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JUNE 2014


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# Lilly's Tale of Trial & Tenacity

**John Lechleiter** and his team weather patent expirations to create a more competitive company. **p. 24**

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# Drug Development – You Get What You Incentivize For

**ROB WRIGHT** Chief Editor

Allowing the application of a "one-size-fits-all" intellectual property policy that affords the same protection for Frisbees as lifesaving and sustaining medicines would be, quite frankly, moronic and short-sighted. It would also be a disincentive for companies to develop R&D-intensive drugs because the longer it takes to develop, the shorter patent life you have. The converse is also true — less costly drugs brought to market more quickly get longer patents. Until fairly recently, this is exactly what was done, and why we had the "me-too" drug era of the 1990s as well as the shortage of antibiotics necessary to treat common infections today. If you want new cures in areas that don't seem profitable, you need to provide the proper incentives for companies to take the risk, along with making sure provisions are in place to properly align industry stakeholders (e.g., how Medicare reimburses hospitals for antibiotics). Now, if you want inexpensive drugs, we need to further rethink drug patent protection to achieve this as part of the outcome.

According to American economist Steven Landsburg, most of economics can be summarized in four words: "People respond to incentives." Don't forget, pharmaceutical companies are run by people and similarly respond to incentives. For example, prior to 1983, industry averaged fewer than one specialty pharmaceutical per year for rare diseases. Apparently, Democratic Congressman Henry Waxman believed this level of productivity to be inadequate and sought to increase the development of rare disease drugs. In so doing, Waxman demonstrated an affinity for Landsburg's economic philosophy. How else can you explain his serving as the principal author of the Orphan Drug Act (ODA), which provided incentives (i.e., federal grants, development assistance, waiver of the PDUFA filing fee, a 50 percent tax credit of clinical investigational expense, and a seven-year period of market exclusivity after FDA approval) to entice companies to develop more rare-disease drugs? Today, our industry averages more than 13 specialty pharmaceuticals annually, proving the point — people respond to incentives. Obviously, the FDA believes this also to be true, having created a number of additional acts to incentivize innovation, such as Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review, and GAIN (Generating Antibiotic Incentives Now). Though all have various enticements and provisions, I have yet to find one which specifies, "And make sure it's cheap too."

In March, Waxman and two other Democratic members of the House Energy and Commerce Committee wrote a letter demanding Gilead Sciences justify the price of its hepatitis C drug. Well, Mr. Waxman, it is what it is. You got exactly what you incentivized for — a breakthrough therapy drug. Cheap was not part of the incentive. Ever consider longer patents? What about tying longer patents to how quickly a company is able to execute its R&D plan or tie it to a step-down, drug-pricing exchange model, or even request price estimate forecasts as part of participating in an incentive program? But if you want companies like Lilly (see feature with CEO John Lechleiter, p. 24) to continue developing drugs such as Cyramza, which received FDA approval for stomach cancer in April, don't demand they justify the price after the fact. This year an estimated 22,220 Americans will be diagnosed with stomach cancer and 10,990 will die from the disease. Cyramza has shown to improve median overall survival by 1.4 months. What is that worth?

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## Q What is your best practice for preparing to present at investor conferences?

**A EVERY INVESTOR CONFERENCE IS UNIQUE BECAUSE THE PSYCHOLOGY OF THE FINANCIAL MARKETS IS CONSTANTLY CHANGING.** Presenting at JP Morgan is no different from any other investor presentation. What is different is the size of the attendee universe. From my experience as former CEO of Chimerix, the focus was on assuring our message was consistent: We completed a successful IPO in April 2013, initiated enrollment of phase 3 SUPPRESS trial of brincidofovir, and anticipated data in mid-2015. Our focus was on the competitive advantages of the candidate, as well as the recent hire of a chief commercial officer to facilitate brincidofovir's commercial positioning. Strive to provide complete and accurate information, so investors, sell-side analysts, and bankers know your goal is to communicate openly and effectively.

**KENNETH MOCH**
Kenneth Moch, former CEO of Chimerix, has 30 years of experience creating, managing, and financing biomedical companies. In addition to Chimerix, Moch has been CEO of several other companies, including Alteon and Biocyte, and he cofounded The Liposome Company (acquired by Elan).

## Q What do you see as an exciting development toward improving pharma manufacturing efficiency?

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**TIM FREEMAN**
Tim Freeman is managing director for powder characterization company Freeman Technology. He has 10+ years of experience in understanding and characterizing powder behavior and works closely with the pharmaceutical and powder processing industries.

## Q What is the best leadership advice you ever received?

**A THE BEST ADVICE I RECEIVED EARLY IN MY CAREER CAME FROM VICTOR BAUER, PH.D.** At the time, he was president of the U.S. division for Hoechst-Roussel Pharmaceuticals, and I was running the cardiovascular laboratory in Bridgewater, NJ. I had been with the company for only about three years when he called to tell me there was an opportunity in clinical pharmacology in the clinical research department that I should consider. When I asked why he thought this to be a good move, he replied, "Be open to new opportunities to better understand all aspects of the business." This led to many opportunities to expand my experience in both the pharmaceutical and CRO industries. He opened the door for me, but I needed to step through and be open to learning new things.

**JOHN HUBBARD**
Dr. John Hubbard is senior VP and worldwide head of development operations for Pfizer. In this position, he is responsible for global clinical trial management from Phase 1 to 4, which includes more than 700 clinical projects.

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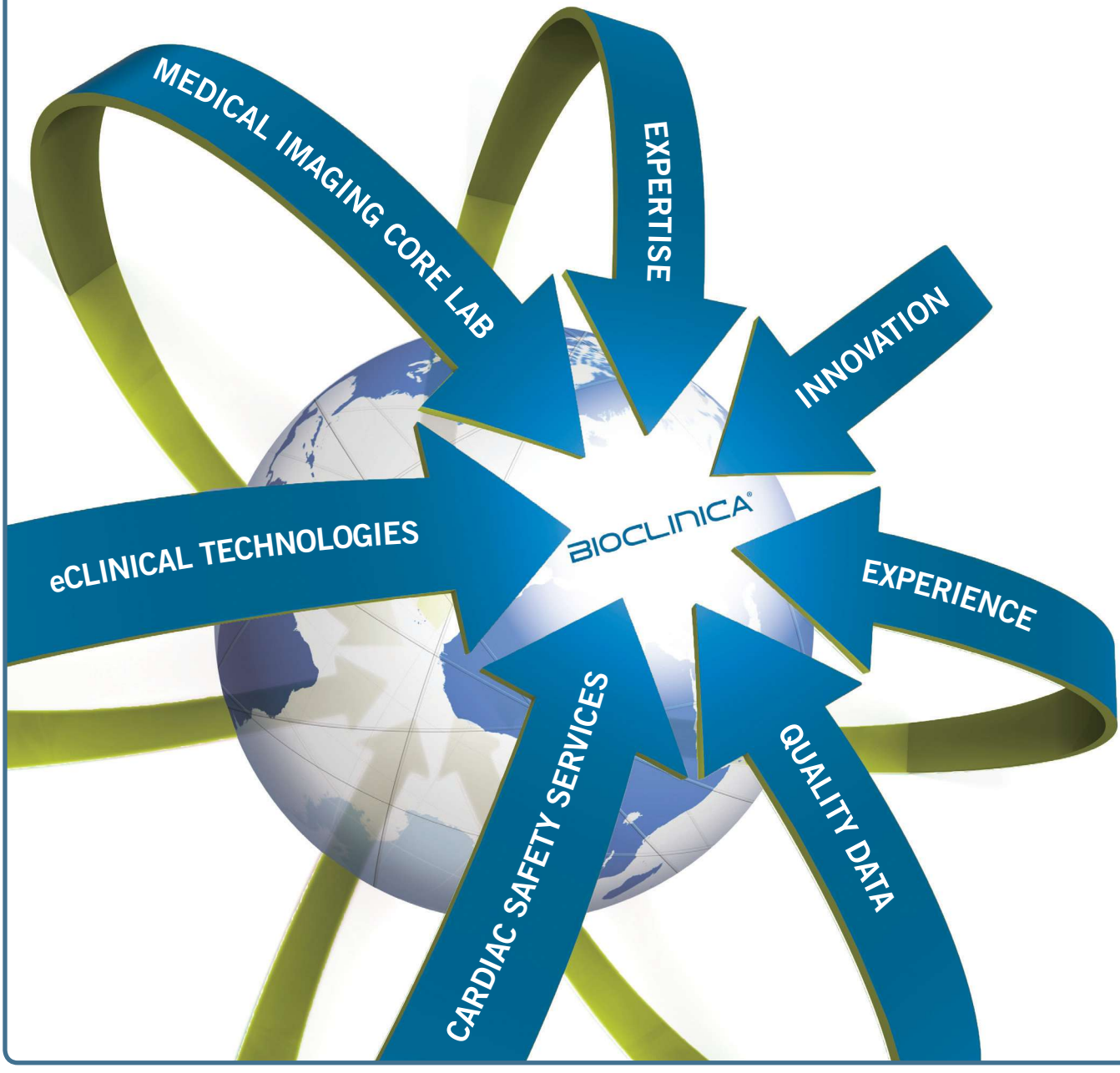


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# Dysfunctional Tax Policy
## Harming Life Science Innovation And Jobs

**JOHN McMANUS** The McManus Group

*(Written May 15, 2014)*

It is now undeniable that federal tax policy has as big an impact on innovation in healthcare as any other healthcare policy that impacts Medicare, Medicaid, or commercial insurance coverage and reimbursement. Two examples now gaining increasing attention in Washington make that abundantly clear:

1. the excise tax on medical devices
2. the corporate tax law known as "inversion," which enables an American company to reincorporate into a lower-taxed foreign country.

### MEDICAL DEVICE TAX COSTING JOBS AND RESEARCH

Congress enacted a 2.3 percent excise tax on medical devices as a $28 billion scheme to extract revenue out of that industry in order to help fund Obamacare. The argument at the time was that the medical device industry would benefit from all the new covered lives that Obamacare would produce, so it should do its part by helping to finance the program.

That logic was flawed because most of the device business is for seniors, which Medicare already covered. Moreover, after the Supreme Court made the Medicaid expansion optional, nearly half of the states refused to cover those low-income, uninsured adults. And a recent McKinsey study found that about three-fourths of the people enrolled in the new health exchange previously had coverage.

Because the device tax is an excise tax on gross revenue, it is far more pernicious than an income tax and grows more expensive over time. Imagine a small device company – which dominate the industry – with $20 million in revenue and a 5 percent profit of $1 million. Assuming it had a 25 percent corporate tax rate, it would pay $250,000 in income tax. The 2.3 percent excise tax on revenue requires it to pay an additional $460,000 tax, which balloons its federal tax by 184 percent!

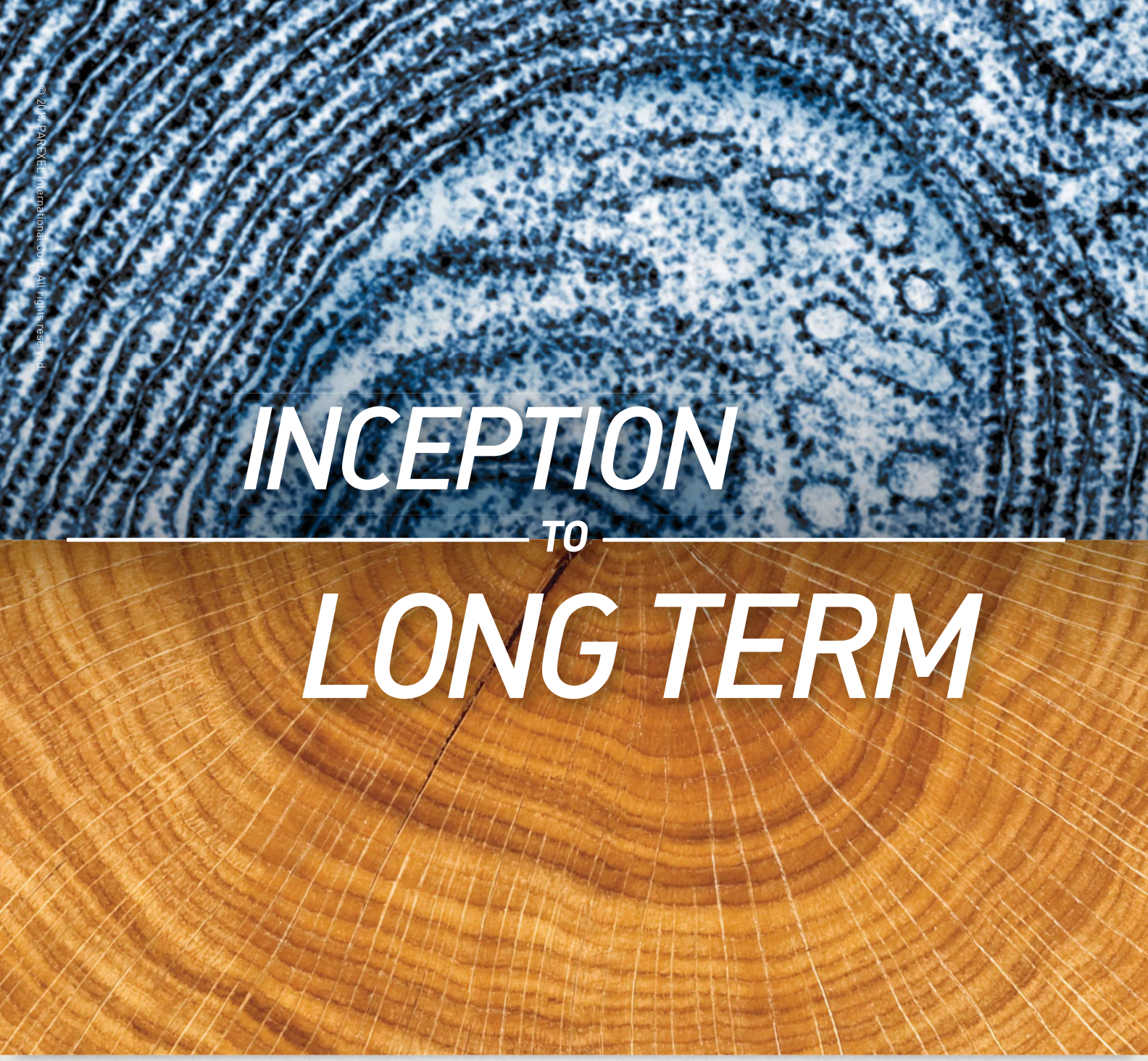
The results are even more dire for companies that are not yet making a profit. A recent survey by the Medical Device Manufacturers Association of its members found that 64 percent work at companies that are not yet profitable, but are generating revenue and, therefore, subject to the tax. One CEO complained, "The device tax takes our profit to a loss."

How are device companies responding to this new burden? Job layoffs and reduced research and development:

- That same survey found that two-thirds of companies were reducing or halting job creation or relocating outside of the U.S. as a direct result of the device tax. More troubling, nearly half of the companies reported reducing R&D to pay for the tax, 18 percent, on average.
- A more comprehensive survey undertaken by Advamed found that in the first year of the tax's implementation (2013), 14,000 workers in the device industry were laid off, and 30 percent of companies had decreased R&D.

The Republican-controlled House has voted numerous times to repeal the medical device tax, but the Democratic-controlled Senate has not permitted a vote on the bill. Majority Leader Reid (D-NV) has employed a parliamentary tactic known as "filling the amendment tree," which denies the Senate from voting on the device tax repeal or any other issue that is not already incorporated in the underlying bill.

However, pressure is building by Senate Republicans to permit a vote on a two-year suspension of the tax as part of the must-pass tax extender package. If the Democratic leadership allows the Senate to work its will, it could be a baby step to earning back its reputation as the most



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*"It is now undeniable that federal tax policy has as big an impact on innovation in healthcare as any other healthcare policy that impacts Medicare, Medicaid, or commercial insurance coverage and reimbursement."*

deliberative body in the world, and this job and R&D killer could be terminated on the installment plan.

### ANTIQUATED TAX CODE INCENTS FOREIGN OWNERSHIP OF U.S. COMPANIES

Meanwhile, Congressional paralysis on comprehensive tax reform has left U.S. corporate tax rates among the highest in the world and continues to distort decision-making of many American pharmaceutical executives by making it irrational to maintain their primary base of operation in the U.S. The latest example is New York-based Pfizer's proposed merger with the smaller U.K.-based Astra Zeneca, in part, to benefit from Britain's lower tax rate.

The deal is known as an "inversion," whereby the multinational U.S.-based company becomes an expatriate by acquiring the smaller foreign company. The U.S. tax code encourages this behavior because U.S.-based companies are taxed at the 35 percent rate for worldwide income, but they can defer U.S. tax on income earned abroad until it is repatriated. Most other countries have a territorial system, which only taxes income where it is earned.

An inversion enables the company to pay only U.S. taxes on its U.S. income, and not its worldwide income. In Pfizer's case, it had $69 billion in foreign profits indefinitely invested abroad because it did not want to subject those earnings to the high U.S. tax rate. Pfizer CEO Ian Read proudly stated that the deal would "liberate the balance sheet and tax of the combined companies."

Valeant's acquisition of Biovail, a Canadian company, enabled it to achieve a low single-digit tax rate. It is now attempting a hostile takeover of California-based Allergan and touting the tax savings that can be achieved to maximize shareholder value and slash Allergan's current 25 percent rate. Allergan is a profitable company that has been growing by double digits for years and devotes about 15 percent of revenue to R&D. Valeant lost money on $500 million less revenue than Allergan last year and devotes only about 3 percent to R&D, preferring to acquire already-successful products. Yet the distorted tax code makes the acquisition of Allergan a distinct possibility.

Of course these mergers do much more than erode the U.S. tax base. They often result in substantial job loss, particularly in the U.S., and reduced R&D for the cures of tomorrow. These "efficiencies" have been publicly discussed as a benefit to shareholder value, even though there may be less value to the society at large over the long run. What happens to these high-wage, high-skilled jobs that beget other good jobs? Who is going to support the economy and provide the tax base for investments in our future? Is America going to cede these jobs to Europe, Latin America, and East Asia?

### WHAT IS CONGRESS DOING ABOUT INVERSIONS?

Ways and Means Chairman Camp (R-MI) introduced comprehensive tax reform legislation that would lower the U.S. corporate tax rate to 25 percent and move to a territorial system that eliminates incentives for inversions.

On May 8, 2014, Finance Chairman Senator Ron Wyden (D-OR) issued a public statement saying that he and Senator Carl Levin (D-MI) intend to introduce legislation to stymie the growing trend of U.S. companies inverting and moving their tax domiciles outside of the U.S. His bill would have a retroactive effective date of May 8, 2014. In addition, the bill increases the current 20 percent threshold of foreign company ownership to invert to 50 percent. While that bill is more punitive than the Camp approach, it does not address the underlying international inequities that are distorting company decision-making.

Unfortunately, with comprehensive tax reform stalled, the prospect of any action in this area looks remote.

### CONCLUSION

Current U.S. tax policy, including the medical device excise tax and the dysfunctional corporate tax, has harmed U.S. innovation and U.S. job creation in the life sciences industry. It is high time that Congress begins solving these problems, even if it's through a piecemeal approach like a temporary suspension of the device tax.

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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# PROTALIX BIOTHERAPEUTICS

Using plant cells instead of mammalian cells to produce protein drugs, plus a partnered product already on the market, could possibly put this company in the lead.

WAYNE KOBERSTEIN Executive Editor

## SNAPSHOT

Protalix has a unique plant-cell platform for therapeutic protein production and an approved product, Elelyso/Uplyso (taliglucerase alfa), for Gaucher disease. In the company's pipeline is a chemically modified version of the recombinant alpha-Galactosidase-A protein for Fabry disease (Phase 1/2), an oral glucocerebrosidase (GCD) enzyme replacement therapy for Gaucher disease (Phase 1), an oral anti-TNF (tumor necrosis factor) fusion protein for autoimmune/inflammatory conditions (preclinical), and a human deoxyribonuclease I (DNase I) for cystic fibrosis (preclinical), and other enzyme replacement therapies in early research.

## WHAT'S AT STAKE

Be careful when someone claims to be number one; it depends on how you define the field. Just after filing my recent story on Medicago (March 2014), I encountered another plant-technology company, Protalix, that made the fine but significant distinction that I might have otherwise failed to mention: Medicago and others in the plant-based production sector grow whole plants, such as tobacco, in large gardens or greenhouses; Protalix produces proteins in plant cells, grown like other cell media in traditional bioreactors. But it is not just its platform that sets Protalix apart — it's also the company's approved plant-cell-produced product and several other candidates in its pipeline.

"In the early days of therapeutic recombinant proteins, manufacturing used bacteria for the simpler proteins, then evolved into using mammalian cells such as Chinese hamster ovary [CHO] cells," explains David Aviezer, president and CEO. "But we offer a new way to transition from using mammalian cells to using plant cells as the cell source for special therapeutic proteins."

Aviezer cites a "substantially lower" cost of goods as one advantage of the Protalix platform. "As an example, it is like comparing the cost of having a pet dog or cat to having a flower pot in your living room," he says. Safety is another factor. "Humans are not affected by any plant viruses so what we have is a built-in biological firewall, preventing any kind of transmission of mammalian-associated infectious viruses or prions."

Why is it significant that Protalix uses plant cells rather than whole plants? Use of bioreactors versus plant-growing operations keeps the technology in familiar territory for engineers, manufacturing personnel, and perhaps above all, regulators. Equipment, guidelines, procedures, and processes remain essentially the same as they have been for decades in the biotech industry. With typically dry humor, Aviezer says, "We grow carrot cells. And, as we like to say, the only carrots we have in our facility are the carrots in chicken soup. But we have a very well-regulated and controlled system for producing our therapeutic proteins that really can comply with all the regulatory necessities needed for high-quality drug production."

Oral delivery is a somewhat serendipitous outcome of the plant-cell product. Protalix takes advantage of the cellulose base in its oral-delivered drugs as a natural way of keeping them protected from digestion until they reach the small intestine, where the physical jostling opens up pores in the cellulose, releasing the active drug where it can be absorbed intact by the gut. Aviezer refers to the anti-TNF drug as "basically a plant-cell expressed Enbrel [etanercept]" that will go into human studies this year.

Although Aviezer says there is room for other plant-based technologies in drug manufacturing, he clearly believes easy adoption, low cost, safety, effective delivery, and protein refinements will give his company's platform the competitive edge. After 10 years in the business, having a healthy product on the market and arguably taking a technology lead, Protalix gives its CEO good reason for careful optimism.

DAVID AVIEZER
President and CEO

### Vital Statistics

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**Finances**

Raised
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in underwritten public offerings

**Research Partnership Funding**

Pfizer
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for Elelyso development and commercialization

**Other Partners**

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Uplyso supply & technology transfer agreement

Teva
R&D with ProCellEx platform

### Latest Updates

**February 2014:** Reported top-line Phase 1 clinical trial results for oral glucocerebrosidase in Gaucher patients.

**2013:** Continued worldwide approvals of Elelyso / Uplyso.

**August 2013:** Added three new plant-cell recombinant proteins to the development pipeline.

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# As Outsourcing Relationships Evolve, Vaccine Production Will Continue To Shift To CMOs

*The vaccine contract manufacturing market currently accounts for less than 1 percent of the total vaccine market — approximately $705M of $33.7B — but it is expected to grow over the next decade. Varying factors will influence the growth of the contract manufacturing market segment, including overall growth of the vaccine market, especially in emerging markets, as well as the shift in the dynamic of outsourcing relationships.*

**KATE HAMMEKE**
Director of Marketing Intelligence
Nice Insight

> *"Advances in both preventative and therapeutic vaccines have renewed interest and brought about competition in this market segment."*

Traditionally, vaccines had been viewed as a low-margin business with high barriers to entry. Complexity of development and production, combined with significant fixed costs, low profit margins, and overregulation had limited competition among vaccine manufacturers and supposedly restricted innovation. However, advances in both preventative and therapeutic vaccines have renewed interest and brought about competition in this market segment.

Among Nice Insight survey respondents, the primary area of therapeutic focus for vaccine production outsourcers is infectious diseases, at 71 percent. Increased global demand for the influenza vaccine has contributed significantly to the growth of the outsourced vaccine market — especially since the vaccine doesn't offer long-term immunity and must be administered annually. Support and media exposure from organizations such as the International AIDS Vaccine Initiative help to keep the important role of vaccines in healthcare in the forefront and drive attention toward developing vaccines for diseases that currently have no cure. This exposure, coupled with recent reports of progress in two separate approaches to provoking an immune response to HIV, certainly contributes to the increasing number of biopharmaceutical companies interested in developing or manufacturing vaccines.

Oncology is another key area for vaccine advances, with 52 percent of vaccine outsourcers engaged in this therapeutic category. Nationwide immunization programs for HPV (human papillomavirus) vaccination established in 2008 in the U.S. and Europe have strengthened this market to an estimated value of $2.2B by 2018. The efficacy of the vaccine, as well as the expansion of the target audience to include both males and females, has secured the HPV vaccine's future and made it a strong candidate for outsourced production.

Anticipated shifts in vaccine production from innovators to contract manufacturers influenced the decision to add this service to the Nice Insight Biopharmaceutical Outsourcing Survey for 2014. At present, the data shows 13 percent of all respondents will outsource vaccine production, or 40 percent of respondents who outsource biomanufacturing. Big Pharma and Big Biotech account for the majority of vaccine outsourcing, comprising 59 percent of the buying market. Emerging biotech and emerging pharma each comprise

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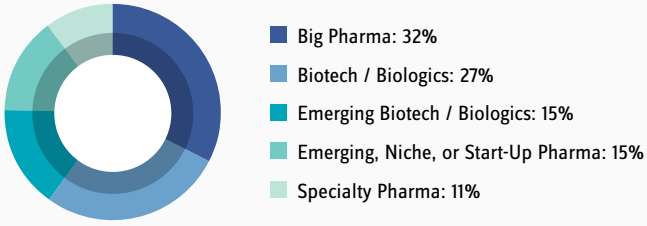
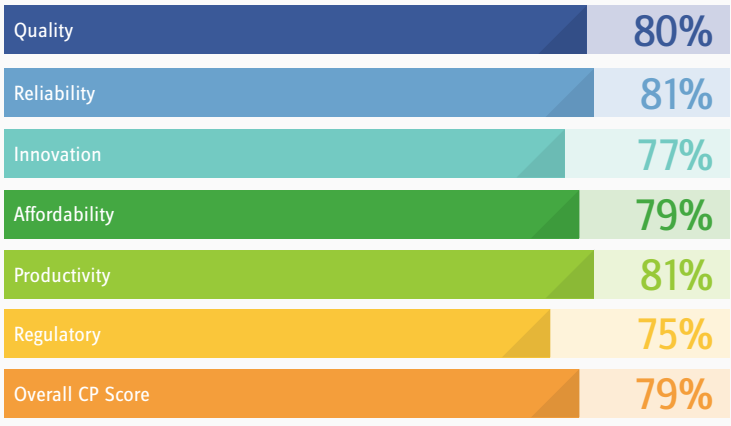
## The Percentage of Vaccine Production Outsourcers from Each Buyer Group




## Rank of Outsourcing Drivers


## Average Score Among the Top 5 CMOs for Vaccine Production




**Survey Methodology:** The Nice Insight Pharmaceutical and Biotechnology Survey is deployed to outsourcing-facing pharmaceutical and biotechnology executives on an annual basis. The 2013-2014 report includes responses from 2,337 participants. The survey is comprised of 240+ questions and randomly presents ~35 questions to each respondent in order to collect baseline information with respect to customer awareness and customer perceptions of the top 100+ CMOs and top 50+ CROs servicing the drug development cycle. 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. In addition to measuring customer awareness and perception information on specific companies, the survey collects data on general outsourcing practices and preferences as well as barriers to strategic partnerships among buyers of outsourced services.

approximately 15 percent of the buying market, and specialty pharma accounts for the remaining 10 percent.

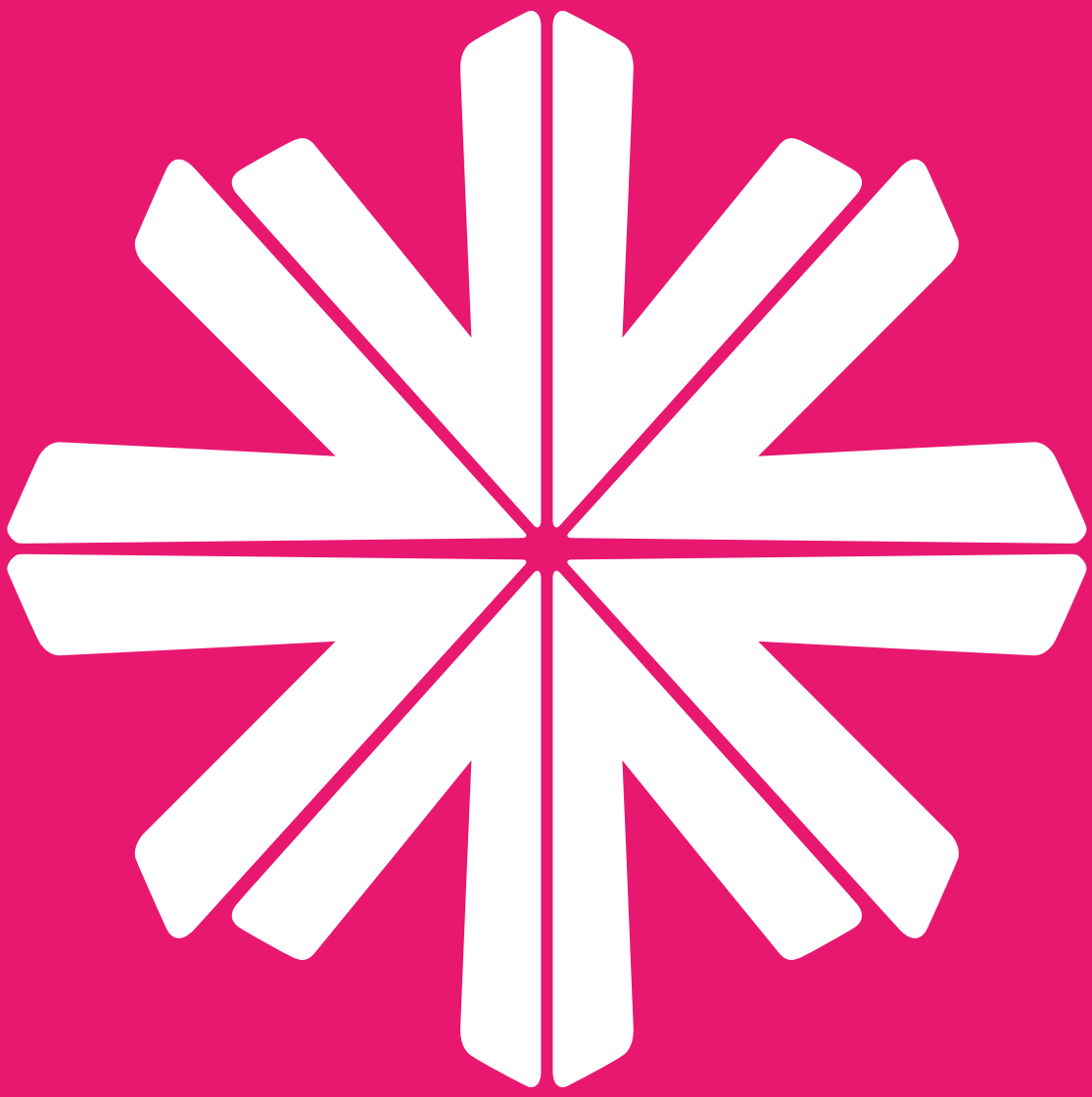
### SELECTING AN OUTSOURCING PARTNER FOR VACCINE PRODUCTION

While quality and reliability consistently hold the top two positions among partner attributes, when it comes to selecting an outsourcing partner for vaccine production, the importance of productivity and innovation moves upwards, causing a company's regulatory track record to shift to sixth position. In fact, when reviewing the companies most likely to be considered for an outsourced vaccine project, the top five companies scored best in quality, reliability, and productivity. This ranking makes sense, as reliability is directly linked to security in supply, and productivity is directly linked to time-to-market. Security in supply is particularly important for routine vaccines, whether they are childhood immunizations or, like the newer HPV vaccine, administered during adolescence. Time-to-market becomes a considerable issue when there is a surge in the need for a vaccine, such as the flu vaccine when a particularly bad strain hits or during times like the swine flu and bird flu outbreaks. As CMOs continue to be viewed as trusted partners in bringing drugs to market, their expansion into segments such as vaccine production will continue to add value to drug innovators in terms of product security, improved time-to-market, and increased capacity — all traits where the positive impact is passed on to the health of the consumer.

N. WALKER

S.FAZZOLARI

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.



# THE FUTURE OF CLINICAL DEVELOPMENT BEGINS JUNE 16, 2014

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# Bioprocessors Demanding Single-Use Sensors

Best Practices: Performance measurements require better sensors

**ERIC LANGER**
President and Managing Partner
BioPlan Associates, Inc.

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

*"Clearly, the industry feels the time has come for the introduction of better sensors."*

Today's biopharmaceutical manufacturers are expecting suppliers to innovate better sensors because regulators continue to require increasingly detailed and complex measurement of processes. Even as the prevalence of single-use equipment spreads, the quality of sensors is not keeping up; few single-use sensors are sufficiently robust enough to handle current requirements. Additionally, sensors are limited to relatively few basic analytes.

Clearly, this is an area of opportunity that is in need of major improvement. And demand is not just anecdotal. Results from our latest study — the *11th Annual Report and Survey of Biopharmaceutical Manufacturers* — confirm that the industry is still calling for innovation in single-use sensors.

## SENSORS NOW SIT ATOP THE INNOVATION LIST

We asked more than 230 industry participants to consider the new products and services being developed by suppliers, and to cite the top five areas on which they expect their suppliers to focus development efforts. Of the 21 areas we identified, "disposable probes and sensors" were the most commonly cited (45 percent), which outpaced demand for innovation in disposable bioreactors (40.3 percent), cell culture media (38.9 percent), and disposable products and bag connectors (37.6 percent).

What's more, the industry's desire for sensor innovation continues to grow. That 45 percent metric is the highest figure we have seen as of yet, up from a high of 30 percent in the past three years.

Demand for sensors appears to be largely consistent across the Atlantic. U.S. respondents put disposable probes and sensors atop their list, while this area was second only to disposable bioreactors for Western Europeans. That growth crosses both sides of the Atlantic. The 50 percent of U.S. respondents interested in single-use sensor innovation represents a step up from the past couple of years, while the 47.4 percent of Western Europeans expressing a desire for innovation in this area represents an even bigger uptick from last year's survey results.

## ARE INNOVATIVE SUPPLIERS READY TO RESPOND?

With the increased demand for sensor innovation, vendors should be paying especially close attention to this area. To some extent, it appears they are.

When we separately interviewed a group of industry suppliers, we found that more than one in six are working on innovation in sensors and probes in some capacity. Although this was not a significant step up from last year, sensors and probes were in the top quintile of focus among the more than 50 new product development areas we tested with this group of suppliers. That's an encouraging sign that vendors are recognizing end-users' requests, though perhaps not quite to the extent that end users may desire.

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## TYPES OF SENSORS IN DEMAND ARE CHANGING

While simple sensors remain the most sought-after by end users, other types are growing in demand. In a separate section of our report, we examined the types of single-use sensors that the industry would like to see introduced or improved.

This year, pH and dissolved oxygen sensors remained at the top of the list, as they were last year. Of note, though, in-line titer sensors moved into the third position, up from the fifth spot last year. Also skipping a couple of positions this year was cell viability technology, the fifth-most-requested sensor introduction or innovation.

It's interesting to see that there are some somewhat contradictory results in our study, at least on the surface. For example, while demand for single-use sensor innovation is at its highest, our examination of specific single-use sensors found significantly dampened demand for many categories. That was the case for the following sensors:

- **conductivity** (22.9 percent this year, down from 37.7 percent last year)
- **temperature** (21.9 percent, down from 40.3 percent)
- **UV** (16.7 percent, down from 37.7 percent).

The only sensors to see appreciably more demand this year were those noted above: in-line titer and cell viability.

## SENSOR TRENDS

Our study offers up two potential trends: increased overall demand for better sensors, and a reduced desire for more specific sensors. In combination, these results suggest that the industry recognizes the need for better sensors, but there is less consensus about which types are most in need.

Nevertheless, there's no doubt that the broad demand for sensor innovation is likely to grow, particularly as sensors are needed for improved assay and analytical methods for process monitoring and control. Continued improvements in sensors, probes, and analytical equipment will indeed facilitate process quantification and process analytical technology (PAT). Thus, as bioprocessing becomes increasingly monitored by improved and new chemical, physical, and microbiological detection methods and assays — including single-use sensors/probes — the resulting data will be used for mathematical modeling and risk analysis. One comment provided by a study participant this year suggested that the lack of availability of reliable sensors capturing relevant data for process control is, in fact, hindering the adoption of PAT.

Clearly, the industry feels the time has come for the introduction of better sensors. L

FIGURE 1

### Selected New Product Development Areas of Interest

Biomanufacturers & CMOs, 2014 (Top Areas Suppliers Should Focus Their Development Efforts On)

| | |
|---|---|
| Disposable Product: Probes, Sensors, Etc. | 45.0% |
| Disposable Product: Bioreactors | 40.3% |
| Cell Culture Media | 38.9% |
| Disposable Products, Bag Connectors, Etc. | 37.6% |
| Chromatography Products | 36.9% |
| Disposable Product: Purification | 34.9% |
| Control Systems | 23.5% |
| Analytical Assays | 22.1% |
| Analytical Development | 22.1% |
| Fill Finish Services | 20.1% |
| Cell Line Services | 10.7% |
| Stainless-Steel Equipment | 4.7% |

**Survey Methodology:** The 2014 Eleventh Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production yields a composite view and trend analysis from 238 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations (CMOs) in 31 countries. The methodology also included over 173 direct suppliers of materials, services, and equipment to this industry. This year's study covers such issues as: new product needs, facility budget changes, current capacity, future capacity constraints, expansions, use of disposables, trends and budgets in disposables, trends in downstream purification, quality management and control, hiring issues, and employment. The quantitative trend analysis provides details and comparisons of production by biotherapeutic developers and CMOs. It also evaluates trends over time, and assesses differences in the world's major markets in the U.S. and Europe.

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# LILLY NAVIGATES THE REALITIES OF INNOVATION

By W. Koberstein

JOHN LECHLEITER Chairman, President, And CEO, Eli Lilly & Company

# LILLY NAVIGATES THE REALITIES OF INNOVATION

**WAYNE KOBERSTEIN** Executive Editor

**You have seen the headlines, reading like obituaries for the about-to-be departed.** You know the drill: repeated failures in Phase 3, nothing to replace the big earners with vanishing patents, mental images of a ship lost at sea. So why is Eli Lilly & Company still here — sailing the same course, undiverted, undiluted, and seemingly undeterred as the uniquely independent Midwestern-based company it has always been?

Right now Lilly is navigating through the most instructive and interesting period a company can traverse, and it appears to be showing remarkable patience and perseverance against a headwind of skepticism from the industry's Monday-morning quarterbacks. There could be no better time than right now to explore its strategic thinking from the viewpoint of the company's chairman, president, and CEO, John Lechleiter.

We catch up with Lechleiter at the latest PhRMA meeting, where he sits and speaks with us about Lilly's scientific strategies, investment and partnering, internal and external research, cost and effectiveness of clinical development, precommercial collaborations, regulation and reimbursement, patient-centered products, and other factors that affect the company's odds of success as an innovator. He tells Lilly's tale of trial and tenacity from the CEO's perspective — executive thought process and leadership, decision-making, and adaptation to changing circumstances — in the context of the corporation, its management team, and its organizational assets.

Later events in the following weeks heighten the drama but do not diminish the relevance of Lechleiter's talk with us. I never get the feeling he is merely parroting the same speech for every occasion, though he makes sure to include his talking points. In conversation, Lechleiter also shares his thoughts as well as facts. As one example, when asked about Lilly's animal-health business, Elanco, he elaborates on the unit's role in a way that seems completely consistent with the company's purchase of the animal-health business of Novartis two weeks later. As the conversation moves through the many areas of Lechleiter's responsibility, we learn not just *what* the company does, but *why*.

### THE DARKEST HOUR: AN IP LOSING STREAK

Lilly was already in trouble when Lechleiter took the CEO job in 2008. So, when asked what were his most difficult days in office, he unhesitatingly cites the first ones. "When I came into this job, we were looking ahead in three years' time to losing a series of patents that probably represents the biggest sort of bolus of patent losses that any company, particularly adjusted for size, has sustained," he says. Patent losses included the antipsychotic Zyprexa (olanzapine) in 2011, depression drug Cymbalta (duloxetine) in 2013, and Evista for osteoporosis (raloxifene hydrochloride) in March 2014.

"At the same time, we looked at our pipeline, and as recently as 2005, we had only seven molecules combined in Phases 2 and 3." Nowadays, he adds, the late-stage pipeline contains 38 candidates, with three potential launches in the near future.

"We knew it was unlikely our new launches would come in time to soften the impact of the patent expirations. They were going to come, as they are now, toward the end of that period," says Lechleiter. "How do you manage the company, finance your business, pay the dividend, and keep investing in R&D when your sales are plummeting, as they tend to do when a small molecule comes off patent, until you can start launching the new products? That is what has consumed me for the last six years."

In December 2009, Lechleiter and his team laid out a plan for investors: "We said, in no single year, from 2011 to 2014, would our revenue fall below $20 billion, our net income below $3 billion, or

## In The First Person — Lechleiter At Lilly

**TO TRACE JOHN LECHLEITER'S CAREER** is to travel an unusually straight line even by pharmaceutical executive standards. He has held 12 previous positions at Lilly since joining the company in 1979. But his course took a sharp turn early on; beginning as a chemist in the company's process chemistry group, he would soon step onto the management path. When his boss left in 1982, Lechleiter accepted the opportunity to lead the group, changing his direction from hands-on science to research management.

"It was a difficult decision," he says. "I wrestled with it for months, because I liked doing science and yet I also knew that I would enjoy essentially helping other people get results and contributing in a different way. I also knew it was a one-way path — once I left the laboratory, it would be the beginning of a new career. But I really never looked back."

After moving up in R&D management for the next 12 years, mainly in drug development, Lechleiter assumed the regulatory affairs leadership, beginning in 1994, and was on the corporate ladder from then on. In some ways, his career-long ties to Lilly belie a considerable diversity of work experiences, including a stint heading product development for the Lilly Research Centre in Windlesham, England, and a unique, decade-long tutorship as a direct report to legendary ex-chairman Sidney Taurel.

Lechleiter credits Taurel with helping bring out the best of his natural bent for management. "He was a great mentor and I had an opportunity to learn firsthand what a CEO does, what the thought process is, and what kinds of decisions one has to deal with in that role," he says. "I come at the job a bit differently from others. I enjoy working with people. I enjoy seeing others getting results, in essence, *through* people. I may have discovered along the way I have a talent for certain things in that vein. I didn't have an MBA and didn't know too much about matters of business, marketing, accounting — all the sorts of things that a CEO has to worry about. But I was able to learn a lot about it along the way."

Since Lechleiter completed his chairmanship of PhRMA in April 2013, he not only continued to face some tough times at Lilly, but underwent surgery for a dilated aorta in May. After only two months, however, he had made a positive recovery and was back on the job, looking fitter and, if anything, even more perseverant in the face of adversity than before.

How can you praise someone for being modest? All you can do, really, is to observe that part of the person's strength that comes from not wasting energy on personal conceit. For other CEOs, it must be highly distracting to act the haughty and vaguely celestial corporate king, a style of unfortunate currency in our time. Maybe it's Lechleiter's Kentucky roots, or a general Midwestern calm, that accounts for his equanimity, but whatever it is, it is genuine and completely unaffected, and at the same time powered by a steely determination. Logically, those are the same qualities that explain how he could plow through the past months and years — perhaps the most difficult time ever for Lilly and for Lechleiter personally.

> “We felt confident that we had the pipeline strength to avoid a large M&A.”

**JOHN LECHLEITER**
Chairman, President, And CEO,
Eli Lilly & Company

our operating cash flow below $4 billion, and we would maintain the dividend at least at its current level. I’m not sure there were a lot of believers that day, but we’ve stuck to those promises.”

With one minor caveat — the revenue guidance this year is $19.4 billion to $20.0 billion, though net income would be at least $2.9 billion — Lilly made all targets set in 2009. Although he says, “We’re not ready to declare victory yet,” Lilly’s stock price hit a multi-year high the day before our interview.

“I believe investors are starting to see that we’re coming through the worst of it, that we’re a better, stronger company now than we were going in. Obviously, we’ve had to downsize. We’ve had to make lots of changes and some adjustments to our business. But we are beginning to launch products, and investor confidence is coming back because of those aspects.”

Many, if not most, Big Pharma companies faced with a similar crisis, would have turned to a simple solution: merger or acquisition. But that was one road Lilly was not willing to go down, as Lechleiter explains. “We’ve studied the whole question of megamergers, or large-scale combinations, going back to the 1990s prior to the loss of the Prozac patent in 2001. We believed then and we believe now that size offers no particular advantage beyond the point where we are today.”

In other words, he asserts, megamergers are a short-term solution at best, wringing cost synergies from tens of thousands of job losses, but at the price of lingering integration challenges well-known in the industry. “We felt confident that we had the pipeline strength to avoid a large M&A. If we didn’t have the source of innovation through our pipeline, we may have had to make a different choice, but we believed we did possess the needed substrate and that was the best path for Lilly.”

Megamergers aside, however, Lilly was not averse to acquisitions that it saw as consistent with the path it was on. Lechleiter began his tenure with the 2008 purchase of ImClone — back then, to boost Lilly’s cancer franchise.

Similarly, he has overseen numerous other deals to bolster its main business units, as exemplified by the Elanco-Novartis arrangement.

### FOCUS – IN HAND WITH EXPANSION

Lechleiter didn't just make promises in 2009; he and his team invested much of their time examining every aspect of the company's strategy, as well as considering alternative approaches to help the company weather the hard times ahead. As a result, they conceived a plan to reorganize the company into five main business units: Bio-Medicines, Diabetes, Emerging Markets, and Oncology, in addition to Elanco.

"The main concern for me was focus," he says. "At that time, we had revenues of close to $25 billion, most of it in human health, and most of that in pharmaceuticals, yet we found ourselves in some of these key therapeutic categories competing against very focused competitors — Roche in oncology, Novo-Nordisk in diabetes, and so on. So we formed a Diabetes business unit and an Oncology business unit. The third unit was our Emerging Markets business. We didn't have enough focus on emerging markets in their own right, but that business now has a seat at the table.

"Bio-Medicines is essentially everything else; it's actually our largest portfolio, including the men's health products and the neuroscience products such as Cialis, Cymbalta, and Strattera [atomoxetine]. It's also responsible for the 'care and feeding' of all of our local operations. Our entire global infrastructure of operations went into the Bio-Medicines unit."

"I've got five people running the five businesses," says Lechleiter. "They are all very capable individuals who are not only able to work through a common infrastructure, our global services group, but also tailor their approach to their businesses in ways that best serve their customers' needs. And that's proving out — we're a more competitive company today in diabetes and oncology, and we are better

## On The Chairman's Watch

**IMAGINE A BIG PIE CHART** of the chairman, president, and CEO's responsibilities, including the R&D, commercial, financial, strategic, and organizational areas. Do some areas take more of the leader's time, attention, and resources than others? John Lechleiter's answer, bemused but sanguine, carries a lot of lessons for people at all levels of responsibility in the industry. In the following, he shares some of his management philosophy and how he has dealt with Lilly's patent losses and other setbacks in recent years:

"You have to have an overall grasp of the business as the CEO, but if there's one thing I worry about, and I believe it's a healthy paranoia, it's that my knowledge of what's really going on in the organization is too imperfect. People are predisposed, I think, to telling you good news, but I'd rather hear the bad news — and I'd rather hear it quickly.

"Still, you can't be into every detail, and you've got to be very careful if and when you decide to put your finger in the pie and intervene somewhere. You always have to work through people, and that's why I spent so much time and effort selecting a team of great leaders. Only I and our CFO, Derica Rice, were in the top 14 executive positions in the company in 2008. I sometimes hear people say, 'These are the three areas the CEO should focus on,' and I think, 'Really. Okay.' Things come along and you get surprised. You can organize your life so there's a certain routine, and that's important, because it puts discipline in the organization. But then you've got to be ready for the unexpected — and not just the things that knock you for a punch, but also the unforeseen opportunities that open up.

"The most enjoyable part for me is spending time with Lilly people at our sites around the world, and in our labs. I do that to get a sense of what's going on. All this change that I think is happening in the company — is it filtering down, do people get it? Do people understand where we're going? Are they excited about that? You can take surveys and can talk to your team, but you've got to get involved at the ground level sometimes or you get very insulated and isolated.

"Expectations of large companies have changed and grown in recent years. There's a political dynamic to contend with every day, in the United States and globally. Healthcare is much more on the forefront now than it was 30 years ago, because we're all getting older, we're demanding more healthcare, and we're trying to figure out who's going to pay for it and how it will be delivered. I'm happy to be in the middle of that, but we've got to be thoughtful and constructive in how we approach those things. So I spend a lot of time speaking externally, meeting with different interest groups and investors to make sure that I'm in the thick of many of those currents that will impact our business ultimately.

"A personal touch can be even more important when things aren't going right. In August 2010, we had a couple of negative patent rulings and lost our oral gamma secretase inhibitor for Alzheimer's, semagacestat. It was on a Wednesday or Thursday; that Saturday I was home and a little bit down about it, and I said to my wife, 'I thought our employees were probably a bit discouraged.' She said, 'Why don't you take out a newspaper ad?' because we have so many employees concentrated in central Indiana. So we put together a one-page ad for the *Indianapolis Star*, with the headline, 'The Path We Have Chosen.' I just looked at it again, after four years, and it's great. It basically said: Look, we've had some setbacks and this is tough for us, but our mission is unchanged. What we do is discover and develop life-saving medicines. There are some huge medical needs, and we have a very good chance of making a difference, and that's what we're going to keep on doing.

"We had a strategy: Invest in innovation, cut our costs and improve productivity, make the most of the products on the market, expand Elanco, and so on. We stuck to that, but it seemed everybody out there at one point or another was saying we should do something else. We should merge, we should spin Elanco off, slash R&D, break up the business, everything under the sun. As CEO, you can't be blind, you've got to listen, but you've also got to have the courage of your convictions. We weren't rolling the dice; we really believed in what we were doing. We just knew it would take time. We were trying to be patient with ourselves and asking others to be patient with us. And I believe that strategy is going to prove out."

positioned to make faster and higher-quality decisions." Each of the business units now runs its own Phase 3 development, he says, creating a stronger connection between medical development and commercialization.

Although Lilly's human pharmaceutical business attracted most of the headlines during the past few years, the company was rapidly expanding Elanco before the Novartis deal. Historically, Elanco brought in about 6 percent of Lilly's revenue, but its share has now grown to the low double-digits.

"We've grown Elanco at industry-leading rates through a combination of internal, pipeline-driven growth and external acquisitions," says Lechleiter. "We've done at least one small- to medium-sized acquisition a year for Elanco for the last six or seven years. We like the business because it is synergistic with pharma, both on the pipeline and the manufacturing sides, where we're able to take advantage of a deep knowledge base and a global manufacturing infrastructure that also helps Elanco on the supply side." Lilly/Elanco counts on two factors in the growth of animal health: increasing demand for meat protein in emerging markets, and expansion of the companion-animal space in the developed world.

## DOING MORE THAN ENDURING

Having restructured the company and developed a long-term strategy for overcoming the patent losses, Lechleiter and his management team took some significant steps to prepare for the long haul, which can be described as simple imperatives:

- Stick with the strategy.
- Keep up morale and confidence.
- Improve and focus clinical trials.
- Globalize research.
- Raise R&D productivity.

Resolution in the face of adversity is not always rewarded. Merely remaining steely faced and bullishly pushing on are unlikely to win much support, of course. Lechleiter sensed he had to do more, to communicate and explain — to his company, and to the outside world — what Lilly was doing, and why it had taken the course it was on. His patient yet insistent style was likely the best antidote for the toxic skepticism that inundated the company every time bad news washed in. (See "On the Chairman's Watch.")

Many of Lilly's challenges came in clinical development, where the effective but perhaps unspoken watchword became, "Learn from failure." As Lechleiter says, "You never plan for something to fail, but you have to accept, after the fact, that not everything that goes into Phase 3 is going to make it. We are going to be better, stronger players as a result of lessons we learned in those cases, and

focusing in certain therapeutic areas has probably helped as well."

Learning and focusing work hand-in-hand, it would seem. "When you focus on trials in cancer, diabetes, or neuroscience, you gain a lot of tacit knowledge that would be difficult for others to replicate. Since the early days of developing Prozac, Lilly and a few other companies have really rewritten the book on how to study drugs in this space. So being focused on key areas helps us make better decisions as we take molecules forward into Phase 2 and Phase 3."

Lilly will also likely enjoy some successes in the clinic, according to Lechleiter. "As our data plays out, we're seeing positive results on the lead ImClone molecules, and from several drugs in our diabetes portfolio. This is a big year for us in terms of data readouts, and we will get more readouts throughout the year."

Those readouts will come from data collected all over the world, reflecting what Lechleiter describes as the globalization of Lilly's R&D — which also reflects a great broadening of the company's culture. Moving beyond its old image in the industry as a lonely battleship on the vast ocean of the U.S. Midwest, Lilly now spans the continent, and far beyond, as he relates. Besides establishing U.S. sites such as ImClone in New York and an R&D center in San Diego, CA, the company has expanded its presence worldwide, especially in the U.K., Italy, China, and Japan, where Lechleiter says it has been one of the fastest-growing pharma companies for the past five years.

While globalizing R&D, Lechleiter says Lilly also made productivity improvements that have lowered its R&D costs and at the same time created the biggest pipeline in its history. Most of the gains so far have come in the research part of R&D, he says.

"We certainly did not exempt our research laboratories from the improvements. We have been challenging our researchers to consider and to take measures that would make everything we do along our value chain more productive. Identifying hits and leads to new targets, which used to take us months and years, we can do now in only weeks and months. We have leveraged technologies, such as X-ray diffraction to image structures of targets and ligands in drug discovery. This hasn't played out yet all the way through the cycle, but there's no question we're much more productive in the early stages."

## ENCOURAGING MANAGEMENT

Lechleiter's style of managing people, and the company, shows up clearly in his handling of R&D. Rather than riding herd on the group and second-guessing its decisions as might be expected given his science background, his approach is broadly nurturing. His relationship to the R&D leadership relies largely on trust:

"It's important for our company to have not only good scientists but also excellent managers and leaders in that R&D endeavor. You can have the best scientists in the world, but unless they are capably led, inspired, motivated, and cared for, you're not likely to get the best result. I let the leaders do their jobs. I'm particularly careful at Lilly that people don't mistake me for the head of R&D. Dr. Jan Lundberg is our head of R&D, and he knows I'm very supportive of R&D, as the CEO."

With the past long gone, and the present quickly becoming past, a doubly seasoned Lechleiter faces a future with light on the horizon. Is the light dusk or dawn? His answer is down to earth.

"I see us remaining a major player in diabetes and in oncology. We are hopeful that we will begin to see some positive data with our Alzheimer's portfolio in the latter half of this decade, and we believe we can establish a presence in the autoimmune space by virtue of three different molecules that we currently have in development for psoriasis, lupus, and rheumatoid arthritis. I see a future where Elanco Animal Health is a more prominent part of Lilly. And I see a company that I believe is well-positioned for growth. The experience we've gone through with the patent expirations has made us stronger and more resilient, and I believe we are a more competitive company having experienced some of the challenges we've faced."

Characteristically, and reliably down to earth, are closer to the truth. L

## EMERGING GROWTH

Lilly's John Lechleiter shares some additional insights into the company's thinking regarding emerging markets:

"We lump the emerging markets together at some peril, because there is a great deal of variation among them. In many of these countries, you see a few very wealthy people on one hand and very destitute people on the other. Realistically, in those countries, our products reach a certain stratum of people who have access to good-quality medical care through private insurance, out-of-pocket, or in some cases, government programs. As their economies grow, we expect millions of people to enter the middle class in this decade, which will enable access to our products and sustain the growing middle class with better opportunities for good healthcare."

Among other reasons for giving emerging markets their own business unit was a long-term strategy: "We want people 20 or 30 years from now to look back and say Lilly was here in the early days, investing appropriately at a point when the market was not as robust as it will be down the road. Lilly has great opportunity in emerging markets because Type 2 diabetes is so prevalent everywhere. The treatment of Type 2 diabetes becomes a de facto point of entry for us because we will have an even more complete portfolio of products in Type 2 in the next few years."

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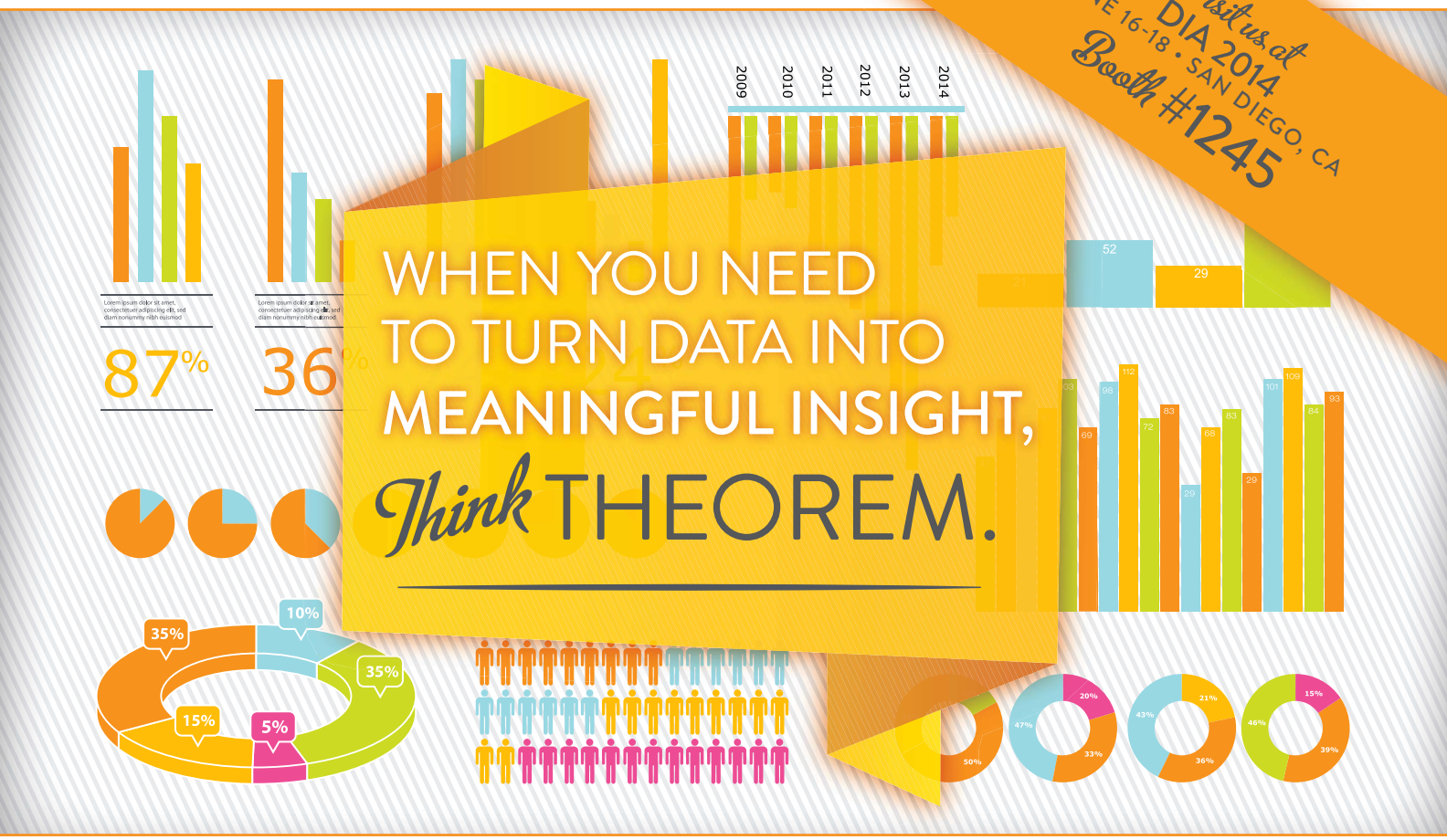


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A POST-GENESIS STORY

# GENZUM PLIES THE ART & SCIENCE OF SCALING UP

Sometimes the smallest bits of evidence light up the largest theories. Like the infinitesimal traces of the Big Bang astronomers recently teased from cosmic background radiation – data showing the effects of gravitational waves in the universe at zero plus one-trillionth of a second – a single company case, stripped down to the bare essentials, can teach fundamental lessons about growth after start-up.

WAYNE KOBERSTEIN Executive Editor

Genzum is such a case. Its singular focus on developing and commercializing first-to-market topical generics requires that almost all of the information companies normally announce, from products to financials, must be kept confidential. What is left? A pure, undistracted view of how the company applied good business principles to a well-known business model to build a valuable product portfolio.

Genzum's CEO Chris Achar conceived and led the company through a relatively swift execution of steps in its formation and scale-up. Genzum was founded four years ago upon a family heritage of business management and investment. The Achars and partner family, the Semlers, have long owned and operated a number of LA-based companies across various industries. Seeking a presence in the pharmaceutical industry, the families more recently ventured into the sector by establishing a large CRO, Semler Research Center (SRC), in Bangalore, India, from where the Achar family originated.

Eight years ago, when SRC started with about 10 employees, its only service offering was in formulation development. Now it is a full-service CRO, with 250 employees, specializing in formulation development, BA/BE (bioavailability/bioequivalence) studies in healthy volunteers, and Phase 1 to Phase 4 clinical studies in patients. The germ for Genzum was an idea for answering a need Achar saw while working with SRC in his post-graduate years. One of the CRO's clients was pursuing the development of a complex topical product, but it lacked the funds needed to proceed into the large clinical trial stages the FDA requires for such products.

"On the CRO level, we saw a lot of our potential clients had great product ideas,

but they lacked the structure, infrastructure, and capital necessary to truly execute on it — and we were seeing them stall out," Achar says. "They would start in product development, but by the time they got to clinical, they just didn't have the bandwidth or the funds to execute on it."

Achar thought a new company, eventually Genzum, could serve as the "incubator" for those companies and products, providing not only funds but also clinical expertise combined with the business acumen needed to out-license and commercialize the product. After going back to school and returning with a fresh MBA in hand, he went to work on bringing his idea into reality. "If we could provide capital and infrastructure for those opportunities, we believed it would produce a great, long-term value, especially if we could help out-license the product to distribution companies that would not otherwise have such products in their own pipeline." So Genzum did just that. "Our very first product, an ophthalmic suspension, was an incubated product out of the CRO, and we were fortunate enough that a Big Pharma distributor found it interesting and in-licensed it from us, and what that did was establish our business model. We then went out and executed, and before we knew it, we established a track record."


## CONCEIVING THE MODEL

Compared to tablets, capsules, and some solubles, topical medicines tend to be highly unstable, complex formulations where the emulsifiers and other constituents play essential roles alongside the active drugs' effectiveness and safety. Thus, the FDA will accept ANDAs (abbreviated new drug application) for most topicals only with accompanying Phase 3 data comparing the generic head-to-head with the original drug.

That means the generics producer must "reverse-engineer" the original product to create a precise duplicate. No wonder few companies have the capability or inclination to compete in the space. But the rare combination of financial strength and special skills at Achar's disposal gave him a leg up on others. Genzum's model would grow to include not only incubator partners but the biggest players in generics.

"Today, the big five generic companies are coming to us with their topical-product wish list, what they ultimately want to see coming down our pipeline, because semi-solid drug forms — creams, gels, ointments — are very tough to reverse-engineer and usually have a very complex and expensive clinical requirement," says Achar. "Traditionally, the big players would develop all of their product pipeline in-house. So why would they go outside? Cost and risk — the costs are too high, and the risks are too high. They turn to a company that is specialized in the area and can create value in a partnership."

Besides the value Genzum offers as a specialized topicals developer, the company also matches the investment of its commercial partner in a development project. "The risk plays right into our strengths," Achar says. "And we also address the cost aspect because in all of our partnerships, we have invested dollar-for-dollar with our commercial partners in the total cost of developing the drug, executing the clinical trials, and submitting to the FDA. It's something we take a great deal of pride in, being able to say we are truly an equal partner."

Another key aspect of Genzum's model is that it does not aim to improve on the original product; instead, it aims to reproduce it precisely. "We're coming on as the generic, joint-existing brand, so we have to be bang-on equivalent. We reengineer to meet and match the same safety and efficacy as the brand. So as the patent nears expiration, we will begin our work with the commercial partner to evaluate, identify, and then develop the product. And we put it in a head-to-head comparison clinical trial."

Reproducing the active drug ingredient is the simple part, according to Achar. "If you don't formulate exactly, then you will probably fail in the clinic. Yes, the ingredients are on the label, but the label doesn't tell you the order, proportions, and other characteristics of the ingredients. That's the actual innovation, figuring that out. It takes about six months in R&D to reverse-engineer such a drug. And of course, once we come out on the market, it's more affordable because we're coming out at a discounted price."

The drawn-out reengineering of topicals makes keeping them confidential while in development especially critical, he says. "You don't really want to tell the market you're doing a new product in advance. And before the product goes to market, for both sides, you don't want to say who the partners are. Once it is FDA-approved, then everyone says who they worked with to develop it."

Just as with its products in development, the company's financials also remain hidden while it courts and forms more partnerships around new product opportunities. But Genzum's business model seems to have a built-in positive forecast, in Achar's view. "The nice thing about our business is we're product-revenue driven, so once we develop the product and share in the cost, we also share in the rewards. The money the product generates comes back to us and to the commercial partner." Another tantalizing hint: In September 2013, the company achieved a successful Series B round of unannounced size, which Achar says doubled the company's valuation. It now has north of a half-dozen products in the pipeline.


## BUILDING RELATIONSHIPS

Many companies in specialized areas of the life sciences have scientist founders. Achar, by refreshing contrast, is a businessman who has founded what is, before and after all, a business. When he started Genzum, he already had a map in his mind of how the company should develop and deliver on the promise of its model. Being a quick learner is another key business skill, and Achar obviously soaked up every bit of knowledge he could from his years at the CRO, "learning the mechanisms of the industry and the dynamics of drug development," as he puts it. Teaming that knowledge with his business sense, he went forth in search of partners.

"What I really understood quickly, and

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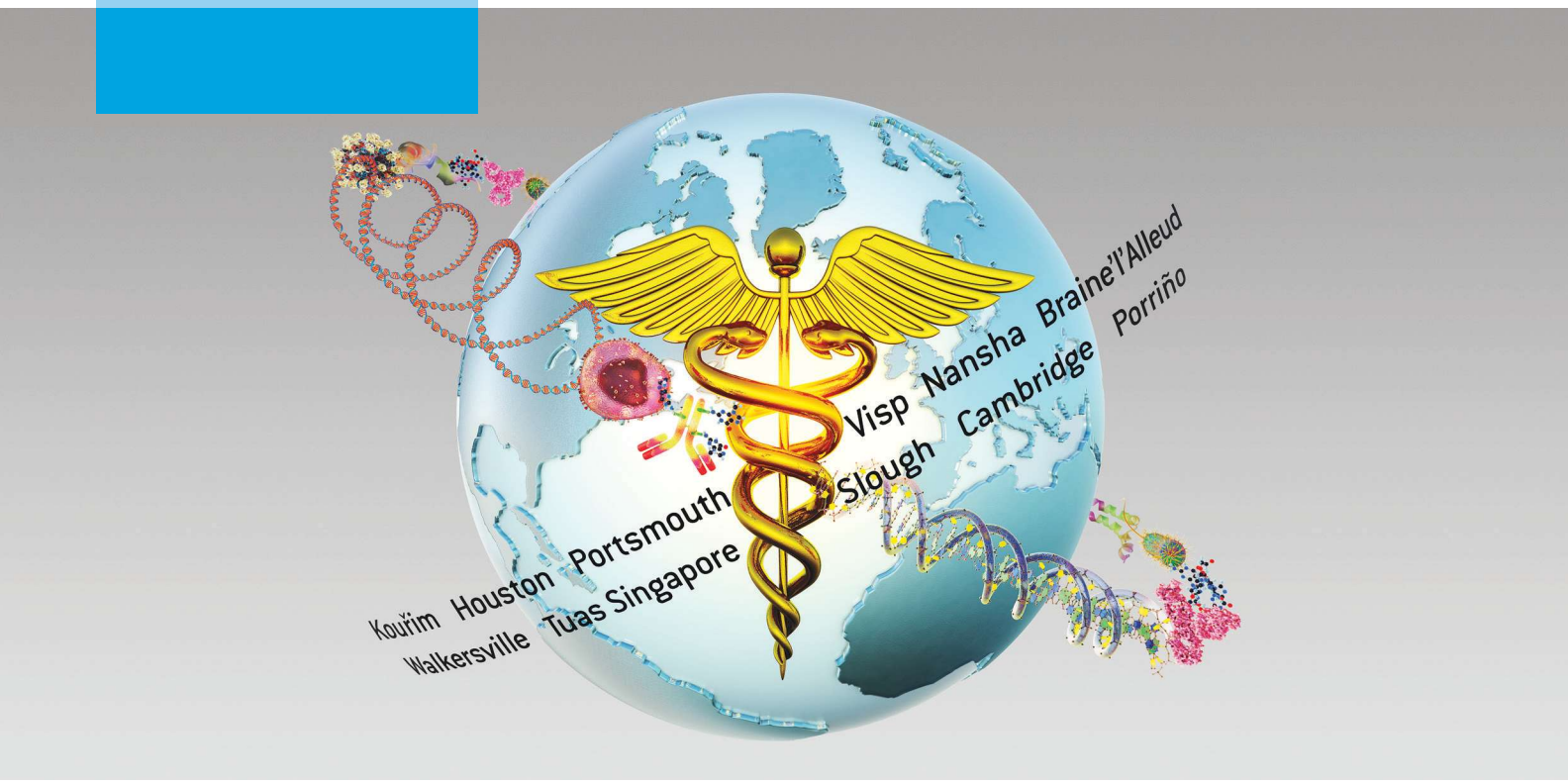


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it was really a lesson that my father taught me, is that business, no matter what the industry, depends greatly on relationships. That was my skill, and I knew it was something I could build this business around. If I could put together all the pieces necessary to make a commercial partner interested in the product, then the rest of it would be relatively easy to go figure out. This is the art in building a business."

Going at a business the other way around — focusing on the product dream and leaving the practical details for later — will hamstring the company's own development, in Achar's belief. "If you say, I want to do this product, let me go do it, and then try to figure out the relationship with a partner, you risk everything," he says. "You work out of pocket; you don't even know whether there's a pathway to the market. Do the potential commercial partners even want it? Are there too many competitors already?

"We started the business working from the market backwards — was there interest, who wants it, how much are they willing to pay for it? Knowing those three things, I understood the boundaries within which I had to operate. I had my budget for the rest of this go-figure-it-out portion. Go figure out who supplies the ingredients, whether we could develop it, or if not, who else could do it, the size and cost of the clinical studies, the raw materials, and so on. You put all of that together and a large portion is then focusing on execution."

Most of Achar's current networking is with the portfolio teams and the executive management of the potential partnering companies. "Once we actually figure out the partnership details, then we work down to their commercial ops and their regulatory, technical, and R&D. Understanding what they want — the decision process and steps on their end — is a huge component, so I can prepare and serve up what they need to push an opportunity internally."

When Achar reached the point of narrowing and focusing his networking encounters, the results added up, but not only in quantity of business deals, he says. "All the relations that I have are genuine. I never approached it as I just want to get something out of it. I've actually struck up some beautiful friendships through the years of meetings. So that's part of the value add; it doesn't show up in a department, it doesn't show up on a balance sheet, but it pays dividends for the business."

Another side of relationships for a growing company is staffing. At the top of Achar's list was a chief scientific officer and a chief operating officer, along with heads of regulatory affairs and clinical development. "We are a lean organization in the sense that we don't maintain our own facilities with bench-level scientists; we contract with our CRO. But having the high-level oversight of those key areas was what we needed."

Achar says Genzum is lucky to have a CSO who has 30 years of experience in Big Pharma and worked on more than 100 generic products, as well as a co-founder turned COO who is "extremely diligent, and scrappy when he needs to be." Achar also emphasizes the critical role of regulatory affairs, "because that determines everything from where we buy our material to what the clinical trial design looks like."


## EXECUTING THE MODEL IN SCALE-UP

Relationships in business naturally lead to commitments to deliver as promised, which was the next, anticipated step in Genzum's construction. Once a topical generic is formulated, it goes straight into a Phase 3 trial to prove its equivalency to the original. "In some of our study designs, we're doing very direct, head-to-head comparisons," says Achar. "In our ophthalmic studies, to control variability, we are dosing patients in one eye with the original drug, performing surgery, extracting fluid, and a week later, we're doing the same procedure in the other eye, but dosing with our drug."

The Phase 3 trials are large; according to Achar, the smallest has been 500 patients and the largest planned currently will be 3,000. At the same time, because topicals tend to age faster than dry powders, the generic must demonstrate stability on the shelf for two years.

> "We started the business working from the market backwards – was there interest, who wants it, how much are they willing to pay for it?"

**CHRIS ACHAR**
CEO of Genzum

Not many small companies can say they have accomplished that level of execution within a few years of start-up. Achar believes more could, if they thought far enough ahead from the beginning.

"There are a lot of start-ups that have one asset, maybe one partnership that they start on, and they just stay there. The difference for us is that we are a post-start-up company — scaling up followed after start-up. Proving ourselves, executing on the model, establishing a track record to the point where companies now want to work with us on identifying the next set of products — that is the scale-up portion. That was a big change for us. And it hinged a lot on relationships, then going out and filling out the remaining portion."

Whenever I finish a story full of lessons for up-and-coming life sciences companies, I am always struck by the seeming obviousness of the principles illustrated therein. Yet, it is equally apparent that many if not most start-ups in this industry are stillborn, or nearly so, because of their science-driven but business-lacking agendas. Achar and his company Genzum highlight three basic business axioms that unfortunately seem lost on too many life sciences enterprises: Build a solid business model, form genuine relationships, and execute on the model with a well-planned scale-up. All other details aside, those are the essential tools of the art.

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LESSONS LEARNED HELP PFIZER ACCELERATE BIOTHERAPEUTIC DEVELOPMENT | By R. Wright

# Lessons Learned Help Pfizer Accelerate Biotherapeutic Development

ROB WRIGHT Chief Editor

Six of the seven blockbuster biotherapeutics belonging to Big Pharma have roots to small biotechs (see Table 1). So too does Tim Charlebois, Ph.D., VP of technology and innovation strategy within Pfizer's biotherapeutics pharmaceutical sciences (BTx Pharm Sci). Part of the company's drug development organization, the 700-person BTx Pharm Sci group operates between Pfizer's biotherapeutics research and biotech manufacturing organizations. One of the challenges facing Pfizer is an increase in the "perceived" distance between internal operations resulting from the company's significant growth.

Since 1990 the company has acquired the likes of Warner-Lambert, Pharmacia, and Wyeth and grown from $2.8 billion, to $51.5 billion in 2013. Charlebois's charge — help Pfizer accelerate its biotherapeutics development program by getting the company's manufacturing and biotherapeutics research organizations to work together more closely — was much like that at the small biotech where he began his career. According to Charlebois, it involves learning what kinds of new products will be emerging from research taking place upstream, and preparing the organization downstream to develop and manufacture. But it also involves knowing the technology existing downstream and communicating these capabilities upstream, and where Charlebois began the process of decreasing the "perceived" distance between biotherapeutics research and manufacturing by applying lessons learned in small biotech.

### THE DIFFERENCE BETWEEN HAVING THE CAPABILITIES AND KNOWING THE CAPABILITIES

Charlebois began his career in 1990 at a small company (< 600 employees) — Genetics Institute — a Cambridge, MA-based biotech which had developed a reputation as a technology powerhouse. Like many biotech alumni, his route to Big Pharma came via acquisition, first through Wyeth and then to Pfizer. Charlebois recalls a lesson he learned while at those smaller companies. "I witnessed really close and integrated processes in which biotherapeutics being developed actually matriculated into commercial products within the same site," he says. Executing end-to-end biologics development is much easier when R&D and manufacturing operate in the same building; people at the beginning stages can see what is going on at the end, are aware of the technology in place, and benefit from being able to have frequent, face-to-face communication.

As you can imagine, when it came to executing end-to-end biologics, it was a different experience for him at a company the size of Pfizer. "When you have very large-scale operations, in order to be competent in any particular area, you have to really focus, because the company's size can be overwhelming," Charlebois says. For example, just in the United States, Pfizer operates eight geographically dispersed R&D centers. According to Charlebois, the practicality of focusing within one's own discipline creates a "disconnect" between R&D and manufacturing. "People early on in research can forget that what they're doing is influencing eight years' worth of work downstream." Conversely, Charlebois has seen and read about disconnects occurring between drug designers and commercializers, including a few cases where, despite R&D proof-of-concept metrics being met, the commercial organization did not want to develop the product.

To eliminate disconnects between R&D and manufacturing and across functional boundaries, Charlebois and his five-member "technology and innovation strategy" team work with multidisciplinary initiative teams to align on long-term direction, establish plans, and provide access to funding and management support. Since teams are almost always composed of members from different sites, a variety of communication approaches are leveraged to ensure people stay on the same page. Technology teams meet regularly via teleconference or videoconference, and common interest groups in areas such as bioanalytics and bioconjugation hold regular virtual meetings across the network to share data and ideas. Pfizer intranet-based tools are used to support collaboration among teams and to make strategy and progress visible and accessible across the company. The company has a Web-based infrastructure to support innovation communities across Pfizer. This can be used to post challenges and stimulate virtual discussions among like-minded stakeholders. BTx Pharm Sci also holds an annual tech symposium where scientists and engineers come together to discuss data and strategy through workshops and poster sessions.

Initially set up as part of the integration of Wyeth, Charlebois' team continued as part of Pfizer's goal to aggressively leverage and integrate science and technology across the company to accelerate biopharmaceutical development. For example, when Pfizer acquired Wyeth, Charlebois put in place a team charged with inventorying and documenting the capabilities of all of the equipment owned within the newly combined company's manufacturing and development networks, and then making that comprehensive catalog available to scientists and engineers across Pfizer from their desktops. "The idea was to provide staff with this information so, downstream, they could incorporate these improvements and benefits," he says.

There is a difference between having the capabilities and knowing the capabilities you have. Charlebois relates the following possible scenario. A biotherapeutic being developed in St. Louis, MO could be clinically manufactured in Andover, MA, which could also be used as a launch facility. But if it's a large-scale biotherapeutic, the process might have to go to Grange Castle, Pfizer's 90-acre, one-million-square-foot integrated biotechnology plant in Ireland.

The benefit of knowing what technology exists within the network helps Pfizer scientists plan for the most efficient — and possibly quickest — design. For example, a manufacturing process designed and proven in one facility could face costly delays and put clinical trials or launch supplies at risk due to product quality

**TABLE 1** Big Pharma Buying Into Blockbuster Biotherapeutics

| 2013 BIOTHERAPEUTIC BLOCKBUSTER SALES | | SPONSOR | ORIGIN |
|---|---|---|---|
| Humira (adalimumab) | $10.6B | AbbVie/Abbott | BASF Bioresearch/Cambridge Antibody Technology |
| Remicade (infliximab) | $8.9B | J&J/Merck | Centocor |
| Rituxan (rituximab,MabThera) | $8.9B | Roche/Biogen Idec | Genentech |
| Enbrel (etanercept) | $8.3B | Amgen/Pfizer | Immunex |
| Lantus (insulin glargine) | $7.8B | Sanofi | Sanofi-Aventis |
| Avastin (bevacizumab) | $7B | Roche | Genentech |
| Herceptin (trastuzumab) | $6.8B | Roche | Genentech |

issues that are caused by subtle changes in the sensitive bioprocessing steps used to product a complex biomolecule.

"We're actually rethinking what 'end-to-end' comprises by going all the way back to the research stage and trying to connect it closer to the supply phase," he says.

## STRUCTURING THE INTERFACES

So how did Pfizer create these teams? Let's start with the structure. As was mentioned, Pfizer's development organization essentially resides between research and manufacturing. "We develop the processes and make and deliver the clinical supplies so the products can be tested in the clinic," Charlebois says. "We develop the technology that will be used in commercial manufacturing if it's successful." This probably sounds familiar. Within the development organization, Pfizer created two types of interface teams. The first type interfaces upstream between research and early development.

The second type interfaces downstream between later stages of development and manufacturing. "On the upstream, the interface is much more technical around the modalities and the impact of those on development," he says. Within this interface team, the focus is on product technologies and modalities, trying to determine what they are going to look like and how will they behave. "In the manufacturing [downstream] interaction, the clinical production technologies tend to be very similar to the commercial ones, except for scale," says Charlebois. "They're not six packs of 15,000-liter reactors, but 2,500-liter reactors." According to Charlebois, the similarity between technologies makes for a much more seamless interface between commercial manufacturing and clinical development engineers to work on the technology. Pfizer built the interface teams to look at where they are now and how they intend to harmonize technology going forward, from development into manufacturing across the drug substance, drug product, and analytical areas. "We basically created an interface group that set objectives together on how to improve processes, how to work together, and what are some key technologies we could use to do so." Both the upstream (research to early stage development) and downstream (later stage development to manufacturing) BTx Pharm Sci interface teams are managed by Charlebois' team.

By managing both the upstream and downstream interface teams, Charlebois' group can help to ensure end-to end connectivity, while not requiring everybody across the entire space to have to take an interest in everything.

**TIM CHARLEBOIS, Ph.D.**
VP Of Technology & Innovation Strategy At Pfizer

Charlebois advises prior to creating interface teams that will work between organizations, to first create a governance structure for the team within your own organization, as this is the most local and under your control with regard to the setting and managing of both budgets and high-level objectives. "Then have teams provide proposals that drive toward those high-level objectives." (For more on how Pfizer creates these objectives, see sidebar — *What Objectives Are On Your Horizon?*)

For the interface between development and manufacturing, there are governance groups which involve senior leadership members. These groups meet regularly to report progress, give and get direction, and receive feedback. Only two layers of management exist between Charlebois' team and Pfizer's executive leadership team (ELT). This illustrates the importance placed on this initiative of striving to operate similar to a smaller biotech. "The top leaders are looking for a big impact from these kinds of initiatives, which pushes us to take a bigger-enterprise perspective," he attests.

## LESSONS LEARNED THUS FAR

"When we originally formed the technology and innovation strategy group, we actually had individuals working in my group who focused specifically on bioprocess, analytical, formulation, and delivery but reporting directly to me," shares Charlebois. "They were working with the respective functional lines. We found this created more distance and less of a sense of technology ownership within each of the functional lines than we desired." These roles were moved instead into the functional lines, and these leaders built "Tech Committees" responsible for overall coordination within their respective disciplines. Charlebois' team then works to bring together the technology initiatives into impactful strategies to improve the speed, cost, and quality of biotherapeutics development and manufacturing.

Charlebois reminds you to be patient. "Try and have a sense of urgency on the one hand, but also recognize progress takes time," he says. "I certainly was very impatient initially, and I learned that with a large organization it takes time for understanding to build and for work that contributes in an impactful way to gain traction and deliver."

To prevent learning a lesson the hard way, such as interface teams developing or taking on too many projects, put a process in place for reviewing, approving, and funding project proposals. It is essential that some funding, and also scientific and engineering bandwidth, be set aside for innovation. With a large portfolio of product candidates to move forward, there can otherwise be a tendency to focus on short-term deliverables and fail to make the improvements that will serve the enterprise in the long term. In other words, if you expect to move the innovation need, don't allow it to be relegated to nights and weekends.

Also, allow teams to develop and share ideas within a diverse network, even outside of their area of expertise. For example, Charlebois connected with his counterpart on the pharmaceutical interface side to gain insight into the technologies being used and developed in the areas of continuous, portable, modular, and miniature pharmaceutical manufacturing. "While the technologies aren't all the same, there are lessons to be learned," he says. In addition, Charlebois was able to help his counterpart network with some people outside of Pfizer who could help them with what they were working on. "It is important to keep in mind, it isn't the interface team doing the actual work," he states. "They simply bring the people together to help coordinate the process and direction of innovation, so that people's efforts are not fragments but rather are connected to a cohesive strategy."

Pfizer tracks how much activity each person across the Pfizer development, R&D, and manufacturing enterprise dedicates to each project. This benchmarking data is used to ensure that each employee working on a project is allocating the appropriate amount of time and that they clearly understand their deliverables related to that project. "We are trying to make sure we have enough people giving enough of their time to make the big changes we're looking for," he says.

If your goal is to accelerate your biotherapeutics drug development and bring R&D and manufacturing closer together, Charlebois has one final piece of advice — plan well. "We have a large portfolio, so there is a lot of planning to make sure the number of drug development projects being taken on is in alignment with our capacity to execute on their development. The last thing you want is to create a process development improvement project and have it end up as a bottleneck, slowing down a drug's development." L

### What Objectives Are On Your Horizon?

One of the challenges of a company the size of Pfizer is to get employees to think beyond their own day-to-day world and focus on how what they do impacts the company as an enterprise. Tim Charlebois, Ph.D., VP of technology and innovation strategy for biotherapeutics pharmaceutical sciences, BTx Pharm Sci, believes that to overcome this, it is essential to create a culture where people can believe in the value of focusing on the long term. "If you create a culture in which it's seen as indulgent to think beyond today, then you're going to get people keeping their heads down and not thinking ahead," he says. Thus, Pfizer management has been working very hard to communicate a constant and consistent culture of accountability and innovation — referred to as "Own It."

To get people to think long term and more innovatively, Pfizer created a science-based strategy for sustainable innovation with three horizons. Horizon 1 involves the most immediate objective – deliver the portfolio. Horizon 2, intermediate, stands for innovating new capabilities. And Horizon 3 involves creating the R&D ecosystem of the future. Folks within Pfizer began working on the aspirational Horizon 3 objectives first, which were five to 10 years into the future. From there, they worked backward. In taking this approach, the company created Horizon 2 (intermediate) objectives, geared toward achieving Horizon 3, and immediate objectives, geared toward achieving Horizon 2. "We've created teams to help guide the expert-based prosecution of ideas and then collect those into bigger buckets that can drive toward those high-level goals," Charlebois states.

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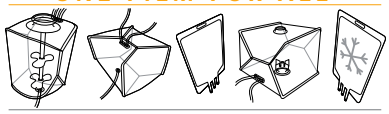

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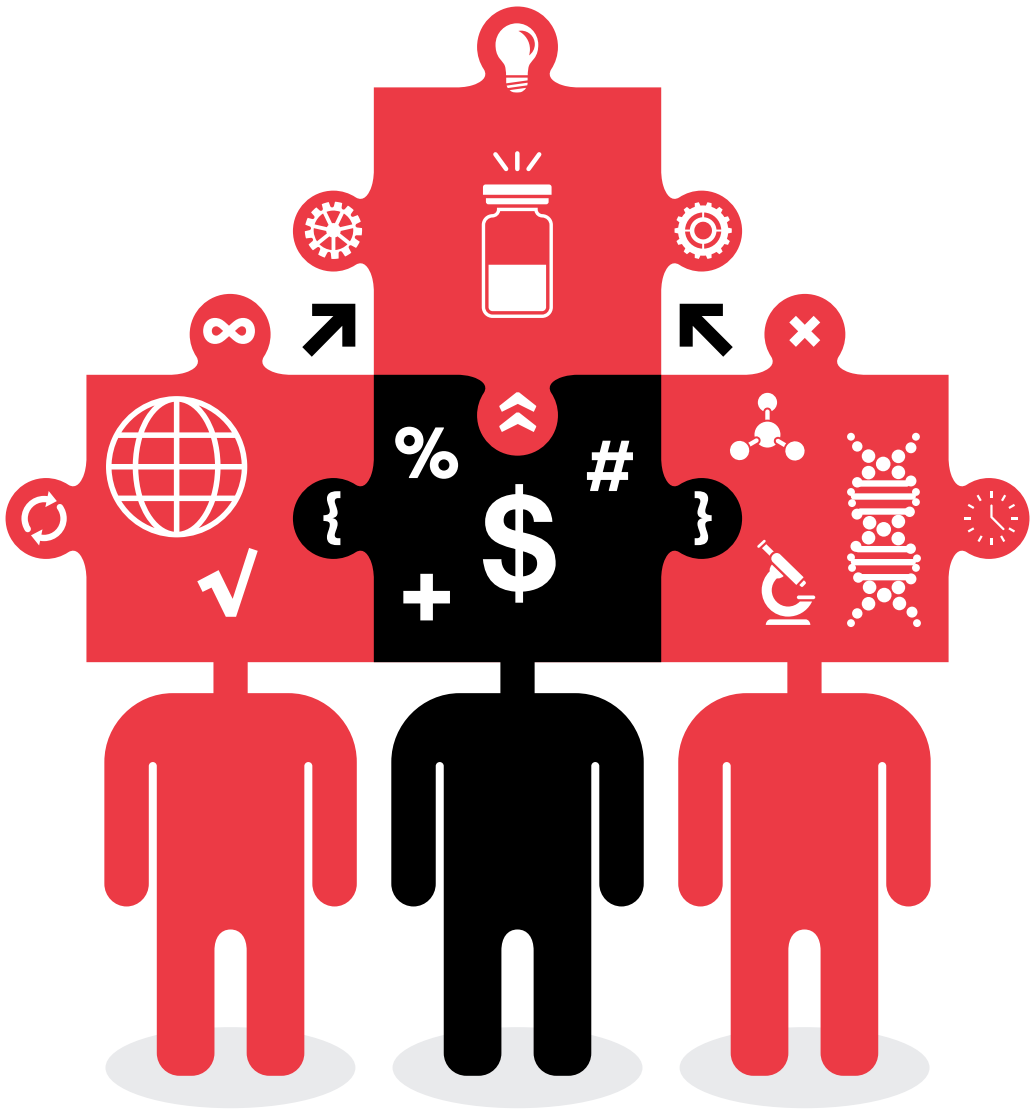
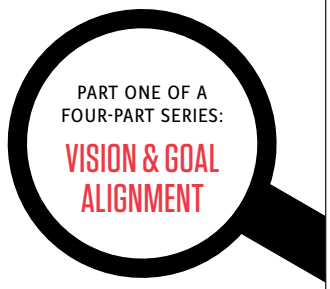
# INDUSTRY PARTNERSHIPS WITH PATIENT FOUNDATIONS: THE BEST PRACTICES

## Voices of BayBio's "Successful Public-Private Partnerships" Survey

WAYNE KOBERSTEIN Executive Editor






# ONE BY ONE, life sciences companies and patient-advocacy groups have been getting together, bound by a common purpose — to ensure development of new treatments for unconquered diseases. Not always an easy marriage, these unions have grown and benefitted from experience.

Such were the basic assumptions underlying industry group BayBio's survey — in collaboration with Merrill Datasite, BIO, and FasterCures — to assess the state of "public-private" partnerships and tease out a set of best practices that would guide new partnerships in the future. (See the white paper at baybio.org.) Helped by further input from some key companies, foundations, and people involved in the BayBio survey, each part of this four-part series will illustrate the best practices in one of the following areas:

1. vision and goal alignment
2. resource alignment
3. partnership structure
4. management paradigms.

In part one, we examine what happens when the two very different parties, a company and a foundation, come together and establish the basic tenets of their relationship. It is a time when the parties must bring their vision and goals for the partnership into alignment while recognizing and reinforcing each other's interests.

Not long ago, the concept of companies and foundations sharing goals and visions was figuratively alien to both sides. Nowadays, functioning public-private partnerships have proliferated in such a variety of forms and fashion, it is impossible to draw from all of their experiences in this context. Partnerships range from targeted data-only exchanges to support for proof-of-concept studies to full-scale funding of clinical trials, and often asymmetrical relationships in size, resources, and other aspects between partners.

Here, we introduce three industry executives and three foundation leaders, all with extensive experience in multiple public-private partnerships, some in partnerships with each other, and every one concerned enough about best partnering practices to have helped with the BayBio project.

Examining the "core sample" these experts represent — further focused by their common involvement in neurodegenerative diseases — keeps the picture as simple as possible while suggesting the great variety of possible partnerships. Hopefully, what these experts have to say will pique your interest in life sciences public-private partnerships, whether for further learning or involvement or for implementation of new, successful partnering entities. However, many of them caution that their learnings can't always be transferred wholesale to a different setting.

## TOWARD A COMMON VISION AND GOAL

From the BayBio survey and the words of those quoted below emerge some essential, arguably "best-practice" steps companies and foundations should take to find the right partners, work their way toward a common vision, and establish shared goals — the genesis of a productive and mutually beneficial alliance.

## RALLY AROUND DEVELOPMENT

Foundations deal with complex diseases that typically affect patients' lives in many ways. And at any time, scientific progress may open up new mechanisms of action and disease targets that need further exploration and proof-of-concept. Typically, a company and a foundation come together to target development of new interventions in areas where science offers an opportunity and their interests intersect. Amplimmune found a match in Fast Forward, the industry-partnering subsidiary of the National Multiple Sclerosis Society, in its early development of a molecule to tame abnormal immune responses.

**MICHAEL RICHMAN** President And CEO, Amplimmune:

When your project is aligned with the objectives of the foundation in a given disease, it's a win-win situation for all involved because you're synergizing your financial resources, access to information, ideas, and materials. All that came together in experiments that would help us figure out whether our molecule had some potential application with MS. Fast Forward brought in scientists from Northwestern University in Chicago who were doing research that could help us, so we triangulated a collaboration with the university and Fast Forward. Then, all three of us were synergizing financial and experimental resources, and all of us focused on a development plan for products to treat MS and other autoimmune diseases.

**A leader of the major MS group explains why his organization – once mainly dedicated to patient care, advocacy, and academic research – founded Fast Forward, which soon intersected with Amplimmune in the beginning of a beautiful friendship.**

**TIM COETZEE** Chief Advocacy, Services, And Research Officer, National MS Society:

Along with many other organizations, we now believe the leads from discovery in the university laboratory setting, which are vital, also require a commercial partner and a translation from one part of the value chain to the next. So we made the decision in 2007 to expand our footprint in research and to incorporate a strategy that focuses on investing in research happening in the commercial setting, typically at small biotech companies, though our portfolio has not been strictly limited to small biotech. That was the impetus behind the creation and launching of Fast Forward within the National MS Society.

**Meanwhile, another group, the Myelin Repair Foundation (MRF), came at MS from a different direction, creating its own area of research to push the industry into a new therapeutic approach.**

**JENNIFER CHANG** Director Of Communications, The Myelin Repair Foundation:

Our founder, who has MS, realized that a lot of the research in academia had a difficult time getting out of academia, so he began identifying the barriers in medical research that prevented novel therapeutics from reaching MS patients. The standard industry approach to MS was to suppress the entire immune system to lessen its symptoms, a treatment that causes its own set of severe symptoms. There was absolutely no focus on how to repair the neurological system once the disease damages it. With his business background, he also noticed a lot of disease organizations didn't have ambitious time lines for achieving their goals. So he started the MRF to change how research was done in this area.

**Identify/validate potential treatments/solutions. For foundations, sorting through and selecting projects from among numerous companies, development candidates, or other industry-partnering prospects require sufficient scientific expertise and methods to vet candidates in opportune areas of intervention. On the company side, it requires preparation and responsiveness to the foundation's validation approach.**

**RICHMAN:** Like any investor, the foundations will do due diligence. We had to submit an application to Fast Forward, and the application was reviewed by an expert committee made up of scientists, neurologists, and autoimmune experts working in the MS space. In fact, they rejected our initial submission because of the study design, but we revised and resubmitted our application and secured grant approval about a year later. Through their due diligence, they can evaluate a company to determine whether it has the right expertise, infrastructure, tools, molecules, and the means to carry out the experiments. And if you don't, they may help you create "collaborative clusters," working with experts in the field.

**One well-known foundation goes further than being a catalyst for developmental research – it has always been a research-oriented organization, parallel to several large patient-support groups, but it is now arguably the lead player in the push for new products to help Parkinson's patients.**

**SOHINI CHOWDHURY** Senior VP Of Research Partnerships, The Michael J. Fox Foundation For Parkinson's Research (MJFF):

We have a scientific advisory board and 10 scientists and one neurologist on staff, so we set priorities and drive the science toward our goals. We look at the science always through the prism of a patient's eyes because our funding comes from patients, by and large. We take a portfolio approach toward the research that we fund, looking both at the here and now in terms of trying to improve symptomatic treatment for patients, as well as a longer-term vision of that holy grail of a way to slow or halt the disease progression.

**It is important to remember that the foundation's vetting process can result in more than a financial boost. Many companies benefit more immediately from the network a foundation can house, as in this example from Fast Forward's initiative with Amplimmune.**

**JEFFREY OSTROVE** Former CEO, Ceregene:

One of our first product candidates was nerve growth factor (NGF), in which we delivered the gene for the factor directly to the brain of patients with Alzheimer's disease in Phase 1 and Phase 2 clinical studies. Not only did we hope to see symptomatic improvement in patients, but we also believed we could slow down the neurodegenerative process. Yet we would have to prove it in our clinical trials. Our Alzheimer's program and clinical stage Parkinson's disease programs were all we could afford with the venture money we raised. A new potential treatment for amyotrophic lateral sclerosis (ALS) using a viral vector-delivering insulin-like growth factor 1 (IGF-1) discovered by Fred Gage and Brian Kasper at the Salk Institute was very exciting and complemented our other programs. Unfortunately, we did not have the resources to carry out development of this potential drug. Fortunately, Project ALS gave us hundreds of thousands of dollars to allow us to start work-

ing on this new product. We then formed a consortium with them, along with the ALS Association and the Robert Packard Foundation and Dr. Jeffrey Rothstein, M.D., a neurologist and world-class ALS expert at Johns Hopkins Medical School. This led to the generation of extensive preclinical data.

**COETZEE:** One of our advantages as a major funder of bench-to-bedside MS research is that we have an unbiased view about what's exciting and happening in a particular disease and, importantly, where the gaps and opportunities are. As in the case of Amplimmune in those early years, we start looking at opportunities if the scientific underpinnings of the program are sound, have strong potential, are innovative, and have a clear runway for development. We also look at whether they have a strong business and science team. Then we step through a process of bringing together scientific and business experts in a VC-like due-diligence process, where we give them feedback on where we see positives and negatives in their program and where it might be improved in order for us to make our investment. We even facilitated a connection between Amplimmune and an academic collaborator, Dr. Steve Miller of Northwestern University.

**The MRF focuses its support for drug development even further back in the PoC process, functioning as a nonprofit research laboratory churning out new discovery, translational, and preclinical tools, such as a new mouse model, for the focus area of the Foundation: to support the drug discovery of myelin repair MS therapeutics. Then it essentially makes the tools readily available, with a low-cost barrier, to any company to test a new drug for myelin repair. It also sponsors and advises MS clinical trials in myelin repair.**

**CHANG:** When MRF began in 2004, there was no pharma company investigating myelin repair in MS. Our five-year goal then was to attract pharmaceutical interest; in 10 years, we wanted to get to Phase 1, and by 15 years, bring a drug to market. In our founder's view, if we don't meet those ambitious time lines, we deserve to fail, but so far we are on track, even ahead of schedule. In our expert research meetings, when the academic researchers present their latest findings, the industry experts on our advisory boards are there to say, "If you want this to reach patients, you also need to think about X, Y, and Z."

**Harmonize constituents.** Matching partners' vision and goals also often requires managing the expectations of their various constituents. Foundations have their patient, contributor, and scientific groups to satisfy. Companies have investors and shareholders, boards, regulators, and so on. It's an ongoing challenge, but both sides can anticipate many of the challenges by communicating and defining realistic expectations during the partnership's conception and thereafter.

**CHOWDHURY:** You don't want to alienate your bases, so while you may begin to do more with industry, you want to make sure it's not at the expense of important activities in academic research labs. Managing patients' expectations is always critical, but the need varies between disease areas and foundations based on the state of the science. At MJFF, we are very optimistic, because the pipeline in Parkinson's disease is incredibly robust. But we are also very grounded in reality. We explain to our patient and supporter community how difficult drug development is and how much is still unknown about the disease. Still, you don't need to know everything to find a solution.

Experience in partnering with foundations at his previous and current companies tempered one executive's enthusiasm with a clear-eyed view of partnering challenges and taught him the need for discernment among the diversity of foundations, a wider view of partnering goals, and an adherence to high principles.

**ANDREW GENGOS** President And CEO, Immunocellular Therapeutics:

The patient populations and not-for-profit disease groups out there are all very different. Some are way ahead in thinking about formal relationships with industry in drug development, and others are in their infancy. If your company is working on a particular disease, you have to understand the landscape of groups that are focused on that disease. I wanted to position our company with the right group that would provide support and potentially amplify our influence with Congress and the FDA. What I finally settled on were the grassroots patient groups. The reciprocity for your partner is honesty about your company and your drug development. You have to be honest, transparent, and build a trust-based relationship. And you've got to be genuinely caring about their plight, as individuals and as a group, so if you ever need their support, they will be there for you.

*Thus ends part one of our four-part series. Watch for part two, "Resource Alignment," in next month's Life Science Leader. Many thanks to Travis Blaschek-Miller at BayBio for his help with this article series.*

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# Navigating The New World Of Value-Based Healthcare

MARY BETH LEWIS; BRIAN GRINER, Ph.D.; & MRIDUL MALHOTRA

*Demonstrating the value of therapies to the many healthcare stakeholders is an ongoing challenge for drugmakers. This involves complex analytics and requires developing appropriate evidence to meet stakeholder needs.*

There are parallels between medicine and baseball in these efforts to use evidence in practice, as described in the 2012 *New England Journal of Medicine* paper, *Moneyball and Medicine*. In his 2003 best-seller, *Moneyball*, Michael Lewis points out that the architects of evidence-based baseball have developed metrics to evaluate player performance in terms of the value they add to the team. "Similarly, architects of new value-based approaches to healthcare delivery have attempted to develop metrics to evaluate the performance of therapeutic strategies, individual practitioners, and organizations," states the *NEJM* paper.

## THE NEW WORLD OF VALUE-BASED HEALTHCARE

Against a backdrop where healthcare costs have increased five times faster than the GDP in the United States since 1960, and despite the fact that services account for most healthcare spending, pharmaceuticals remain an easy target for criticism and pricing pressures. This applies particularly to high-priced drugs for cancer and rare diseases. These trends are driving a need for value-based pricing. In the U.S., the Patient Protection and Affordable Care Act (PPACA) of 2010 has far-reaching implications for the cost structure of the healthcare market. Other key trends include the rise of accountable care organizations (ACOs) and the linking of reimbursements to quality metrics and reductions in the total cost of care. In the EU, the fact that fewer players are involved in healthcare than in the U.S. means that cost containment efforts are highly sophisticated. Here, new pricing frameworks are being based on perceived value rather than cost plus a profit margin, on evidence rather than historical experience, and on the perspectives of many stakeholders rather than just one. Levels of adoption of these frameworks vary by country and are supported by recent legislative changes.

For biopharma companies, the implications of value-based healthcare include the need to:

- **change the focus of R&D** so that companies focus investment on treatments that make significant advances in clinical performance
- **redefine pricing evaluations** for new medicines so that pricing reflects true societal value and takes account of wider economic benefits of treatments beyond direct health gains
- **improve patients' access** to new therapies that their clinicians believe may provide benefits.

Defining value remains a challenge, with no consensus among stakeholders. Physicians typically focus on evidence of a new product's effectiveness, while patients demand more assurance regarding a drug's safety, and payers require proof of a therapy's cost-effectiveness. Additionally, policy makers demand confirmation of a product's real-world risk/benefit profile in large populations. *The 2011 New Health Report* found that biopharma executives were the only group in which a majority included outcomes as part of their definition (Figure 1). For patients and physicians, the process (quality of care) appeared to matter as much as the outcome when it came to value, although nearly one-third of patients did not feel they could define value.

## A VALUE-BASED FRAMEWORK

Pressures to develop a value-based framework include:

- **declining R&D productivity** despite increased investment, with the potential of proteomics so far not fulfilled, and significant funding gaps

- **limited revenue and growth** due to patent expiries, regulatory issues, promotional saturation, and restricted access to physicians
- **external pressures** such as high public expectations, patient dissatisfaction, pressure from investors, and safety concerns
- **pricing issues** including reimbursement challenges, pressures from buying groups, and high costs to patients.

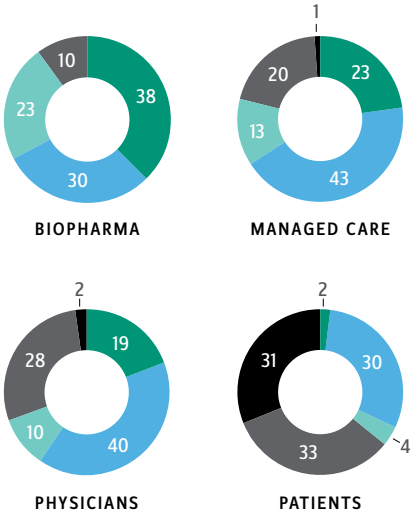
A strategic approach to a value-driver's assessment encompasses five key market-facing considerations:

1. **price sensitivity:** What is the relationship between price and demand?
2. **performance:** What is the product's cost/benefit relationship?
3. **profile:** How does the product compare to the competition — current and future?
4. **practice/organizational economics:** How do pricing and volume impact the economics of the organization?
5. **positioning for value:** What attributes, for which patients, provide the greatest value and fulfill unmet needs?

When modeling stakeholder decisions, biopharma companies typically optimize the profile and strategy for each group in isolation. This "divide-and-conquer" approach to research does not measure the real impact that each stakeholder's

FIGURE 1

**In Your Own Words, How Would You Define "Value" In Healthcare?**

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***Source:** 2011 The New Health Report, Quintiles

decisions have on other stakeholders in the healthcare system. A more holistic approach takes account of the fact that each stakeholder reacts to a manufacturer's offering directly and also to the reactions of other stakeholders.

An integrated approach to product potential and optimization research uses an interlocking research design and holistic modeling across all audiences simultaneously to provide a more comprehensive assessment. This provides a truer sense of actual expected share and optimal pricing information, as well as identifying the real leverage that may be available to influence demand.

A multistakeholder-linked value driver model simulates the real-world market dynamics due to changes in the product or marketplace to measure price sensitivity and changes in product demand. This type of model incorporates bidirectional influence dynamics that occur in the long and short term to provide a more robust and realistic view of the key drivers of overall market potential and revenue-optimizing pricing strategy.

Linked value-driver models are constructed in several steps. First, the decisions made by each stakeholder are identified (the dependent variables). Second, the likely degree of influence of each stakeholder on product adoption is determined. The experimental design then reflects these factors.

The model reflects payers' likelihood of reimbursing a product, healthcare providers' likelihood of prescribing, and patients' chances of accepting or requesting the therapy. The model also considers that in the marketplace each stakeholder responds to the strengths and weaknesses of an individual product and its competitors and also responds to the reactions of other stakeholders.

## VALUE-BASED PRICING

Value-based pricing triangulates both stated and revealed value metrics to provide a robust measure of value at different price points that more closely reflects the true value of a product. This approach includes a health economic appraisal, a willingness to pay assessment, and reference price benchmarking to develop a pricing and access strategy that maximizes uptake and profit. A case study using a linked value-driver model is described below.

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CASE STUDY

## Linked Value-Driver Model Of Product X

### Background & Objectives

Company Y is developing a new product, Product X, to follow its current formulations as part of its life cycle management strategy. In addition, there is the possibility of a generic entering the market in the future. The Company Y team needs to understand the impact of this market-changing factor on potential demand for a new formulation.

Research addressed the following objectives:

- Develop a linked value-driver model of physicians, patients, and payers to identify product features that optimize market demand for a new formulation.
- Determine optimal pricing given different market-access scenarios.
- Evaluate future market scenarios to measure the impact of likely payer decisions and the availability of generics on demand for Product X.

Payers are key to the success of Product X — determining reimbursement, inclusion on formulary, and imposing cost limits on doctors and practices. This study also aimed to determine how much benefit there might be in providing direct-to-patient information.

The relative importance of attributes to the overall market share of Product X is illustrated in Figure 2, which shows that generic availability and rebating have a substantial impact, while tolerability and mode of delivery have a smaller but still significant impact. Dosing and formulation drive a very small portion of overall preference share for Product X.

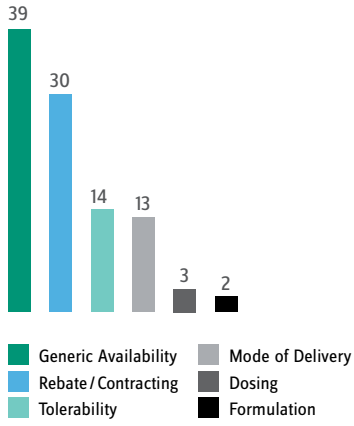
An analysis of attribute sensitivity using the linked value-driver model indicated that rebates and contracting are the largest positive drivers, and generic competition is the largest negative driver of base-case market share.

The linked value-driver model's forecast for adoption and utilization confirms that adoption of Product X depends heavily on market access, which depends on price and the presence or absence of generic competitors.

Overall, the linked value-driver model provides comprehensive predictions on many elements of the likely future performance of Product X. A major feature is that small differences in market-access pricing can have significant impacts on the product's revenue stream over long periods.

FIGURE 2

**Relative Importance Of Attribute On Overall Market Share**

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# How Genzyme Got Its Manufacturing Mojo Back

**NICK TAYLOR** Contributing Editor

*In the summer of 2009, Sandra Poole, newly appointed head of Genzyme's Allston Landing biologics plant, and the site's leadership team were confronting arguably the toughest job in biotech at the time. Days before her arrival, Genzyme shut down the site after discovering a viral contaminant. There would be no settling-in period. The entire company and thousands of patients were relying on this team to fix the problem.*

Looking back on that summer, Poole admits it was a very challenging time, with staff working night and day to resolve the issues and resume production at the facility. The sixth and final bioreactor came back online around 2:30 a.m. one August morning, but the saga was just beginning. Earlier that year, Genzyme had received a warning letter from the FDA following inspections of the Allston Landing plant. The FDA also indicated that additional information was needed regarding a pending drug marketing application. The warning letter was followed a year later with the FDA's announcement that it would seek an enforcement action, which resulted in a consent decree and a $175 million fine. Activist shareholder Carl Icahn got his people on Genzyme's board, and in 2011, Sanofi bought the company.

The events and the headlines they generated placed additional pressures on Poole and her team, but the biggest hit to morale came from elsewhere. A combination of low inventories of Fabrazyme and Cerezyme, the facility shutdown, and reduced output during remediation meant Genzyme was unable to meet demand for the products. Patients were initially understanding, Poole says, but as the supply shortage dragged on into 2010, tensions grew. "We could feel the frustration," recalls Poole. This was the low point. "The worst thing was the feeling of having failed. We tried our hardest, but yet … ."

By the time the staff reached this low point, they had fallen a long way. Allston Landing was the foundation on which the Genzyme success story was built, and staff was proud of its role in turning the company from an upstart biotech into a major force in the biopharma industry. In 2008, the future looked bright. Having added a third product and expanded a manufacturing suite, the metrics showed the plant was in good health. Everything suggested its second 15 years would be as successful as its first, but the forecast was wrong.

## WHY GOOD PRODUCTION PLANTS GO BAD

Rebuilding confidence after such a dramatic and public decline became a major part of Poole's job. In the short term, equipment needed upgrading, and quality systems required remediation, but Poole felt the plant's people were central to achieving a sustained transformation. In the systems-thinking model followed by Poole, a plant's people and culture sit at the center of an interconnected ecosystem. Each part of the system must function well in relation to the others for the plant to succeed. The problem? When you are in the middle of the system, it is really hard to see and keep track of the interactions.

Poole thinks this limitation played a role in the problems faced at the Allston Landing site. As the plant grew and added new product lines, the system became more complex. Many facilities go through this process, with the early years of rising confidence and capabilities giving the owners sufficient faith in the plant to increase volumes or change the product mix. Yet if the staff, processes, and equipment are not individually and collectively prepared to deal with the increased complexity this brings — and attuned to signs it is causing problems — the situation can unravel.

This is the Allston Landing story, Poole says. The plant was built to produce Cerezyme, and output tripled in the first few years. Fabrazyme was then added, and, while the system became more complex, the site continued to thrive. In retrospect, the addition of Myozyme in 2004 and subsequent need to expand output above anticipated levels may have been the tipping point, though. While on the surface the plant prospered, Poole thinks elements of the system were unprepared for the new level of complexity. Strengthening

just a few parts can be counterproductive. "You can actually make the system more fragile," says Poole.

Having arrived at the start of Allston Landing's decline, Poole and her team began strengthening the system as a whole in a bid to not only fix the problems but also prevent them from ever happening again. To simplify the site from an operations standpoint, Genzyme began narrowing the focus of the plant exclusively to Cerezyme bulk drug substance production, moving the manufacturing of Fabrazyme and fill-finish and packaging operations to other parts of its industrial network (Myozyme had already exited the site).

Just as significantly, the Allston "People Plan" was created. Town hall meetings and luncheons were held to connect people, share stories, and rebuild morale, but Poole says programs to help staff with systems thinking, collaborative skills, emotional intelligence, and resilience were most impactful. "We wanted to ensure we had the talent and that the leadership and the workforce had the capabilities to adapt to all the changes," says Poole.

## EQUIPPING LEADERS TO REJUVENATE A DEMORALIZED PLANT

At the core of the People Plan were two initiatives: a change-leadership-capacity building program and the Allston DNA Cafe. For the change-leadership project, Poole gathered 80 of the facility's top leaders for a series of workshops. A practitioner of systems thinking was brought in to help the team see the plant for the complex ecosystem it was, not the series of simple linear cause-effect relationships their brains were wired to spot. This led to practical tasks like building feedback loops, which adapt an organization to change, and how to solve real-world problems using systems thinking.

The Allston DNA Cafe complemented these workshops. Poole again gathered the plant's 80 leaders, but this time broke them up into groups of eight peers. Each group was coached by internal and external experts in action learning, the process of acquiring knowledge through actions and practice, as opposed to traditional instruction. The groups met once a month, with part of their time dedicated to building skills, such as how to ask a really good question. Each participant would also share real-life problems with the group and discuss potential solutions with their peers.

Poole is effusive about the initiative. "That program has been hugely successful. Testimonies from the individuals show this was impactful in their jobs and personal lives," she says. Giving the leadership these new skills and renewed faith in their abilities helped them weather the setbacks that occur in any remediation effort. Having gathered the very personal metric of participant testimonies and seen the improvement at Allston Landing, Poole's successor at the plant,

Pat O'Sullivan, has continued running the change leadership program and smaller action-learning gatherings.

In her new role of senior vice president, biologics manufacturing at Genzyme, Poole is tasked with taking the lessons learned at Allston Landing and replicating them across the production network. The work has its origins in the early days of the Allston Landing crisis when Genzyme's leadership decided to use the problems as the trigger for a companywide transformation. Other production plants throughout the industry face pressures similar to Allston Landing, whether it is the need to add more products or a combination of technological, social, and regulatory changes. Genzyme wants to prevent history from repeating.

As Poole sees it, increased complexity is inevitable. What matters is how a plant copes. "Companies that develop the ability to really understand and master this complexity, to be able to anticipate and adapt to all these forces of change, and reorganize themselves after a significant disruption will really have a huge competitive advantage," she says. Tests of whether the lessons learned at Allston Landing have helped Genzyme master complexity await. If Allston Landing continues its revival, it may one day be presented with opportunities that could introduce further complexity. However, considering the journey the site has been on, it would be much better positioned to handle this complexity. Poole's objective is to ensure the rest of the sites within the Genzyme biologics network benefit from the Allston experience.

## THE METRICS TO TRACK TO FORESEE DECLINE

Genzyme's plant in Belgium, which Poole led before moving back to the United States to manage the crisis, is at a stage of development comparable to Allston Landing in the early 2000s. The site has available capacity and infrastructure, but Genzyme is still determined to learn from its past experience in Allston. Poole says, "We're having very thoughtful conversations about the Allston Landing experience and asking, 'How do we know the Belgian site is capable enough to handle increased complexity before we introduce it?'"

If the process is handled well, Poole sees no reason the Belgian plant will suffer as a result of the increased complexity. The trick is to match the plant's competence and capabilities to the new level of complexity. This means helping the leadership understand the new system and their teams' roles within it, instead of just adding staff and equipment and expecting the rest of the site to carry on as before. "It's when you add products and increase complexity without taking into consideration all parts of the system — including people

*"We track a ton of things, but are they really the right metrics to measure organizational health?"*

**SANDRA POOLE**
Senior Vice President
Biologics Operations
at Genzyme

and culture — that you fall into trouble," says Poole.

Throughout the expansion, the Belgian team will monitor the plant's metrics and key performance indicators (KPIs), but the failure to predict the Allston Landing crisis has shown Genzyme one cannot rely on data alone. While Poole believes lessons learned at Allston Landing have left Genzyme better equipped to foresee and avert crises, she knows there are limitations to how well past experiences can help fix or prevent future problems. "Could I sit here today and reassure you that we would never have another setback or lose confidence in the future?" says Poole. "No one could honestly make such a claim about any plant. The task of today's leadership is to complement technical leadership competence with the adaptive and systemic leadership capacity that is well-matched to complexity." For Genzyme, and all manufacturers, part of the challenge is to pick the right metrics. In hindsight, the factors tracked at Allston Landing before the crisis were clearly imperfect. Poole thinks there is still room for Genzyme and its peers to improve. "I'm not convinced that as an industry we have the right metrics. We track a ton of things, but are they really the right metrics to measure organizational health?" The question can only be answered by decades of accurate forecasts — or one very bad prediction.

At Allston Landing, a five-year period that is described by Poole as "truly the most challenging and painful in our company's history" was neither predicted in advance nor evident in a review of metrics after the fact and was perhaps a perfect storm. "You can be sitting at the top feeling confident, but in fact you may not yet know that you are already sliding in terms of erosion in your capabilities. While nobody who worked there in the summer of 2009 will forget how quickly the situation can change, the plant is on a positive path forward and bears little resemblance to the site that faced such significant challenges five years ago. That's the Allston story," says Poole. L

# 3D Bioprinting Could Speed Up Drug Development

**CINDY DUBIN** Contributing Editor

*Three-dimensional (3D) printing is a 20-year-old technology whose time finally seems to have arrived. Interest in the equipment rose sharply last year; in 2012, the market for 3D products reached $777 million and could reach $8.4 billion by 2025 as medical uses for the printers are being developed, according to Lux Research.*

One company focused on the medical use of these printers is San Diego-based Organovo Holdings, a biotech firm that designs and creates functional, 3D human tissues for medical research and therapeutic applications. In January 2014, Organovo delivered its first 3D liver tissue to an outside laboratory for experimentation, marking a milestone toward commercial launch of a 3D liver tissue product. "These 3D human tissues have the potential to accelerate the drug discovery process, enabling treatments to be developed faster and at lower cost," explains Keith Murphy, Organovo's CEO and president, who previously worked at Alkermes and Amgen.

## A TOXICITY PREDICTOR

Organovo has focused its attention on the liver because, as Murphy explains, about 10 percent of all drugs in Phase 3 clinical testing fail due to liver toxicity. "One reason for that failure is because we currently test the drugs on animals or on cells on a Petri dish surface, and that just doesn't work for liver testing," he says. "We see projects get green-lighted to move into clinical trials, but subtle effects of the drug on the liver come out over time."

As an alternative to animal testing and Petri dishes, Organovo is building what Murphy claims is a better model of the human liver. The company's proprietary bioprinting platform enables the reproducible, automated creation of living human tissues that mimic the form and function of native tissues in the body. The 3D bioprinted human tissues are constructed from tiny building blocks made of living human cells using a process that translates tissue-specific geometries and cellular components into 3D designs that can be executed by an Organovo NovoGen Bioprinter. Once built, the bioprinted tissues share many key features with native tissue, including tissue-like cellular density, presence of multiple cell types, and the development of key architectural and functional features associated with the target native tissue.

Organovo's 3D human tissues offer many advantages over standard cell-culture platforms due to the fact that three-dimensionality is achieved without dependence on biomaterial or scaffold components that would not be found in native tissues. Organovo's bioprinting technology was developed by the company's scientific founder, Prof. Gabor Forgacs, at the University of Missouri Medical Center at Columbia in 2003.

The living cells, taken from an individual, are bioinked (i.e., cells are treated and formulated to form the bioink), loaded into a cartridge, and inserted into the 3D printer, which is about 2' x 2' x 1.5'. If printing liver tissues, a 24-well plate is printed in about 45 minutes and usable for testing in just two days.

"Three-dimensional bioprinted tissues can help pharmaceutical companies speed up the drug discovery process allowing R&D teams to test new and promising drugs on functional human tissues during hit-to-lead (H2L) and lead optimization stages of drug development," says Murphy. "This will help identify potential toxicity and efficacy issues before drugs ever enter clinical studies." In addition, these tissues last more than 40 days, which is a vast improvement over their 2D counterparts, which can only last for 48 hours. This would enable researchers to dose, monitor, and sample the same tissue over a longer period of time, allowing them to detect more subtle or longer-term effects.

In addition to liver tissues, Organovo can biopsy cancer cells from a patient, grow them, and make 3D bioprinted tumors to test new drugs. Entering into 3D bioprinting at the right stage of drug development is critical. For instance, it would not make sense to pursue 3D bioprinting for a pharmaceutical or biologic company that wanted to screen

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10,000 compounds. Doing so would be too costly to build the tissues at a reasonable price. A better scenario would be if there were 100 or fewer compounds to test, and the company was seeking the perfect molecule to move forward with — without liver toxicity issues. "The model allows a company to put its faith in a molecule that represents the desired potency and efficacy to move into a clinical trial," says Murphy. "While the current drug discovery process typically takes between three and six years, this would help pharmaceutical companies reject an ineffective or dangerous drug in a matter of months."

## BUILDING THE DATA

The benefits of rapid drug discovery and early identification of toxicity issues have caught the attention of pharmaceutical companies. For instance, Organovo signed a collaborative research agreement with Roche last year. While Murphy cannot describe the scope of the work, it is presumably to test Roche's compounds.

Unrelated to Roche, Organovo has released quite a bit of data on its 3D liver model. Organovo's 3D liver tissues exhibit dose-dependent responses to acetaminophen, a known liver toxicant. And Murphy explains that the liver tissues successfully produced albumin, fibrinogen, and transferrin. The bioprinted liver tissues also possess the ability to synthesize cholesterol.

While Murphy admits that no test can be 100 percent accurate, he says 3D bioprinting represents a huge leap forward from animal testing and Petri dishes. For example, he says the small tissue being created is indeed representative of the larger tissue. "We are starting from a place where it's so bad that slight improvements are incredibly good, and we're creating what we think is a dramatic improvement," he says. "We may fall short of being perfect, but we are so much closer to perfect than the available methods that the benefit is huge."

Murphy says the promising data is not only a story to be shared with pharma, but also with federal regulators. "Remember that regulators are scientists, and they want to see good data. That is what they will use to determine a drug's approval. The bottom line is if we provide the scientific value that we think we can, which is a better model than some of the existing animal models, the FDA should be extremely comfortable letting people move forward."

Organovo has already been speaking with the FDA. Murphy says the agency is aware of how the company's science works and how it can potentially be beneficial. "If we show that 3D bioprinting is a predictive tool, the FDA will accept the test and could theoretically ask that pharma use the technology," he says.

## FIGURING OUT WHY GREEN-LIGHTED DRUGS GO BAD

But until that point is reached, more work needs to be done. Going forward, Murphy says Organovo will test drugs that failed in the clinic but were initially green-lighted based on the results of animal models and 2D cell-culture testing. "We want to discern what things light up that we could have seen to help pharmaceutical development become more predictive."

Organovo will also commence the commercial launch of its 3D liver and start generating revenue through a contract research service model before the end of the year whereby a pharma client would provide its compounds and Organovo will perform a set of tests for the client. While the cost for such a service will depend on the tissue, Organovo will work with each customer on an individual basis and build tissue specifically to a client's need. Murphy does say, though, that the cost for tissue for liver fibrosis would be different than tissue for liver toxicity testing.

While Organovo anticipates that preclinical toxicology testing services could command prices in the high tens of thousands per compound for standard liver screening alone, Murphy points out that the cost of drugs that fail is estimated at about 40 percent of all drug spending. "So if the drug spending is more than $50 billion per year, there is an opportunity to save more than $20 billion. Even if using 3D bioprinting testing only causes modest improvement, there is significant potential benefit."

> *"Three-dimensional bioprinted tissues can help pharmaceutical companies speed up the drug discovery process."*

**KEITH MURPHY**
CEO and President,
Organovo Holdings

And Murphy says that, under the right circumstances and with the right partner, Organovo could license the bioprinting technology to a life sciences company to perform its own testing.

Organovo also plans to release additional data in 2014 on its 3D kidney tissues and breast cancer tissues, which are now in development.

Organovo is about six years away from entering clinical studies to make tissues for surgical implant. "Everyone quickly thinks about large organs; bioprint an organ and implant it into the body. But, instead, we are focused a little smaller. Think of a 3D bioprinted liver patch to help repair a damaged liver. We could take cells from the patient to create the patch, which would almost assure no immune response."

The applications and the implications are plentiful. Organovo will continue to work with liver and kidney tissue, but other 3D bioprinting research will include oncology, lung tissue, muscle tissue, and blood vessels.

Murphy says: "Three-dimensional bioprinters are a powerful tool, and while they might not solve every issue in drug development, they can be leveraged to make headway in areas where traditional animal models and 2D cell-culture methods aren't allowing pharma to make good progress." L

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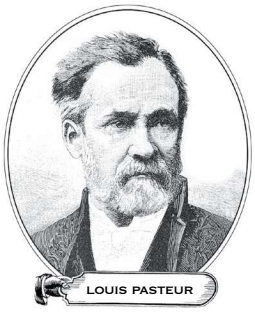


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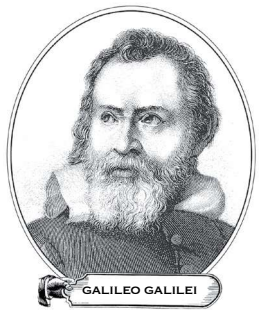


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# Bridging The Gap In The Clinical Development Business Model With Patient Involvement

ABBE STEEL

Abbe Steel is founder and CEO of HealthiVibe. She is a 23-year veteran of the life sciences industry, leading clinical development and postmarketing patient-directed initiatives.

In March of this year, Sanofi appointed Anne Beal, M.D., MPH to the position of chief patient officer (CPO). It marked a first for a top 10 biopharmaceutical company and is a sign that patient engagement may finally be coming, albeit slowly, to the one area within pharma where it's been most lacking: clinical development.

Recruitment and retention problems have long plagued clinical trials and frustrated top-level executives. The bottom-line impact has been enormous (e.g., trial cost overruns, protocol amendment delays, postmarket difficulties that highlight a widening gap between trial design and patient needs). The problems are well-documented. Solutions have remained elusive, in part, because of a prevailing culture within pharma that still emphasizes providers and regulators over patients. It's an antiquated and inefficient model that needs to change.

There are obvious reasons for the current model. Investigator initiation is necessary to get a trial moving, and regulators hold the ultimate authority. Patients, meanwhile, have historically been kept at arm's length, due in part to privacy concerns. Patients have been kept at a distance for so long that they're not even recognized as a true core constituency, which undermines the principles of sound study design and makes the root problem that much harder to identify. And it leaves those same top-level executives scratching their heads over how to find a solution.

## THE MISSING LINK

Every clinical-trial patient faces challenges. By necessity those challenges are unique to the trial, to the patient's underlying conditions and comorbidities, and to the logistical considerations imposed by the study design — considerations that are only revealed to be daunting when considered in context. The missing link in study design has been grasping that context.

Pharma clinical development teams will point to increased engagement with advocacy groups, online communities, and low-risk patient-centric innovation pilots as evidence of a shift toward patient engagement across the product life cycle. But within clinical development specifically, the benefits are marginal because the engagement isn't study-specific, or else it comes too late to impact protocol design. The patient is still at arm's length throughout protocol design and often throughout the study itself. Trial patients are rarely asked for feedback about the studies in which they've just participated. Detailed patient feedback is absent or lacking in specificity, exactly when it's most critical and when clear market research is most beneficial.

An interesting angle here is that patients, more than ever, want and are able to share their insights. They seek out engagement. The last 10 years have seen an explosion in mobile device technology and social networking use, and the two factors together have directly led to patients taking a more active role in their healthcare decisions. Elsewhere in the healthcare space, even within pharma, this is well-recognized and even starting to be embraced. Only in clinical development has it been largely ignored.

For all the talk about advocacy groups, patient workshops, and the changing culture of pharma, little has changed in how trials are designed and conducted, and the improvement on cost and time to market has been minimal. It's emblematic of a pharma culture that pays lip service to the ideals of patient-centricity, but remains content with half measures.

## SHIFTING THE CULTURE

If there's a gap in pharma's understanding of patient needs, it can be addressed with effort. The more critical problem is the lack of a true corporate emphasis on shrinking that gap.

A solution requires nothing less than a culture shift, so that the business model tilts for the first time to include the patient.

As the Sanofi announcement demonstrates, such a shift has to originate from the top. It requires a dedicated budget item for patient engagement. It requires the creation of a C-suite position with true ROI accountability. It requires the same allocation of resources and commitment that any other business-critical initiative demands. And it requires, finally, an acknowledgement that patient involvement is a core component of the business and a corresponding mandate that no study can move forward without it.

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# Molecular Imaging Cuts Time And Cost From Drug Discovery

SCOTT HALLER

Scott Haller serves as the director of the Translational Imaging Center at MPI Research. He has 15+ years of experience in strategic leadership and scientific advancement, business development, and integration of service offerings.

Everyone involved in drug discovery is seeking ways to lower costs and improve efficiencies. One process that may help pharma and bio firms achieve both goals is molecular imaging (MI). MI is a process which uses imaging platforms, similar in concept to the cameras used to detect white light, to detect the radioactive decay products of a specific radioisotope.

There are different types of imaging platforms which can be used in this process, the difference being the detection of decay/emission patterns of radioisotope(s). Imaging platforms will detect radioisotopes in animals but are also used on humans in clinical research and diagnostic evaluations. Application in both the preclinical and clinical domain gives researchers the ability to leverage preclinical data sets as a direct translational foundation upon which to develop a clinical program. As MI becomes more robust and its applications better understood, it will lead to improved program design and management. The technology has significantly progressed in informatics, which is our ability to evaluate and understand the information contained in the imaging data.

The process commonly starts with a sponsor sharing its chemical structure with the imaging lab. The lab determines the appropriate radioisotope to bind to the test material. This essentially places a homing beacon within the structure of the material so it can be followed through the animal or patient to whom it is administered. The treatment of cancer is a common use for the technology because it provides the ability to evaluate uptake in tumors and determine the size, growth, or reduction of the tumor. MI can be successfully applied to CNS, bone redevelopment, inflammation, and many other therapeutics.

The real power of MI is its flexibility to effectively address objectives across many development programs. MI can provide solutions to the sponsor or development group to answer various study objectives. This flexibility is achieved through modifications to study design, radioisotope (whether it is bound to the test material or to a surrogate biomarker), chemistry, and image acquisition parameters.

## SPEEDING THE DEVELOPMENT PARADIGM

Incorporating MI into drug development paradigms can cut the cost of drug development by getting answers to sponsors in a timely manner. In the traditional paradigm evaluating biodistribution, tissue is harvested from an animal at a particular time point (i.e., three days). The radioactivity is quantified against what was originally administered to the animal. This approach does not provide the opportunity to obtain multiple time points from a single subject. With MI, the same animal is imaged at multiple time points, which is less costly and less labor-intensive.

The amount of time saved on a study can vary widely and is dependent on the program design. A time reduction of only 1 to 2 percent could still be significant, especially in a large program. Savings of as much as 50 percent are possible if clear target engagement is demonstrated in early studies. Cost savings will also vary, but depending on the study could be millions of dollars.

The other improvement is the increase in resolution of activity within discrete segments of target tissues. With MI, the focal point can be a very finite position, allow for a three-dimensional analysis, and provide an understanding of the detailed distribution within a single organ. MI provides a robust data set which may not be attainable when performing a general tissue collection and counting methodology. This difference can be significant for many development efforts.

## HAVE AN ACCURATE UNDERSTANDING

Although the MI process could be used in most therapeutic areas and with almost any molecule, the benefits can be overlooked by development teams. We find this commonly attributed to misconceptions about the cost, a lack of understanding on how best to apply it, or a lack of access to the technology or individuals who understand how to apply MI to the needs of their development efforts. These issues can be avoided via proper up-front discussions and collaborative approaches to program design.

Development of commercial imaging centers providing these services to drug development teams eliminates concerns with capital investment needed at the sponsor end and allows them access to the technology and expertise from collaborative, multidisciplinary teams. The time and cost savings are real, with MI providing needed medicines to patients in a more timely manner. L


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# The Essential Leadership Practice To Inspiring Employee Engagement

MARK CROWLEY

Recently I gave a speech to a group of CEOs from all over the world. When it was over, I received a standing ovation.

It was exhilarating to experience such a validating reaction to my work — and to know that everything I'd done to ensure the success of that presentation had paid off. You see, I'd spent weeks mapping out a script, thoughtfully building compelling slides and rehearsing my remarks over and over until they became instinctual. And while no one in that room could have known how much time, energy, and heart I'd devoted to preparing for that one speech, the resounding response afterwards assured me that *every bit* of my effort had been worthwhile.

While still standing (and glowing) on that stage moments after my presentation, an inner voice reminded me that our job in leadership is to ensure all of our employees — the people who invest so much of themselves in *their* work — routinely feel as I felt at that moment. The simple truth is that recognition is essential to the spirit that motivates human performance, and without it, our engagement withers.

However, in our day-to-day operations, we often forget how important recognition is to sustaining the passion, drive, and initiative in people. Following a successful month, quarter, or project, we direct our focus to the next goal and completely ignore the hard work and effort just made by our subordinates. Employees are given no time to catch their breath, savor the moment, or feel a sense of satisfaction with what they just accomplished. And without validation that their recent efforts truly mattered, our once high-performing and committed people instinctively lessen their determination to excel going forward.

To help ensure your team routinely knows their work is appreciated and never taken for granted, here are three ideas I hope you'll always remember:

**1 Never Assume Your People Know You Appreciate Them**

I've had leaders tell me, "My people already know I'm grateful," and use this as an excuse for never expressing it directly. But, unless you have a team skilled at mindreading, there's no way employees can know with certainty that you do value them. Ambiguity in this regard is highly destructive; so never leave your people in doubt as to how you feel about them and their work.

**2 Get Comfortable Telling People Directly How Important They Are To You**

We think we'll be exploited if we tell our people how much they matter and how much we depend on them. The truth is few things affect people more deeply than knowing their boss thinks the world of them. So tell people directly, "I'm so grateful you're on my team. The work you do here makes an incredible difference to our success." That kind of honesty is uncommon, as will be the engagement it inspires.

**3 Institutionalize Recognition**

People will work extremely hard when they know they can count on receiving your recognition. So build a routine; devote the start of every team meeting to acknowledging achievements, and tell people in advance what specific performance you'll consistently honor. Then get ready for soaring performance. L

Mark Crowley is leadership consultant, speaker, and author of *Lead From The Heart: Transformational Leadership For The 21st Century*. A regular leadership contributor to *Fast Company* magazine, his work has appeared in numerous publications, including *USA Today* and *CEO* magazine.

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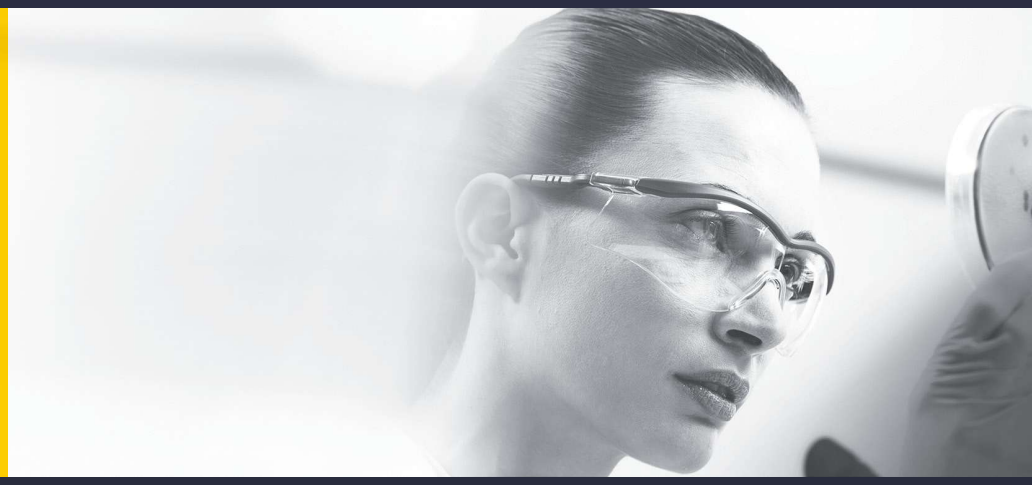

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