophisticated entities that they essentially functioned as partners and even peers. But as I noted in some of my recent tweets, the consensus at the meeting was that none of the supplier/partners offered "one-stop shopping" for everything the R&D people would expect or desire in a true peer.

The last point brings up another potential aspect of the partner definition: How equal do partners have to be? If parity in size or capabilities were a requirement, few partnerships of any kind would form. It is almost a good sign for the contractors that their clients willingly regard them as partners even without buying the one-stop-shopping sales pitch.

It would seem from what I just described, however, that only the big-boy contractors can aspire to partner status — that is, if it were not for the obvious asymmetries among players in every direction. A big boy to a brave little start-up with a novel pipeline could be small potatoes to a Big Pharma. The scale of a partnership can be appropriate to the scale of the partners. And there is nothing wrong with a Mutt-and-Jeff relationship if the chemistry is right; a tiny CRO may be just the ticket for a huge company exploring a niche area. Finally, even the largest contractors would not surrender claim to the smallest clients, and, generally, they all have systems in place to deal with the life science Lilliputians.

No, being a partner, or becoming one, has no absolute relation to size, degree of specialization, or range of capabilities. What is it, then, that defines a partner as compared to a supplier? Any fair definition will not stray far from an assumption of shared risk and responsibility. That means that suppliers become partners when they decide to understand, accept, and help manage the total set of circumstances that determine the success or failure of their clients.

Replenishing Pipelines By Repurposing And Rescuing Pharmaceuticals

By Fred Olds

About 80% of drug candidates fail in phase 2 trials because they don't reach endpoints for efficacy. Of those drugs that get FDA approval, little is known about possible applications outside the narrow science of their original indication. Repurposing marketed drugs or rescuing compounds that failed in clinical trials offers entrepreneurs the potential to replenish pipelines with reduced risk and time in drug development. Yet these potential advantages may be moot if one can't overcome the main barrier of repurposing — intellectual property exclusivity.

Seth Lederman, M.D., co-founder, president, and chairman of TONIX Pharmaceuticals, says the risk of abandoning repurposing projects is lower than trials with new chemical entities (NCEs). "Looking back at the past 15 years," he says, "there's been a credo in early-stage research, 'fail fast.' You don't want to end up in late-stage trials and fail. It's just too expensive." He feels this led to a bias toward early discontinuance of trials with NCEs that might have succeeded otherwise.

With repurposing, research starts with defined pharmacokinetic (PK) data and a compound already proven safe through possibly millions of human exposures. If an apparent safety issue arises, investigators are more likely to approach it as an anomaly rather than to consider dropping the project. TONIX is developing the muscle relaxant cyclobenzaprine (CBP) in a sublingual form (CBP SL) for use in fibromyalgia and post-traumatic stress disorder (PTSD). Lederman says, "Even if a toxicity signal arises in an animal model during our research, we wouldn't be discouraged. We can't shrug it off; you have to take every piece of data seriously; but we may go and test in two other species."

A company may shave years off R&D by repurposing, and the savings can affect the strategic positioning of the compound. A new drug application (NDA) can be submitted under the 505(b)2 provision. This allows a company to support its application using the existing safety and PK data the FDA sanctioned for the drug in its original indication. Lederman says, "It's hard to say, but I think the provision helped TNX-102 SL (CBP SL) shorten R&D by as much as five years because we were able to go directly to dose finding." Michael Coffee, chief business officer of MediciNova Pharmaceuticals, says having the pharmacokinetic and safety data saved a year or two of research repurposing the anti-asthmatic ibudilast for chronic neuropathic pain and drug dependency. He says, "These advantages can move a project's priority up significantly when you're looking at six or seven potential projects you could invest in."

MAKING THE DISCOVERY

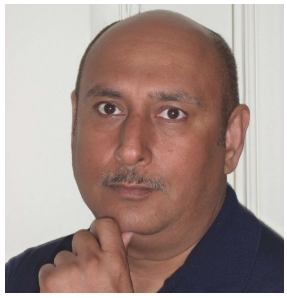
Historically, new uses for existing drugs were found by practitioners observing patient reactions to medications and linking those observations to an unmet need. TONIX is advancing the research of Dr. Iredell Iglehart, who noticed CBP had a positive effect on his fibromyalgia patients. Lederman says, "This kind of practice: a careful doctor, making a clinical observation, and then expanding on it, I think really goes back to Edward Jenner and cowpox. But, it is not necessarily reproducible in a systematic way."

Advances in science and technology now make systematic approaches feasible. Using high-throughput technology, like phenotypic drug screening, investigators can screen libraries of compounds against banks of cellular assays to uncover potential therapeutic links. Millions of assays can be tested, and the results reported within days, that might have taken months or years to find by manual laboratory methods.

Eli Lilly's proprietary phenotypic drug discovery system (PD^2) screens human cells with a known disease-related biology or defect against a battery of compounds to see if there

is a therapeutically positive change in the cell. Ash Bahl, Ph.D., Lilly's senior director of global external R&D, says, "With phenotypic screening we see the positive effect (phenotype) but may not know what caused the change. It tells us we're chasing something of value, and then we use the technology to deconvolute the disease signal and work backward from it."

The Internet provides researchers the technology to access and screen knowledge worldwide, often with surprising results. Kirk Johnson, Ph.D., chief scientific officer at MediciNova, and his collaborators were researching the role of glial cells in chronic neuropathic pain. He found that the cytokine interleukin-10 (IL-10) acted on glia in a way that reduced chronic pain, but IL-10 had to be injected intrathecally to be effective. Johnson wanted to find a more patient-friendly alternative. His team conducted a painstaking literature search screening for studies of oral agents that reported effects on glia similar to IL-10. They found ibudilast, an oral medication available in Japan for 20 years.



"It's about collaboration, and new science, but it's also about Big Pharma saying, 'We're not here to own everything.'"

Ash Bahl, Ph.D., senior director of global external R&D, Lilly

To assist researchers in the discovery process and speed translational research, NIH created the National Center for Advancing Translational Sciences (NCATS) in late 2011. NCATS director Christopher Austin, M.D., says, "The center was created to speed new therapies to patients by reducing or eliminating bottlenecks in the translational research pipeline." He characterizes NCATS as something of a cross between a matchmaker and a catalyst among academia, pharma, and patient advocacy groups. NCATS has the resources to assist with the identification of potential compounds and support research and the connections to foster collaborations among its constituents. Austin says, "Investigators, patient groups, or the industry can approach us looking for links, and we can match them with partners."

INTELLECTUAL PROPERTY EXCLUSIVITY: THE 900-POUND GORILLA FOR INVESTOR FUNDING

"Ninety percent of FDA-approved drugs are off patent, and there's no good way to commercialize them," says Austin. He cites the example of auranofin, an anti-arthritic. NCATS screening found a potential positive therapeutic connection between auranofin and chronic lymphocytic leukemia, but auranofin is off patent. "Here we have a therapy with apparent efficacy for a serious disease in its current dosage that costs pennies a day, and we have no way to fund a phase 3 trial. We're looking for a solution to this sort of situation."

Finding an existing drug that meets an important unmet medical need is half the equation. Coffee says, "You need both a scientific case and a business case to proceed viably." For survival in a for-profit enterprise, establishing exclusivity is equally important as proving a medical theory. "While our scientists were researching the scientific case for ibudilast, we were very careful and thoughtful about laying down a strategy for intellectual property. We got five years exclusivity under Hatch-Waxman and developed strong method-of-use patents for ibudilast, in some cases out to 2030."

Funding is not always easy, even with known compounds. Lederman says, "Two problems right now are that investors are impatient and risk averse. Even Big Pharma is too impatient to wait for an NCE." Repurposing lowers these obstacles, but the major challenge is convincing investors that repurposed products can get exclusivity.

Grants can be an important source of funding. The NIH is the largest grantor, but patient advocacy groups are playing a larger role, particularly in small-market drugs for rare or neglected diseases. They are more interested in outcomes than profitability. Nonprofits, such as the Nicholas Connor Institute and CureDuchenne, have been able to focus financial resources on translational research that might not normally receive commercial support.

RESCUE OPPORTUNITIES WITH BIG PHARMA AND NCATS

In 2011, the NIH held a roundtable with industry experts to discuss rescue and repurposing drugs. The question was asked, "Are there drugs that failed to show benefit in their primary indication that could be used for other diseases?"

NCATS responded to the question by collaborating with eight pharma companies in a pilot program called "Discovering New Therapeutic Uses for Existing Drugs." NCATS is providing funding, peer review, and research data for the project. The eight companies are offering 58 high-quality compounds to academia for further development. "These drugs have been proven safe but ineffective," says Austin. The compounds have undergone extensive preclinical, and in some cases, Phase 1, studies. Austin says these products are like a football that's been carried to the five-yard line and just needs a new offense to get it across the goal line.

Lilly is collaborating in the project by providing compounds and screening compounds with PD^2. Bahl says, "It's apparent that our compounds may have applications in therapeutic areas outside our strategic areas of expertise." These compounds did not meet their original hypothesis, but they may have an application in an as yet unknown area, or they have shown promise in an area outside Lilly's focus or expertise. Bahl says, "We felt it was very important to offer quality products to the project that have at least 10 years of patent life left."

If a researcher's proposal is selected to study a compound in the project, the pharma companies involved will supply the clinical materials and all the data on the compound an investigator will need to file an NDA. Any new IP developed by the academic is theirs. The company will retain the original patent on the compound and the original-use IP. The academic and the company may then collaborate to develop and market the product. Bahl says, "It's about collaboration and new science, but it's also about Big Pharma saying, 'We're not here to own everything.'"

Researchers may decide to collaborate directly with drug companies. Lilly has extended an open invitation to investigators to use PD^2 to research possible therapeutic activity between compounds and cellular assays for diseases. Any discoveries belong to the investigator. They may choose to work independently, but Lilly invites investigators to collaborate with the company to develop the compound for clinical trials. Bahl says, "For discoveries in our own areas of expertise, we would pursue the collaboration ourselves. For discoveries on the fringes of what we'd do internally, we could enable small, project-focused companies sponsored by either venture capital or a public-private organization like NCATS."

BE OBSERVANT, BE CURIOUS

For repurposing, Coffee says, "There are two words of advice — be curious. Read, listen, talk to people, and be aware of nuances," he says, "There is serendipity, but it's a kind of mosaic. You need to be observant and put the pieces together."

Lederman agrees. "Be observant," he concludes. "As general advice, if you work on medically important problems, and you can add value from a medical and managed care point of view, you will be richly rewarded."

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Starting A Biotech Company In The Midst Of Recession

Mansour Bassiri, Ph.D.

Dr. Bassiri is the founder and CEO of Bioxiness Pharmaceuticals, a company focused on developing a new class of antibiotics targeting gram-negative and drug-resistant bacterial pathogens systemically.

Drug discovery is inherently a tough business and a high-risk investment with huge costs and lengthy timelines necessary to bring most products to market. The industry is further challenged with overwhelming regulatory hurdles and the complexity of the science itself. Compounding that picture today is a number of disturbing events and trends, including restraint or lack of aspiration toward the industry by many investors in both public and private capital markets and a corresponding major shift in some parts of the venture capital sector. Additionally, the lack of public market liquidity, escalating new product discovery costs, and similar conditions continue to threaten young companies and their respective entrepreneurs.

HOW DOES A START-UP BIOTECH PREVAIL?

Small biotechnology companies are essential components of the intellectual infrastructure of America's 21st century economy. Developing important treatments and cures by our industry will play a critical role in reducing healthcare costs, improving quality of life for patients, and creating high-quality, high-paying jobs. New antibiotics are especially important given the growing number of resistant strains of bacteria being spawned by the abuse and overuse of antimicrobials worldwide.

In the United States, we urgently need to create public-private partnerships to contain and combat antimicrobial resistance. To achieve an effective goal, federal funding such as Therapeutic Discovery Project (TDP) grants are needed to fund a wide range of projects focusing on basic research, strategies for the prudent use of existing antimicrobials, development of new antimicrobials, and development of point-of-care diagnostic tests.

In 2010, TDP tax credits and grants provided $1 billion to small biotech companies throughout the United States. Companies with fewer than 250 employees which had made qualified investments in the development of promising new therapies designed to treat or prevent costly and chronic diseases were eligible for the program. Nearly 3,000 small companies received funds from the program for more than 4,500 innovative projects. With this funding, these small companies were able to save and create high-quality, high-paying American jobs.

S. 3232 would extend the Therapeutic Discovery Project for an additional $1 billion to cover qualifying therapeutic investments made in 2011 and 2012. It would also refine the program to ensure that taxpayer dollars go to the most deserving and innovative companies and to projects with the most significant potential to meet the medical challenges America faces. This proposed reauthorization of TDP comes at a crucial time for the biotech industry, as capital availability is significantly constricted for growing companies. According to the National Venture Capital Association's quarterly report, the number of first-time financings for life sciences companies in 2011 was at its lowest level since 1996. The crucial capital injection from a reauthorization of TDP would allow companies such as ours to continue their work of speeding treatment and cures to patients whose lives depend on them while also creating high-quality, high-paying American jobs.

Our company was a recipient of a TDP grant, which led to matching investments from other sources, enhancing our credibility with investors. Consequently, we were able to leverage the TDP grant and quadruple the impact of the funding, resulting in a net gain of more than $1 million that is being used to further our research. The funding enabled the company to extend its R&D activities by two years, hire highly-skilled researchers (consultants and U.S.-based CROs), and advance its patent portfolio from the international filing stage to the national stage in multiple countries around the globe. Without this TDP grant, start-up companies like ours would essentially not have been able to continue research on a potential new class of life-saving antibiotics. The future survival of start-ups will involve a dynamic blend of public-private partnerships with solutions that tackle both scientific and financial holdups while identifying the essential components of the intellectual infrastructure of America's 21st century economy.

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Want to Create An Innovative Environment?

Max Michael, M.D.

Innovation in the life sciences is rapidly improving our daily lives. But the magnitude of each change along the way seems increasingly small as the time to explore an odd hunch or an ah-ha moment — often a vital criterion for innovation — lessens. Within companies of all types, the motivation for transformational ideas is often sacrificed in favor of profits and near-term thinking.

Conversely, many innovation experts claim the best opportunity for new ideas to emerge and flourish occurs when there is time to think and incubate an idea, hold interdisciplinary discussions, encourage a willingness to fail, and spend time with one another in an unencumbered space. Some companies and universities have begun adopting these principles. For example, the University of Alabama at Birmingham (UAB) School of Public Health recently opened a dedicated space called The Edge of Chaos to promote such an environment for transformational innovation. If you want to create a similar climate in your organization, consider taking the following foundational steps:

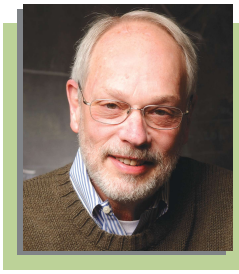
Carve Out Time to Think

Investing in time for ideas has dividends that translate into new products and increased earnings over time. For example, Google incorporates this into its workplace cultures, allowing employees to spend 20% of their time during a workday to pursue hunches. This has led to the creation of vital pieces to its portfolio like Gmail, Google News, and Adwords. Time alone, however, is not a solution. It must also be supported by progress reports, the involvement of peers in approving or contributing to the work, and an active management team that sees value in the potential for something big. Like capitalism, freedom with some parameters creates a thriving environment for new ideas. Make it a point to bring people together from diverse backgrounds and perspectives to grapple with a complex problem. Remember, innovation dies in silos.

Failure is Success

Many successful entrepreneurs have failed on their way to success. Yet the concept is still taboo. Innovation thrives when taking risks and embracing failures. Thus, life science companies should look at how to incorporate an acceptance of failure as a part of their culture, which starts at the top. C-level leadership needs to communicate healthy risk-taking. Just look to Silicon Valley, where Facebook employees are encouraged from the top down to "fail faster." Failures of the incremental variety often lead to a larger discovery.

In a business world that strives for order and structure in a quest for ROI, try inviting a little chaos into your company. Organization and efficiency can often stifle innovation, which is an uncomfortable thought for most of those in the board room. Instead, dedicate the time, open up your environment to new influences, and promote the benefits of failure. You might just "randomly" stumble across that next great life science advancement.



Max Michael, MD is a general internist who has served as the dean of the UAB School of Public Health for more than 11 years.

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