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"Like you, our readers, we believe quality matters."

If you are not getting better, you are getting worse. The team at *Life Science Leader* has always taken pride in the quality of our content with continuous efforts to improve what we deliver to you. However, the look and feel of the magazine has lagged behind those improvement efforts. Until now. In this issue you will see a total redesign of the layout of the magazine, starting with the cover. We worked with marketing agency That's Nice, who understood what we were looking for and designed a magazine that equals the quality of the content. We hope you enjoy it. If you do, please go online and renew your subscription to continue receiving the magazine for another year without disruption. As always, your feedback — good or bad — is welcomed.

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Paul Stoffels crafts the pharmaceutical company of the future at J&J and Janssen p. 22

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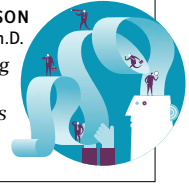

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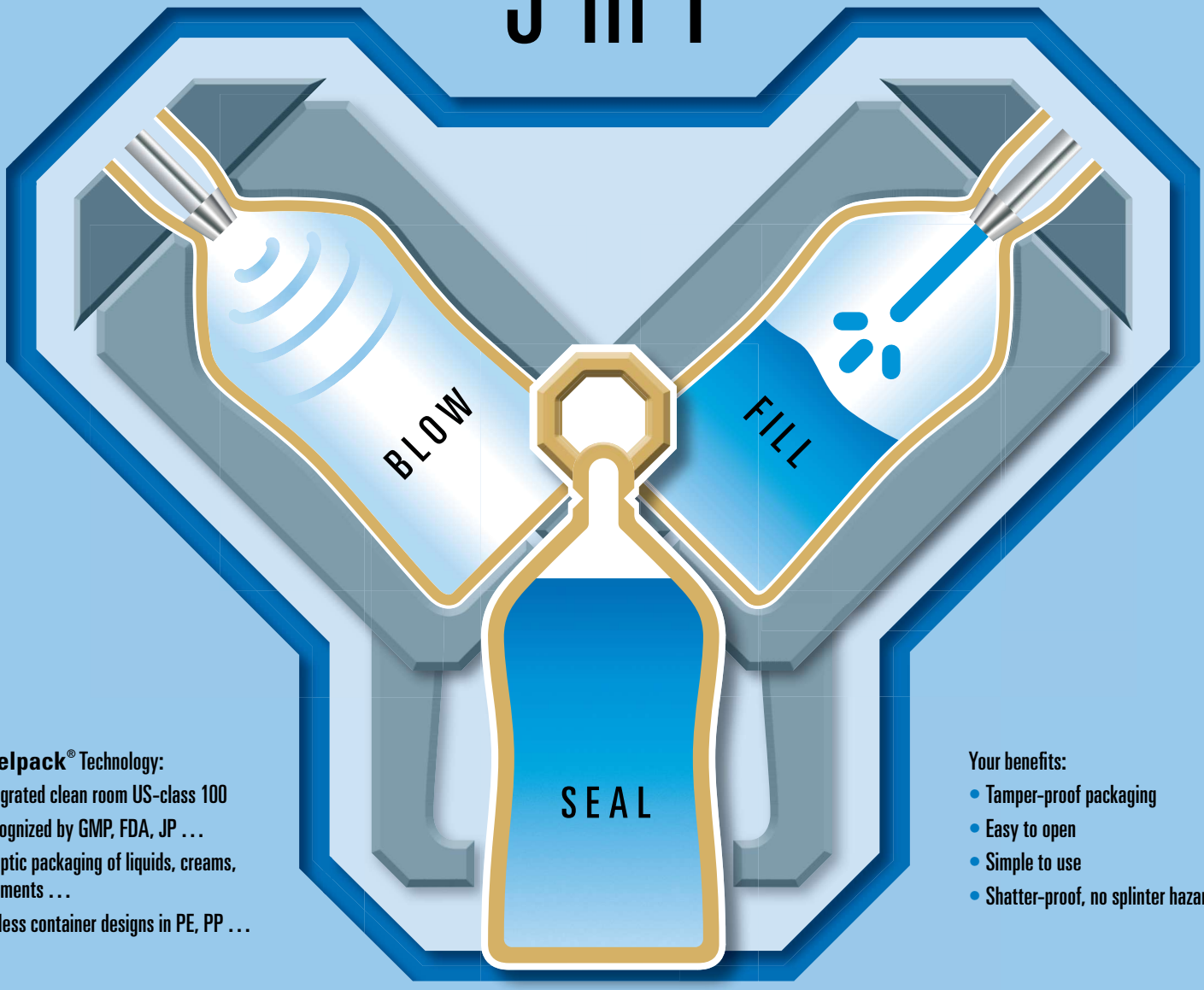

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What Gives
With The New Look?

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Unless this is your first month as a subscriber to *Life Science Leader* magazine, undoubtedly you have noticed this issue looks significantly different than previous issues. If you're the type of person who is not a fan of change, I assure you this new look is restricted to aesthetics and not indicative of some broader alteration to our content or market coverage. Go ahead, flip through a few pages. I think you'll see the monthly features you have come to enjoy and find valuable are all still there, just with a different design.

When I worked in the pharmaceutical industry, I experienced a number of changes, such as corporate realignments, acquisitions, mergers, downsizing, rightsizing, and various other forms of restructurings. Immediately after the change, if you were still employed, you probably sat through a seminar on "change" complete with a PowerPoint presentation. After reviewing the stages of change (shock, denial, frustration, depression, experiment, decision, integration) visually via a diagram of the Kübler-Ross change curve, you would typically receive a parting gift. I personally collected three copies of *Who Moved My Cheese* by Spencer Johnson and Kenneth Blanchard, as well as two copies of *Good To Great* by Jim Collins. If you have been around as long as I have, you probably already have a copy of the necessary books which might help you with adjusting to the new look of *Life Science Leader*. If you don't, I will be happy to share my copies.

According to Rosabeth Moss Kanter, professor of business administration at Harvard Business School, "The best tool for leaders of change is to understand the predictable, universal source of resistance in each situation and then strategize around it." Prior to making changes that affect others, experts say it is important for change agents to think through carefully as to what the change will include, who it will impact and how, and the potential reaction. For this redesign, we took nearly a year to come up with what you see today. We gained input from a variety of sources before landing on the final design. As for your reaction, I am eager to hear it. Feel free to drop me an email, or better yet, pick up the phone and tell me what you think.

Why did we make the change? The answer is simple. Leadership is about leading. But as you have undoubtedly experienced in your careers, leadership is also about implementing change. Good leaders understand the proverb, "if you aren't the lead dog, the scenery never changes." As one of the industry-leading publications now entering our sixth year in print, we at *Life Science Leader* thought a fresh look was in order — one that matched the quality of our content. Consider this — Apple sweats every detail when it comes to their products, including an obsession for product packaging. The company's cofounder, Steve Jobs, wanted customers to feel a certain emotion when opening Apple products. And while many subscribe to the notion that you can't judge a book by its cover, we often do. We hope you judge our new look favorably. L

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Q What Is The Best Leadership Advice You Ever Received?

A KEEP FOCUSED ON THE STRATEGY, AND KEEP REMINDING THE TEAM OF WHAT THE STRATEGY IS.

They forget, they get misfocused, they need to be constantly reminded about what we are doing and why. Martin Gerstel, CEO of ALZA, told me in the mid-1970s that after running ALZA for years he realized that keeping the team "on focus" was the most important thing a CEO could do. Also, remember that determining what the strategy is and the tactics to achieve it are critical – and not easy. But once figured out, staying on task is fundamental.

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

A ALWAYS *DO THE RIGHT THING*.

While this Spike Lee movie title seems too simple, it is a reminder that sometimes we overly complicate decisions. I encourage emerging leaders to stop and ask themselves what is *the right thing*, separating out all of the "noise" of other interests. Much of the time, the *right thing* to do is actually very clear.

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

A TWO PIECES OF ADVICE STAND OUT TO ME. THE FIRST IS TO REMEMBER YOU'RE DEALING WITH PEOPLE, NOT MACHINES.

Everyone has a life outside of work, and if that's not in balance, then work will suffer. I tell the people in my group two things: First, family comes first, and I expect you to work hard while you're at work, but not to do that more than 8 or so hours a day except on rare occasions. The second piece of advice is that you need to be a champion for your staff. They need to know that you stand behind them 100 percent of the time. This doesn't mean you believe they're always right. It means being willing to hear their side of the story every time and doing your utmost to validate and protect them.

MARK SNYDER, PH.D.
Snyder is manager of the process R&D applications group in the Process Chromatography Division of Bio-Rad Laboratories. He spent five years at Scios (then California Biotechnology) on basic fibroblast growth factor cloning and purification, followed by four years as manager of process development at XOMA.

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Distortions Bedevil Obamacare Implementation

JOHN McMANUS
The McManus Group

As the "rollout" of Obamacare staggers into its fifth month, the distortions the law has inflicted on America are only beginning to ripple through the economy. The nonpartisan Congressional Budget Office (CBO) recently provided new analysis that the subsidies for Obamacare would result in the equivalent of 2.5 million fewer jobs. That's right — 2.5 million Americans now have less incentive to work because more work means higher incomes, which results in less means-tested subsidies. The worst is yet to come: CBO said, "The ACA's [Affordable Care Act's] largest impact on labor markets will probably occur after 2016, once its major provisions have taken full effect."

White House spokesman Jay Carney exclaimed that this was actually a positive development, because it "reduces what economists call 'job lock' or, more colloquially, it gives more opportunities for entrepreneurism and moving from job to job."

For Carney's contorted contention to hold water, overall employment would remain stable or possibly increase as workers switch into more desirable jobs. But that's not what CBO predicts.

Keith Hennessey, former National Economic Council Chairman, observed, "If you make work less financially rewarding you'll usually get less of it. Subsidized health insurance helps the people who receive it. When those subsidies phase out as income increases, they also reduce both the number of hours worked and the number of people working. The reduced labor supply hurts the economy as a whole, and is generally bad for those people receiving subsidies as well, because they are being pushed by government policies to forgo economic opportunities that could help them even more in the long run than the immediate benefits they are getting."

In addition, Obamacare is layered on top of other social programs, which have similar income phase-outs that disincentivize work in an already weak job market.

Indeed, the labor participation rate has dropped from about 67 percent in 2000 to 62 percent today — the lowest in American history, on par with Portugal and less than Azerbaijan. Certainly, a large factor has been the anemic recovery that has not produced enough jobs and discouraged millions from even looking for jobs. But there is no doubt that Obamacare will exacerbate this phenomenon.

Safety-net programs designed with the best intentions can turn into a hammock that traps individuals in suboptimal conditions.

Meanwhile, millions of individuals below the poverty level who live in 25 states that have not opted to expand Medicaid have no access to coverage, while across-state families with incomes close to $100,000 can receive a $5,000 premium subsidy. How can any rational person explain this?

The architects of Obamacare assumed all states would accept the generous Medicaid subsidies and expand coverage to everyone with incomes below 133 percent of poverty. But when the Supreme Court made this expansion optional, many states opted not to undertake the expansion, believing they would be on the hook for greater obligations than they could afford. At the same time, the Affordable Care Act statute expressly prohibits anyone under the poverty level from enrolling in the subsidized insurance policies offered on the exchanges.

Despite this irrational unfolding of events, the Obama administration has refused to offer any proposals to fix these fundamental problems with the president's signature legislative achievement. There has been zero dialogue with the Republican leadership in Congress or committees of jurisdiction on how to address these issues — possibly because that would require recognition of a co-equal branch of government and compromise where the administration would inevitably have to negotiate and accept some Republican priorities.

For now, the Obama administration is fixated on only addressing politically damaging aspects of Obamacare, getting the president's party beyond the 2014 midterms, and doing so unilaterally without congressional input. The latest example was another year delay of the employer mandate to offer "qualified coverage" for midsize businesses (50 to 100 employees) and softening the mandate for large employers.

Why push off this statutory requirement now? The administration fears employer layoffs this summer as November approaches. It is the 18th time the administration has unilaterally ignored clear language in the statute.

It is time to fundamentally rewrite the law. That would require the Obama administration to work with Congress. How revolutionary! But coming from a man who devoted his State of the Union speech to announcing his expanded act-by-fiat administration, don't bet on it. L

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.

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OTONOMY

Not to build a platform, but to create new, FDA-approved therapeutics for unserved indications in the ear, this developer focuses on novel delivery.

WAYNE KOBERSTEIN Executive Editor

SNAPSHOT

Otonomy is a private company developing a line of new therapeutics for the ear using its own proprietary formulation of existing antibiotics and steroids. Its OTO-201 (reformulated ciprofloxacin) is now in Phase 3 trials for use during ear-tube placement surgery, and OTO-104 (reformulated dexamethasone) has completed a Phase 1b trial, the first of two pivotal studies for the treatment of Ménière's disease. The company also has initiated a third development program, OTO-311, that utilizes a new molecule, the N-Methyl-D-Aspartate (NMDA) antagonist gacyclidine, for the treatment of tinnitus.

WHAT'S AT STAKE

Whatever flows in can also flow out. At least, the simple rule applies to the ear, as anyone who has ever used ear drops knows well. Otonomy chose its modus operandi for that reason. Clinical research already had shown the usefulness of "intratympanic (IT) drug treatment," as in ear-drop delivered antibiotics in the treatment of otitis media and steroid solutions to treat patients with Ménière's disease or acute onset hearing loss. But the swift elimination of the drops from the ear limited treatment efficacy, and no one had addressed the problem. Thus Otonomy began with the aim of developing special formulations of existing drugs rather than original molecules for the ear conditions.

The company developed its proprietary "sustained-exposure" formulation not to get into the platform business, but to overcome the ear-drug delivery problem for the large patient groups suffering from the curse of dizziness, hearing loss, and other discomforts of ear disease. Backed, it says, by a strong vault of patent protection, it is going after indications where the FDA has never specifically approved a drug. For those reasons, says President and CEO David Weber, "Otonomy is able to maximize its market opportunity and support a premium-pricing position." Weber says the same strategy also limits risk.

Heretofore, doctors have improvised dosing to the inner ear. "Physicians use oral and local injections (called intratympanic injections) of steroid solution off-label to treat these conditions," Weber says. "However, dosing to the inner ear is limited and variable, which necessitates repeat administration and likely compromises efficacy." Otonomy's formulation uses an injectable thermosensitive gel to slow elimination of the drug from the inner ear, thus boosting effectiveness and eliminating the need for more frequent injections. Short-acting ear drops are approved only for outer ear and recurring middle-ear infections following ear-tube placement, but not for OTO-201's lead indication: intraoperative use during ear-tube placement surgery. According to Weber, ear specialists have identified many additional indications for OTO-201 — infections throughout the ear left unaddressed by short-acting ear drops or any other treatment.

Although combination of components in the sustained-exposure formulation is novel, the parts themselves — the gel, APIs, and injector — are all off the shelf. Thus, says Weber, there are no pricing, licensing, or availability issues for these materials. "We manufactured clinical trial material for our OTO-201 Phase 3 studies at commercial scale, and are doing the same to support the OTO-104 late-stage program."

Otonomy's recent C round will fund the Phase 3 trials it now has underway. The company must continue to explore other alternatives such as global partnerships for further clinical development. But, because the physician audience is relatively small and would require only about 100 reps in the U.S. market, the commercial partnering strategy has more nuance: "Our current business plan is to self-commercialize our products in the United States and work with partners for all other markets." For a company with broad worldwide patents and original products for unserved indications, the strategy seems logical and appropriate. It is also a good example of how a novel platform, even a new creative assembly of existing pieces, can be put to an immediate, targeted therapeutic use. L

DAVID WEBER
President and CEO

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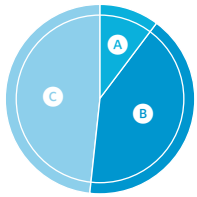

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Enrolled first patients in pivotal Phase 2b clinical trial of OTO-104 in Ménière's disease and two Phase 3 trials of OTO-201 in pediatric patients undergoing ear-tube placement surgery.

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Trends In Outsourcing Solid Dose Manufacturing In 2014

In 2014, the contract manufacturing market for solid dosage forms is anticipated to be $19.6B, representing 58% of the total CMO market value of $33.7B. While the market value percentage for solid dose has been drifting downward — likely related to the shift towards biologics, which are more expensive to develop and manufacture — the propensity to outsource oral solid dosage forms continues to grow modestly.

KATE HAMMEKE
Director of Marketing Intelligence
Nice Insight

"Both outsourcing and offshoring have shown their efficacy in cutting costs for pharma companies when it comes to solid dose manufacturing."

Of the 25 percent of respondents who will engage a CMO for commercial scale manufacturing projects this year, more than half of them will outsource solid dosage form manufacturing, showing a 4 percentage point increase over last year (51 percent in 2013 up to 55 percent in 2014). Nice Insight's annual survey results indicated that solid dose manufacturing will be outsourced with the greatest frequency, followed by injectables (50 percent), semi-solids (44 percent), then specialty dosage forms (42 percent). In general, respondents reported they would outsource finished dosage forms with a greater frequency than API manufacturing (for both large and small molecule APIs).

When it comes to outsourcing behaviors, respondents who will contract solid dose manufacturing in 2014 showed a greater likelihood for considering emerging market providers than the general population, with nearly 9 out of 10 stating they include CMOs in emerging markets on their short lists (87 percent vs. 70 percent). Among those who consider emerging markets, 63 percent are already working with a manufacturer in an emerging market, and 25 percent are aware of reliable CMOs but haven't offshored yet. With that said, CMOs in the U.S. and Canada still receive 23 percent of outsourced solid dose projects. China and Western Europe follow, securing 15 percent of outsourced projects, and India is a close contender with 13 percent of the work.

There are still anxieties among 13 percent of respondents who outsource solid dose manufacturing when it comes to offshoring. The most frequently voiced fears include the "quality level is too risky," "regulatory compliance concerns," and "intellectual property concerns." Since respondents who will outsource solid dose manufacturing ranked quality as their top priority driving CMO selection, it makes sense that quality also topped the list of concerns. Similarly, a CMO's regulatory track record ranked third (after reliability), which corresponds to regulatory compliance concerns as an apprehension for offshoring. It is interesting to see IP concerns in the top reasons for not considering emerging market providers since this worry corresponds much more strongly to primary manufacturing/API production than secondary manufacturing of dosage forms. Productivity, affordability, and innovation ranked fourth through sixth respectively, and this prioritization of outsourcing drivers among solid dose manufacturers happened to match the ranking of the overall respondent group.

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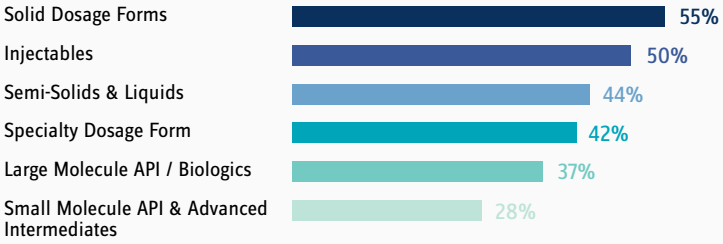
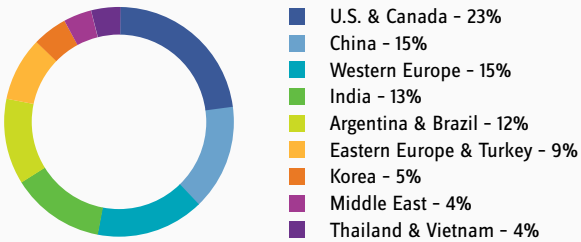


Outsourced Solid Dose Manufacturing Projects Assigned To Each Region



Rank Of Industry Drivers When Selecting A Solid Dose Manufacturer

1 Quality	2 Reliability	3 Regulatory Track Record
4 Productivity	5 Affordability	6 Innovation

"In general, respondents reported they would outsource finished dosage forms with a greater frequency than API manufacturing."

Both outsourcing and offshoring have shown their efficacy in cutting costs for pharma companies when it comes to solid dose manufacturing. Another potential development to emerge from reducing capital outlay on in-house manufacturing equipment and technologies is a shift from tactical relationships for OSD projects toward more strategic, long-term agreements with manufacturers. Interestingly, 65 percent of respondents who will outsource solid dosage manufacturing in 2014 expressed interest in a strategic partnership, which was considerably higher than the overall average of 48 percent interested in a strategic partnership. However, the factors that carried the greatest influence on strategic partnership selection closely coincided between outsourcers of oral solid doses and the overall respondent group. They are experience, track record of success, and financial stability of the organization.

N. WALKER

S.FAZZOLARI

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 comprises 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.

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

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Best Practices In Biomanufacturing Supplier Relations: Reducing Raw Materials Risks

ERIC LANGER
President and Managing Partner
BioPlan Associates, Inc.

If you want to learn more about the report, please go to **bioplanassociates.com/10th.**

"CMOs are more likely to audit their suppliers than biomanufacturers."

Quality management is a matter of increasing importance to the biopharmaceutical manufacturing industry. In recent years, facilities have been gravitating toward quality-related analytical programs, and our data tells us they are also getting tougher on suppliers.

Respondents to our latest industry survey — the 10th Annual Report and Survey of Biopharmaceutical Manufacturers (www.bioplanassociates.com/10th) — are adopting several key steps to manage and protect their supply chains. We asked 250+ qualified decision makers from around the world to identify what their organization had done in the prior 12 months to assure consistent quality in raw materials and ingredient supply.

Half the industry respondents have "demanded our suppliers demonstrate higher levels of GMP/GLP compliance," a figure substantially higher than the 39 percent who had done so in the 2012 survey. Another 47 percent said they "implemented more dual-sourcing," up from around 40 percent in 2011's study. In addition, 47 percent stated they had audited secondary suppliers.

Clearly the industry is intent on managing its suppliers by more closely vetting those companies and expanding the scope of the vetting process. But those aren't the only measures being taken.

Respondents also said they had audited their suppliers more frequently (46.9 percent), verified vendors' certificates of analysis (37.5 percent), specifically identified secondary suppliers (37.5 percent), and verified the origin of individual ingredients more carefully (34.4 percent). Interestingly, relative to prior years, the proportion of respondents auditing their suppliers more frequently has retreated, while a greater percentage attest to more careful verification of individual raw materials and components. However, facilities still relying on their suppliers rather than manufacturing some components in-house (7.8 percent) said they had adopted this approach in the previous year.

U.S. VS. EU: DIFFERENT APPROACHES TO MATERIALS MANAGEMENT

Looking at the critical ways facilities manage their materials supply chain, we compared the responses from end users in the U.S. and the EU, and we compared CMOs with all global biotherapeutic developers.

With the trans-Atlantic breakdown of supply and materials management, our study found variations in approaches between U.S. and Western European companies:

- Western European/EU respondents were more focused than their U.S. counterparts on auditing suppliers more frequently (58.8 percent vs. 34.3 percent).
- Specifically, EU companies identify, and presumably validate, secondary suppliers more often than U.S. respondents (58.8 percent vs. 37.1 percent).
- U.S. respondents were interested in implementing more comprehensive audits (45.7 percent vs. 23.5 percent for EU).
- U.S. facilities tend to develop new, more rigorous tests for incoming raw materials/supplies (31.4 percent vs. 17.6 percent).

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We also evaluated how CMOs behave. In this instance, we found:

- CMOs audit their suppliers less frequently (30 percent vs. 40.7 percent for biotherapeutic developers).
- CMOs implemented dual sourcing less frequently (30 percent vs. 50 percent).

Consistent with that study, though, was the trend for CMOs to be more likely to audit more of their suppliers and secondary suppliers (60 percent vs. 44 percent of biomanufacturers). In our study, CMOs also appeared more likely to verify vendors' certificates of analysis (60 percent vs. 33 percent) and to manufacture some ingredients in-house (20 percent vs. 5.6 percent).

The differences between how CMOs and biomanufacturers approach elements of materials supply-risk mitigation are likely due to their varied business models rather than to a differing commitment to the task. For example, biomanufacturers could request that their CMOs audit certain suppliers for them. Further, because CMOs deal with more diverse products and suppliers, they are necessarily going to be conducting a broader array of audits.

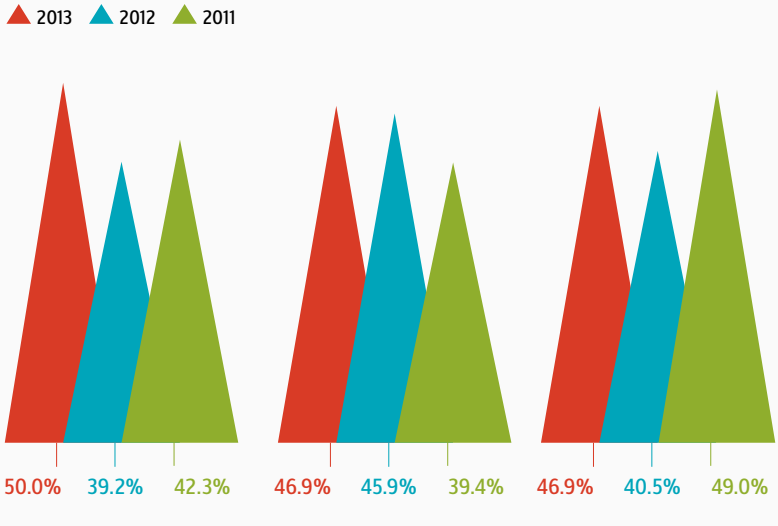
Both CMOs and biomanufacturers do agree on the value of more and better communication with their suppliers. Our study found a hike in the percentage of respondents who reported holding more frequent meetings or calls between their quality staff and their suppliers' quality/manufacturing staff. This jump appears to have been largely driven by CMO respondents, none of whom in prior years had reported increasing their communication efforts. This is consistent with separate results from our survey in which communication problems with their clients shot to the top of CMOs' complaints. In fact, every single CMO respondent to the study said that "clients not communicating effectively" was at least a "common problem" in dealing with their clients. That 100 percent rate was up from 80.4 percent just three years prior. Together, the data strongly indicates that CMOs' best practices in client management include paying more attention to better, more effective communication in order to resolve potential issues.

FOCUSING THE MATERIALS MANAGEMENT MICROSCOPE

Materials and supply chain management and oversight are becoming even more essential as the industry continues to adopt single-use/disposable bioprocessing equipment. Here, bioprocessing equipment is repeatedly purchased, used, and disposed of, rather than being permanently installed and operated by internal staff. Repeated equipment purchases (with essentially every piece of equipment in contact with the process stream) involve hundreds of new and fully sterile products for each bioprocessing run/batch. Single-use systems require more rigorous control of related supply chains, compared with rather standardized stainless-steel equipment. Going forward, we can expect users will want more documentation from suppliers showing component suppliers' compliance with regulatory requirements. This will lead to more pressure on suppliers to demonstrate higher levels of compliance, broadening the scope of their audits.

FIGURE 1

What has your organization done to assure consistent quality in raw material and ingredient supply?



Source: 10th Annual Report and Survey of Biopharmaceutical Manufacturers, April 2013.

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

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PAUL STOFFELS EXPANDS THE JANSSEN LEGACY | By W. Koberstein

Photos by A.E. Fletcher Photography

PAUL STOFFELS expands the JANSSEN LEGACY

WAYNE KOBERSTEIN Executive Editor

Speaking with Paul Stoffels is like continuing a long-ago conversation with the late Paul Janssen. A generation younger than the original Janssen company founder, Stoffels now has responsibilities similar to his former boss and mentor, but for a much bigger and more complex company now under the Janssen name.

Stoffels is the chief scientific officer of Johnson & Johnson and worldwide chairman for the Pharmaceutical Companies of Johnson & Johnson, now called Janssen. He was also the young student-colleague of Dr. Janssen and made a name for himself in the early 1990s leading breakthrough research in HIV drug resistance and drug development, starting on the path Janssen had discovered.

Stoffels joined Janssen in 1992, about the same time I last visited the company headquarters in Beerse, Belgium. I had met and interviewed Paul Janssen several years previously, an occasion I shall never forget. Visiting him at his lair in Beerse was a pilgrimage of sorts — to the place that produced more significant new-drug introductions at the time than any other company in the world, by a large margin.

Stoffels' story parallels Janssen's in several respects. He entered medicine in much the same way as Janssen, as a young physician-researcher in the Democratic Republic of the Congo, the former Belgian colony in Africa. He came back home to Belgium determined to fight a disease then still widely perceived as a threat only to third-world or minority populations. To that end, he used the basic method he had learned from Paul Janssen: Investigate the chemical interaction of drug molecules with the disease agent. Specifically, in the case of HIV, Stoffels turned to looking at how the virus adapts to drugs that block its replication by inhibiting reverse transcriptase.

Thus, Stoffels serves as a direct human connection from the original Janssen company to the new Janssen, the large, global J&J pharma organization he now runs. As did Janssen, Stoffels works alongside a co-chair, now Joaquin Duato, who heads the commercial end of the pharma group as worldwide chairman of Janssen. Stoffels is officially chairman overseeing the R&D, business development, and global commercial strategy for pharmaceuticals, but CSO of all Johnson & Johnson. Also as it was in the original company, it is the R&D organization that sets the agenda and direction for all subsequent business and commercial activity at the contemporary Janssen group.

Yet a meaningful difference also exists: Janssen was still a relatively small, regional company when it joined J&J more than three decades ago; today, the legacy Stoffels oversees has expanded to include a huge group of global R&D and commercial organizations.

DOWN TO BUSINESS

The story would be less interesting if Stoffels had simply stayed with Janssen his entire career. Instead, the search for more effective ways to treat HIV infection took him into entrepreneurial territory. In 1994, he cofounded two companies to carry on the quest: Virco, to phenotype all the viral strains found in patients, and Tibotec, to develop new drugs that would defeat drug-resistant strains. Tibotec's name stems from the type of molecules his team at Janssen had thus far tried and failed to move forward, the TIBOs (i.e. tetrahydro-imidazo[4,5,1-jk][1,4]-benzodiazepine-2(1H)-one and –thione). Viral resistance to earlier drugs had defeated trials of the first TIBOs tested at Janssen.

"I learned from Paul Janssen how failures help you come to the solution," says Stoffels. "As we worked on HIV, the first drug failed, the second drug failed, the third drug failed, and for only one reason — we did not understand yet how the virus behaved in the body. When we started to do experiments in vitro, we learned that the virus, after a few days of exposure to the drugs, became resistant. That gave me the idea that we should start testing patients to see the subsets of HIV they carried."

Stoffels began by setting up a diagnostic effort at Janssen to find the multiresistant strains, and eventually the effort produced some drug candidates. After Janssen retired in 1991, however, Stoffels decided to take his research outside of the company, leading to the startup of Tibotec and Virco. The business grew quickly, attracting widespread attention and capital from the start.

"We raised a significant amount of money, and in a short time we went from being five people in a garage with an incubator and two office tables to a significant biotech company of about 350 people. My business partner, Dr. Rudi Pauwels, was an extremely good basic scientist and biologist, a brilliant guy who did everything in the laboratory and discovery, and I did everything in drug development and business."

> "We organized ourselves very much in the biotechnology way but completely focused on certain therapeutic areas."
>
> – PAUL STOFFELS

After the FDA observed that the Tibotec-Virco group had the technology for learning about multiresistant HIV strains and finding drugs to fight them, Stoffels says pharma companies and researchers beat a path to its door. "We built a vast network of hospitals and pharmaceutical companies. We also built and investigated a library of more than 10,000 strains of viruses, and we used the resulting knowledge to advise physicians on how to treat patients and companies on how to develop HIV drugs." Tibotec's own discovery and development efforts eventually yielded two new drugs, Prezista (darunavir) in 2006 and Intelence (etravirine) in 2007.

Stoffels had put Tibotec together as an integrated pharmaceutical group to develop the new drugs, but when the market crashed in 2002, he could no longer raise the money to fund the needed Phase 2b trials, so he and Pauwels began to look for a partner. By then, there were many candidates, but they chose to go back home to Janssen and J&J because, says Stoffels, "J&J was prepared to leave us alone as a small company in the group, and we could continue to do our work."

By the time Stoffels rejoined J&J/Janssen, however, he had become as much a businessman and lawyer as a scientist. "I trained myself, and was trained by lawyers, in contract negotiation and writing. I sat in on acquisitions, worked with analysts, did the tour of analysts in New York, gave a hundred presentations in two weeks trying to go public — all of it part of growing up as a biotech CEO and chairman." (Stoffels was chairman of Tibotec and CEO of Virco; Pauwels played the opposite roles at the two companies.)

Once back in the J&J fold, and after Stoffels saw the first two HIV drugs off to market, J&J's senior management asked him to take on more responsibility for a larger part of the R&D group. Then, in 2009, he became head of the entire group in the position he now holds. As he puts it, "I applied all my capabilities learned during my lifetime in biotech and pharma, and I started working on the pharmaceutical R&D company of the future."

INTEGRATING CAPABILITIES: ONE JANSSEN FOR ALL

The Janssen twin-chairman structure reflects the company's "unmet medical need and best science-first" strategy — looking for business opportunities where scientific understanding reveals them, as the best way to meet a major medical need, to paraphrase Stoffels. He says his responsibility as CSO for all of R&D gives him access to early science and technology, including the discoveries and developments of the alliances managed by the company's "external innovation" organization. That group is an "integrated team," operating globally, with regional headquarters in San Francisco, Boston, London, and Shanghai, "on the front line where the majority of company innovations happen."

The external innovation group includes teams for running business development, legal, finance, IP, and all other capabilities needed to establish and maintain collaborations with other companies. Stoffels also oversees the business development group responsible for accessing late-stage science and technology through licensing and acquisitions, the company's own ven-

PAUL STOFFELS
Chief Scientific Officer
at Johnson & Johnson

ture capital group, which invests in early-stage technology, along with Janssen labs, an incubator that assists small start-ups, now numbering about 50 companies.

More than just imposing the Janssen name on former units such as Centocor and Ortho Biotech, the company has aimed at making its technologies, proficiencies, and special knowledge available throughout the Janssen universe. Under Stoffels' direction, the current Janssen units cooperate on discovery and development in all five therapeutic areas of focus: cardiovascular and metabolic diseases, immunology, infectious diseases, neuroscience, and oncology. In addition to Janssen units, the company fully funds a number of "internal ventures," and other ventures such as the alternative-scaffold enterprise Centyrex.

Has all the reorganizing and integrating of R&D paid off for Janssen? Stoffels believes the reforms have succeeded by many measures, including an increase in the actual productivity of the R&D organization. "We organized ourselves very much in the biotechnology way, but completely focused on certain therapeutic areas. And, like every biotech company knows, to be successful you must have the top experts leading the disease or therapeutic area. They need to make all the important decisions about which science or type of development we adopt."

On the other hand, he says, an organization that develops a high number of new drugs must be efficient on a global basis. "Because we have worked on significant unmet medical needs, we have learned how to speed up the process."

For example, Stoffels cites the development of Imbruvica (ibrutinib), with Pharmacyclics. The FDA halted the drug's pivotal Phase 3 trial, in chronic lymphocytic leukemia and small lymphocytic lymphoma, when its interim analysis showed significant PFS (progression-free survival) and OS (overall survival) improvement. "We brought the drug from early Phase 2a to the market for the first indication for MCL (mantle cell lymphoma) in only 23 months," he says. "That is only possible if you have an outstanding global development organization that can develop and file medicines globally, in Europe, the United States, Japan, and all the rest of the world."

He caps the point by mentioning the company's first-ever success in launching a new drug initially in Japan: the NS3/4A protease inhibitor Olysio (simeprevir), for the treatment of chronic hepatitis C infection. "The global system really works. In drug development, we say do it high speed, do it high quality, and do it global. That's one of the most important value creators. Don't be inhibited by where the science comes from, internal or external. Just make sure you win access to the best possible drug, with the best possible science. That was a big change for this organization — not that easy in the beginning but now everyone is fully embracing it."

Recently, J&J announced Janssen's pipeline produced 13 new-drug launches since 2009, "more than doubling its productivity over the past four years." The company anticipates submitting more than 10 new product filings and more than 25 "significant brand-line extensions" by 2017. Five of its new-drug indications now have FDA breakthrough status. New products launched since 2009 accounted for 17 percent of total pharmaceutical sales in 2012, up from 9 percent in 2011, and the company expects the same products to bring in nearly half of the total sales in the segment by 2017.

THREAD FROM THE PAST, PATTERN FOR THE FUTURE

Although the most sanguine pharma executives don't like healthcare cost-cutting any more than anyone else, they may be quicker to recognize the challenge, shrug their shoulders, and move on. Stoffels quickly turns a question about pressures on the industry into a view of positive solutions.

"The answer to economic pressure is innovation. If you bring innovative new drugs into the market, society will be prepared to pay for it. We need to produce more and more significant innovation to be reimbursed by the payors in the world. It is a scientific, technical, and global development challenge to develop the best drugs, pick up the best technology, and make sure that we have the best profit margin possible."

Stoffels sees great promise in the direction of pharma science and technology, such as the growing understanding of the human genome, disease pathways, immunology, and personalized medicine. "With new biomarkers coming on line, we probably will be able to diagnose much better who will respond best to therapy. That means we have to develop drugs and diagnostics together — on one hand, a

burden; on the other hand, an opportunity."

Janssen has an expansive armamentarium, far beyond what even Paul Janssen could ever have imagined. Within the set therapeutic areas, the company can now aim to use all therapeutic tools available in its kit: small molecules, biotechnology, and vaccines — its three "centers of excellence" serving the entire Janssen organization. Janssen Diagnostics develops biomarkers and tests, to be used either independently or in companion diagnostics.

"The melding of all our capabilities is already in place," Stoffels says. "But no organization is ever at its end-stage. We must always continue to think about how we can improve. And when we fail, we learn how to succeed. We learn from all things, but especially from our failures."

Earlier, Stoffels used the phrase "pharmaceutical company of the future," so I asked him to elaborate. "The pharmaceutical company of the future is one which is having strong internal science, combined with a vast network of collaboration in the world. It is a global company, which can execute fast global development, combining all types of technologies with a single objective — improving the quality and length of life — and that is the metric which, in the end, results in a good business outcome. It also produces extreme motivation in the organization, and that's also a very significant part of the success."

For a glimpse of the present and future Janssen, Stoffels refers once more to the past: "Paul Janssen looked his whole life for a TB drug, one effective against multi-resistant strains. I carried on the search with my team and said, 'Let's get this done.' And we found a spectacular new drug for TB." Launched in late 2012, the TB drug Sirturo (bedaquiline) has a new mechanism of action, inhibiting mycobacterial ATP [adenosine 5'-triphosphate] synthase. "Nobody ever believed ATP inhibition would be a drug target at all," he says.

Stoffels says the Sirturo story is emblematic of the expanding Janssen legacy. "The character of the organization and the heart and soul of the organization have been carried on through the years and through the ages. We still have many people who worked with Dr. Paul. We have added our own flavor to that, of course, going into the new age of biotechnology and so forth, but it is still all about making a difference for patients, and it works. It is what Dr. Janssen did the first 50 years of the company, and I believe it will continue to be our strategy for the next 50 years."

Based on how I have seen the company grow and develop during most of its past years, Stoffels may be right about its future. I doubt, at the least, Paul Janssen would disagree. L

MEDICAGO APPLIES INNOVATION AT THE PLANT LEVEL

By W. Koberstein

Medicago Applies Innovation at the Plant Level

In the American South, below the old Mason-Dixon Line, you can walk down some house-lined streets in summer and see tidy plantings of tobacco growing in the front yards. Tobacco barns, built for drying, not storing, are as common down there as hay barns in Wisconsin.

WAYNE KOBERSTEIN Executive Editor

The tobacco culture runs deep, which may help explain why a company from Canada found its way to North Carolina to build a new facility using tobacco plants as the means of vaccine production. The new "plant" in Durham, near Research Triangle Park, greatly expands capacity from Medicago's original model facility near its headquarters in Québec City, Québec, Canada.

You can certainly read about Medicago's technology and product pipeline on its website, but you may come away with an appetite for more than the terse and fairly general explanations therein. Even the technical descriptions leave much to the imagination, and you will not get much of a sense of how the company came to be. Though still a virtual unknown after nearly 17 years in business, Medicago is a late-stage clinical developer that has built itself an infrastructure of seemingly commercial dimensions.

The Durham plant, at 97,000 square feet, quadruples the original production space in Québec. It includes a huge, automated greenhouse and equipment to extract product from the tobacco leaves, purify it, and package finished doses — up to 30 million vaccines for seasonal flu or 120,000 for pandemic flu.

The company's proprietary manufacturing platform, Proficia, is nothing if not revolutionary, perhaps even worthy of the highly prized appellation "disruptive" — if all your bets are riding on traditional technology for making vaccines and antibodies. The Proficia process inserts genetic material into live tobacco leaves to induce a temporary or "transient" expression of what the company calls "virus-like particles" (VLPs) that mimic viruses but cannot reproduce or cause disease on their own.

Although VLPs lack the genetic core of the disease-causing virus, they display the same antigens on a similar structure and thus mobilize the immune system against it. Medicago employs its related "high-throughput" platform, VLPExpress, to rapidly identify the key antigens and design the VLP "presentations." With further refinement, Proficia will also produce antibodies.

GROWTH WITH DIRECTION

Medicago's current president and CEO, Andy Sheldon, joined the company in mid-2003 with an extensive background in vaccines at Rhône Mérieux, then part of Rhône-Poulenc Rorer, and later at Shire Biologics. Sheldon was attracted both to the opportunity for a new manufacturing technology and to the potential for developing new products on the platform, he says. But the company was still largely research-based — founder Louis-Philippe Vézina, now the CSO — was also its platform inventor. And, like the typical early start-up developing new technology, the company was unsure of its commercial direction. (See "The Micro-Innovators," *Life Science Leader*, December 2013 and January 2014.)

"The whole plant-based manufacturing concept was focused principally on making large quantities of product. Many of the initial companies in the plant world wanted to be contract manufacturers. But it was always difficult to see how we could possi-

Proficia Pluses

Medicago's 97,000 square-foot vaccine-production plant in Durham, NC — using tobacco to produce vaccines made of "virus-like particles" grown in tobacco — cost only $40 million to build, versus the hundreds of millions to more than $1 billion required for a typical cell-based plant. That means Proficia, the company's name for its VLP (virus-like particles) platform, is "less expensive than others and certainly more cost-effective — even for things like a quadrivalent influenza vaccine, which is a complex project," according to president and CEO Andy Sheldon.

Speed of production is very important with certain vaccines, such as one for pandemic flu. In 2009, in a test of its H1 flu candidate, the company "managed to put a protein in a vial with high purity within about 19 days," Sheldon says, "and we did it again with H7 earlier this year, and the H7 project has continued on.

"That year, H1 flu surfaced in Canada in April 2009, but the Canadian vaccine for H1 was not available until mid-October in any meaningful numbers, and we know that we could have certainly beaten that time line by several months."

The method Medicago uses to configure any vaccine, called VLPExpress, resembles an IT technology, based on Sheldon's description: "We just need the genetic sequence. We can just download the sequence from the Internet and away we go. We go to the lab, we make the DNA fragment, and we put it in a column where we start the phases of manufacturing. The process allows us to program our tobacco leaves. Meanwhile, others have to wait for the viral strain to arrive from the CDC and other authorities."

The Proficia Process

1. **Synthesis**
   Gene synthesized from sequence of pandemic virus.
2. **Vacuum Infiltration**
   Genetic material introduced into plants through vacuum.
3. **Incubation**
   Plants are incubated four to seven days in growth chambers for protein expression and VLP formation.
4. **Harvest**
   Plants are harvested to extract VLPs.
5. **Purification**
   VLPs are purified to obtain clinical-grade material.
6. **Finished Vaccine**
   - Potent immune stimulation
   - Immunological memory
   - Lower dosage
   - No genetic material (noninfectious)

bly be a contract manufacturer if we had never actually taken our own products to market," Sheldon says.

In 2005, Sheldon introduced his board to the idea of the company starting work on a pandemic influenza vaccine and permanently adopting the product-development model. Since then, he says, "We have demonstrated we do have a major role to play in the protection of citizens in any country against a pandemic." The next step for Medicago is to demonstrate how its new-product development, based on the same platform, can expand into other areas beyond vaccines, such as those now reserved for antibodies and peptides. Meanwhile, the company continues to improve the quality, capacity, and efficiency of its tobacco-plant vaccine technology, according to Sheldon.

He suggests that, although scientific freedom creates opportunities, business depends on inspiring company scientists toward some common goals — in this case, products and platform quality. "The real value of the company lies in what differentiates it from everyone else — how we strategically position the product, and also our platform's ability to produce consistently, cost-effectively, and efficiently." Quality, an oft-heard industrial term, can sound as unfamiliar to company researchers as does "product focus," and Medicago's manufacturing base offers them another "learning experience," he says.

"Getting our scientists to start thinking about documentation and traceability, and all the other aspects of production, has really paid off in spades for us. Today, our people in research are the first ones to think about those things, which is very rewarding."

The emphasis on manufacturing also has aided Medicago in its clinical development programs — led by an H5 pandemic flu vaccine preparing for Phase 3 and a quadrivalent seasonal flu vax entering Phase 2. Unlike many other life sciences start-ups, the company has scaled up its capacity and facilities internally to match demand for its Phase 3 trials, and with obvious order.

"From creating VLP technology to working on extremely complex products such as rotavirus, quadrivalent flu, and pandemic flu vaccines, we have come to see what else this technology can do, not only in the world of vaccines, but eventually in other areas such as biobetters and biosimilars," Sheldon says. He believes the company has proved its concept, giving it good reason for confidence in its technology. The VLP approach is further validated, he says, by Medicago's DARPA (U.S. Defense Advanced Research Projects Agency) and Canadian government financial support through a number of grants — and its recent acquisition by Mitsubishi Tanabe.

FUNDING BY PURCHASE

Yes, I said acquisition. Mitsubishi Tanabe Pharma (MTP) purchased 60 percent of Medicago in September 2013, delisting Medicago's stock and leaving the remaining 40 percent of shares in the hands of Philip Morris Investments.

So, why am I still writing about Medicago and not Mitsubishi at this point? Well, for

the time being and as long into the future as anyone can see, the Japanese company seems to value the acquired company's distinct identity, management, and operations. Sheldon is optimistic about the business- and product-development prospects for their combined businesses, but he is also sanguine about the underlying rationale for the merger: the cost of late-stage clinical trials.

"As we moved forward with our Phase 2 and Phase 3 trials in flu, it became necessary for the company to look at all the options — either licensing or selling the company, or trying to continue on with private or public financing. Right now we have CROs to ensure that the trials are done appropriately and in a timely fashion, and with the merger, we have the financial resources to do that. All companies face the same choices at some time, and I believe we have found the right solution with a perfect marriage of shareholders, which allows us to continue on and drive these products to the market."

For Mitsubishi, the acquisition is a big step forward into biologics, a goal for company expansion. Sheldon says MTP was "looking for a leap-ahead technology that could allow them to be a world player in biologics." The two companies have been partners since March 2012, working together on a rotavirus project and other collaborations. "Now Mitsubishi has the technology platform and development products to start building a brand new vaccine entity, and our goal is make Medicago part of what will become a major leader in vaccines worldwide."

PLOWING NEW GROUND

"You'll hate this word, but I'm going to say it anyway, because I like it — we believe we have a disruptive technology," says Sheldon. He argues Proficia's plant-based process is, "by definition," a great improvement in production speed, efficiency, cost-effectiveness, and outright cost-of-goods. Even though worldwide vaccine production would require building even more capacity, he figures the company has time to grow because market penetration would be gradual.

> "It was always difficult to see how we could possibly be a contract manufacturer if we had never actually taken our own products to market."
>
> **ANDY SHELDON**
> President and CEO

"But if truly our first product proves to be a better vaccine in the elderly, which we believe it will be, we will be in the position where people see we can actually manufacture better product. Then I think we're

on a winning ascent, and our technology will be disruptive — and yes, it could change the way people think."

Medicago's story recalls how biotech first got started: mainly as a manufacturing alternative, only then with E. coli or yeast cells. "We've got this plant in front of us, a living system, and it can make very complex molecules. And it's quite likely we'll find out over time that we're able to do things existing technologies cannot do."

It would not be surprising if Medicago meets with some pushback from traditional as well as other innovative vaccine makers as the company gains more visibility. Some companies are developing vaccines based on DNA technologies or other platforms that might or might not be compatible with VLPs, and long-established doctrine favors live, animal-based vaccines for invoking a strong immune response.

But so far in the clinical trials for its pandemic flu candidates, Medicago's approach appears to produce potent immune stimulation and immunological memory, according to the company. "We are doing a lot of extra work to demonstrate what we've always believed — we can make better vaccines with this technology than existing technology, with a strong parallel between us and live viruses."

Regulators might be expected to take a longer look at such a different means of manufacturing. Sheldon expresses no qualms, however. "When we work through clinical trials, the rules are the same. We must be able to demonstrate safety and efficacy and purity of product, exactly as with cell-culture, egg-based, or any other vaccine types."

Sheldon says the main distinction between Medicago vaccines and all others is in the upstream production phase — it uses biomass generation of plant tissue — but he says downstream purification technologies are standard. Still, anticipating some additional regulatory hurdles with a new technology, the company compensated by attending to its quality and documentation systems from the beginning. "We were even ahead of where we needed to be as a biotech company, and over time we'll work as closely as possible with the regulatory agencies."

PLANTS OVER THE HORIZON

Even at best, the company faces a long road to its ultimate goal: expanding its technology beyond vaccines to generate scaffolds for therapeutic antibodies, most likely to improve on existing mAbs (monoclonal antibodies). The expansion is not commercially driven, according to Sheldon; instead, the company's deepening investigation into its own technology revealed a broader potential.

"When we first started to produce these virus-like particles, we had no way of knowing the plants would produce these complex antigen structures, where you have an antigen sticking out from the lipid layer, looking just like a virus. People have been making VLPs, for example, in insect cells, where you need to add various proteins to hold the particle together. Lo and behold, the plant expresses the same proteins in its plasma membrane. Now we know we may be able to use these particles as chimerics — the stem sticking out from the lipid layer could be something other than a viral antigen. We'll see where the science takes us, but we may find some rather interesting solutions to very complex problems."

The Novelties Of VLPs

Medicago's CEO Andy Sheldon expounds on the characteristics and potential advantages of the "viral-like particles" (VLPs) produced by the company's tobacco-based vaccine technology:

"VLPs confer all the great benefits of a live virus in a vaccine, but they are not live, they do not have any genetic material, and therefore they have better safety aspects. The virus-like particle for influenza is very similar in size to the naturally occurring influenza particles. We have seen now, through our clinical trials on H1 and H5 flu vaccines, that we have the opportunity for some cross reactivity, and thus cross protection. In other words, the VLP structure may confer a better immunity than existing technologies by protecting against more strains, as well as elucidating both of the pathways needed to induce cell-mediated immunity. And we're working hard to demonstrate that. A simple example would be in the elderly, who often lack the antibodies but resist influenza because they have cell-mediated immunity, or T-cell responses. So we believe we may have some huge advantages in the marketplace with a more efficacious product, all due to the structure of the virus-like particle."

Among the possible areas of application for Medicago's platform are cancer immunotherapy and HIV vaccination. "Although we have actually produced a virus-like particle for HIV, we've never taken it anywhere," says Sheldon. "It is blue sky, but nonetheless, it's a real blue sky."

Because Medicago is building a new, plant-based technology, it finds itself in a leadership position, compared to companies in the same space that lack a product focus. (One company, Protalix Biotherapeutics — using plant cells rather than growing plants to produce proteins — has a hormone-replacement product on the market.) If Medicago succeeds in validating its leading role among the plant-growers in vaccine and protein production, Sheldon would credit its "adaptability" for putting it ahead of the pack. Fair to say, when you're pioneering a way to make medicines from tobacco, adaptation is your game —by definition. L

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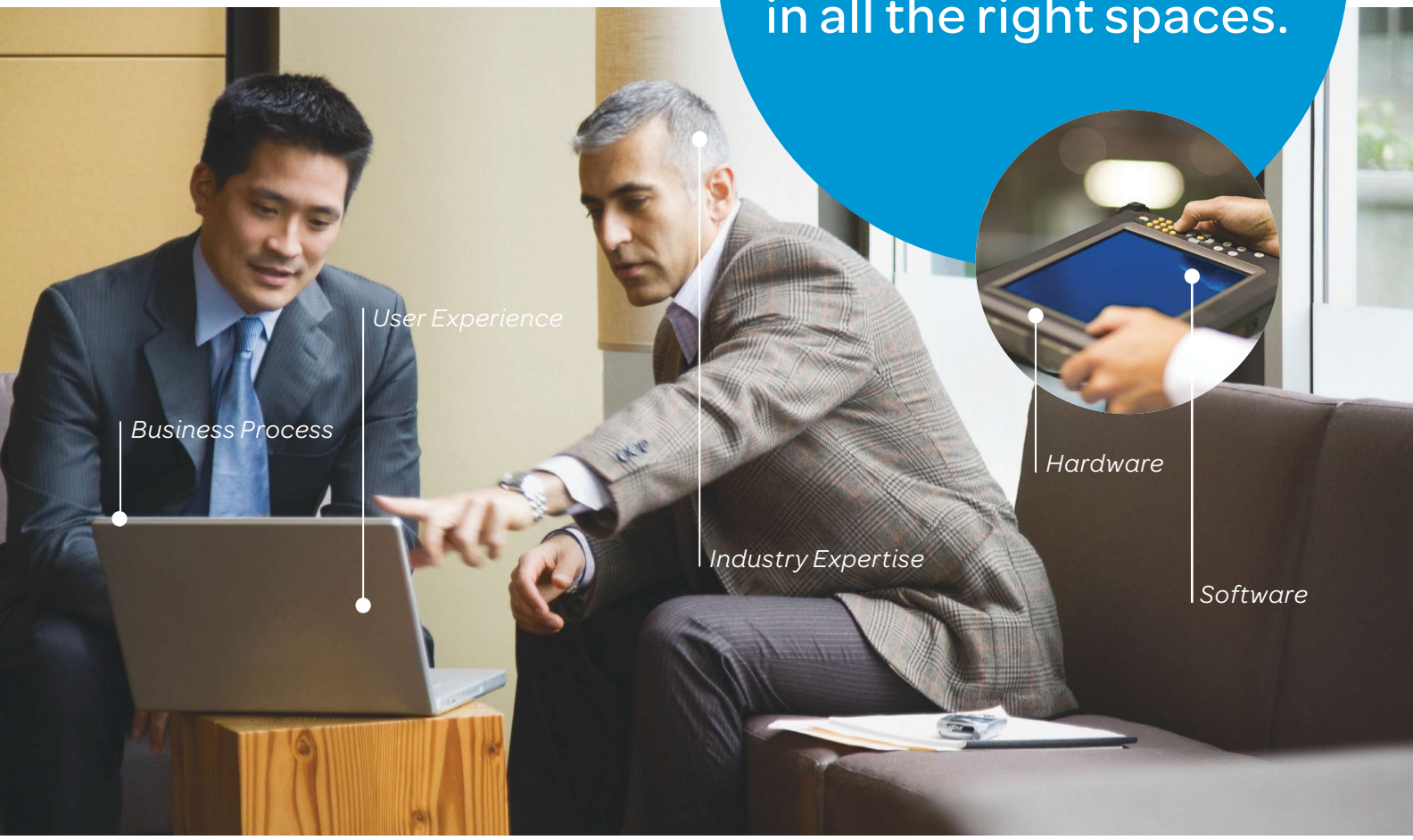

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DENNIS PURCELL* BUILDING ON LAST YEAR'S BIOTECH BOOM IN 2014

WAYNE KOBERSTEIN Executive Editor

YES, 2013 was a great year for biotechs, with 65 small-cap IPOs in the sector globally (52 in the United States), along with new interest from both generalist and venture-capital investors. A late surge in IPOs toward the end of the year silenced the doomsayers who predicted a fall-off. But what did all the positive action mean for the industry's long-term future, and where is it headed in 2014? **For answers, we spoke with an experienced hand in life science investment, Dennis Purcell, senior managing partner at Aisling Capital.**

PURCELL discusses the boom-and-bust dynamics of biotech, including the difficulties in small-cap valuation in the sector. He offers strategic and historical context for the biotech's spectacular gains last year. And he shares some sage advice, sobering cautions, and provocative thoughts for the coming year — and beyond.

LSL How would you characterize the small-cap life sciences/biotech sector peformance as a whole in 2013, especially in contrast to previous years?

PURCELL: In 2013, Wall Street opened up to biotechology again. Companies were raising capital, and their stocks were going up, so there was good momentum, and many more generalist investors came into the sector. Consequently, a lot of new capital flowed into biotech from sources we didn't have before. In the past, only the venture-capital community and the pharmaceutical industry funded those companies, and the new investor interest began after a long drought of seven to eight years, during which the science continued to get better and better, but Wall Street wasn't recognizing it.

LSL How are all the new IPOs doing now in company and stock performance?

We were pleasantly surprised some earlier-stage companies were able to go public and raise capital and that the pharmaceutical industry was also willing to acquire or do deals with some of the companies at an earlier stage than they did before. We also found a whole new set of buyers in the bigger biotech companies, such as Gilead and Celgene. The biotech sector has gone through a big boom-and-bust cycle over the past 25 years — now the question is, how do we "capitalize" on what's going on, and what should the companies be doing to make sure that they remain stable?

LSL Do you think one of the reasons biotech historically follows a boom-and-bust cycle is that the bigger the boom, the more volatile the stocks and market caps thereafter?

Yes, I believe that's true. The biotech sector is one of the really hard ones for doing traditional valuations, so you see these wild swings either on the upside or on the downside, even for minor news. Companies now have an obligation to manage their cash better, to make sure that they have enough reserves if the industry goes into a bust cycle. They need to reassess governance, because a company just getting started has different governance needs than a company that's about to launch a product. We have to get better at not duplicating infrastructure; in other words, outsource whenever we can. If someone else has the expertise, let them do it. And given where stock prices are now, it's a good time for biotechs to be somewhat bold and figure out whether they can build their businesses either by acquisition, licensing, or other means. Whenever a company has only six months of cash left, as was too common in the past, it has few options and is just trying to stay alive. Companies are in a position now where they can really think about shaping their own future.

LSL Do small companies have trouble managing information and expectations? Sometimes the story a company develops about itself can catch up to it later when things don't go according to plan.

I can't think of a single company that has traveled a straight line to accomplish what it thought it was going to accomplish. When Amgen went public, the company listed Epogen and Neupogen as number seven or eight in its pipeline, but they became two of the biggest-selling drugs in the world. This is complicated science; you're learning as you go, and every company that I know has had to make midcourse corrections.

LSL Two interesting companies riding the stock waves are Ariad and Sarepta. What do their examples tell us?

One of the good things about 2013 is, on average, the IPOs are up about 40 percent; on the other hand, we've had some recent IPOs that have disappointed, for example, Ariad and Sarepta, which hopefully will not drive generalist investors too far out of the sector. Did Ariad get out ahead of itself with a $4 billion market valuation? Probably. But it's a real challenge to keep investors' expectations in check because, in a booming market, any little bit of good news drives the stocks significantly, and any bit of bad news gets the stock killed. That is where we have boom-and-bust cycles.

An interesting exception to this cycle is Regeneron, where the pipeline is deep enough so that any one piece of information does not materially have a significant impact on the stock.

LSL Have regulators played a positive or negative role with small biotechs?

Ariad actually had an accelerated approval, and for the past couple of years, the FDA has been acting pretty well toward these companies. In 2013, the FDA did a very good job of approving new drugs, particularly on the oncology side. We had 27 approvals last year, which was down from 39 approvals in 2012, but was still a very good year on the regulatory front.

Investment regulation is catching up as well; for example, the new GAIN [Generating Antibiotics Incentives Now] Act will help get new anti-infectives to the market. So the science is moving quickly, and the federal lawmakers and regulators are trying to keep up with it. The press about 23andMe later in the year is an interesting story in the sense of, "Do I have the right to know what's in my genome or not?" The FDA is trying to figure out how it should regulate the personal genome business, so we're in new territory, but investors are giving the companies the benefit of the doubt. In gene therapy, which has been a real problem for years, bluebird got public.

LSL Any advice for the large pharma and bigger biotech companies in light of the small-cap boom of 2013?

Given the new interest on Wall Street, the biotechs gained a little more negotiating leverage on the big pharmas, because if biotechs don't get the deals that they want, they will try to go to Wall Street and raise the money. But Big Pharma is doing interesting stuff in the many new collaborations they are forming with academic institutions. Just in New York, Takeda has an alliance with Sloan Kettering, Rockefeller, and Cornell. Big Pharma companies are trying to adapt, and clearly the large majority of

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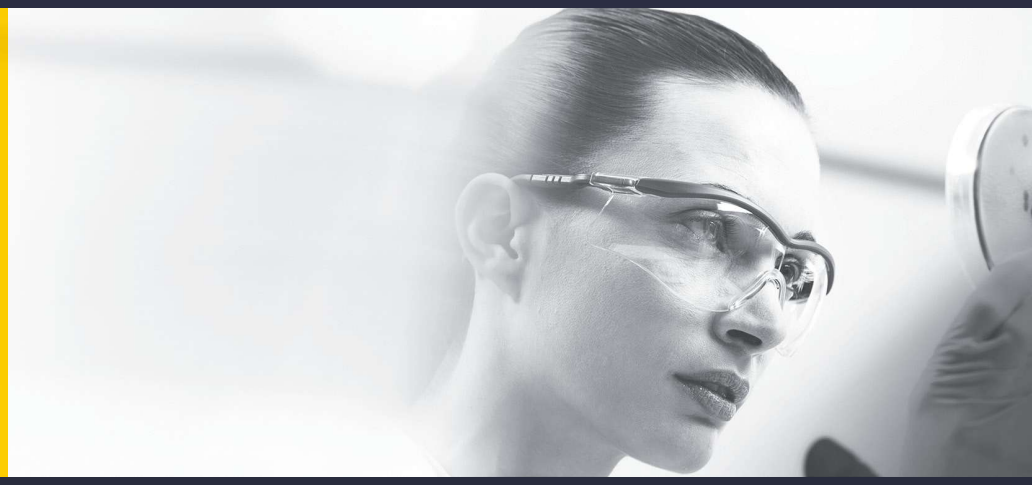

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drugs in their pipelines are coming from outside their R&D, not inside. You see more innovation coming out of pharma in dealing with academics, who themselves are entering deals where the venture community funds Phase 3 projects and the Big Pharma companies can buy them back later.

But the pharma companies face the same issues as the biotechs: once you have a little more cash on the balance sheet, should you stick to your knitting, like Regeneron or Acorda, or do you go out and acquire other companies, as Cephalon or Alkermes has done? When I say it is a chance for the biotechs to be bold, I mean it's a real chance for them to reassess what they want to become as they mature. The following is an interesting question I heard posed the other day: Is it better to own 50 percent of four products or to own 100 percent of two products? That is the kind of fundamental question that biotech companies will have to answer.

LSL Does the investment climate for small biotechs look as good going into 2014, and what investment trends do you see?

We had a really good run in 2013, and we can't expect to have the same kind of gains in 2014. We must deal with three issues for the industry to continue to do well, and I call them "The Three O's." First is "output," or how we can use our capital more efficiently to generate better output. Second is "outcomes," which is about sharing clinical data. Right now, half of all clinical trials are not reported, but we need to learn from each other's mistakes — not only from the positive outcomes, but also the negative outcomes. Third is "originality." We will see biotech companies develop new kinds of business plans, because the time-worn business plan of doing your Series A, Series B, and so on is not the best way for everybody to make money, so consequently we're starting to see Series A rounds that are $100 million or more.

2014 will be a year of transition as we build on the success of 2013. Take a step back and look: There is about $30 trillion in the world right now that's earning less than 2 percent a year, so as an industry, we don't need to give people a 10X return — there are not a lot of other places for them to put their money. If we can show investors a more stable way to make money and money starts flowing into the industry, so much the better.

LSL Are there issues that concern you about the industry in 2014?

We have to concern ourselves about funding for the NIH and the FDA. The NIH, really over the last decade has lost about 25 percent of its purchasing power to budget cuts and inflation and now faces even worse cuts in the future. FDA's budget sits in limbo, and the agency is dealing not only with past cuts, but also continued uncertainty. So the cuts are disturbing because they hurt the NIH's ability to put out research money and the FDA's ability to keep up with the science and its increasing responsibilities.

If this industry had not figured out a way to make AIDS a chronic rather than a fatal disease, most hospital beds in New York City would be filled with AIDS patients. And if we don't make progress on brain disorders like Alzheimer's and dementia, 20 years from now most of the beds in New York City and across the country will be filled with Alzheimer's and dementia patients. So, it's really important that we invest government dollars to help keep innovation going.

LSL It seems the biotech industry has a twin burden to bear — innovation on one hand and economic stimulus on the other.

I agree. The industry has the burden of innovation, but the people who actually fund the industry — by and large, endowments, state pension plans, and teachers' retirement systems — have their own issues. They need to fund their retirees or endowments. So we rely greatly on people who sometimes need a quicker return than biotech can give them.

LSL What other, larger issues in the industry will affect its fortunes this year and beyond?

"Companies now have an obligation to manage their cash better, to make sure that they have enough reserves if the industry goes into a bust cycle."

DENNIS PURCELL
Senior Managing Partner at Aisling Capital

I would emphasize three big issues: personalized medicine, biotech business models and infrastructure, and public perception of our industry. Regarding personalized medicine, look at cancer treatment: We really treat cancer as a problem at the molecular level, and it's now targeted at specific patient groups, so we've done a good job of moving that ball along in cancer. But companies must think about their business models. In the past, if your drug was safe and effective, you were okay — now it must be safe, effective, differentiated, and reimbursed. Also, immunotherapy may be the next wave in cancer, but if you're going to do autologous cell transfer, that's a very expensive proposition. As for infrastructure, I believe we must avoid too much duplication of efforts in biotech. In Boston, just as we have three hospitals within a mile of each other all doing heart transplants, we now have almost 200 biotech companies in the area, many of them working in the same areas. Finally, in the pharma/biopharma industry as a whole, we need to be more sensitive about how we're perceived in the public. For example, Forbes put out its list of the 100 most valuable brands, and there was not one drug on the list.

I'll leave you with two last thoughts. One, if you took the U.S. healthcare system and made it a country, it would be the fifth largest country in the world — after the United States, China, Japan, and Germany. And my final thought is this: Every 12 years, we're adding one billion more people to the planet.

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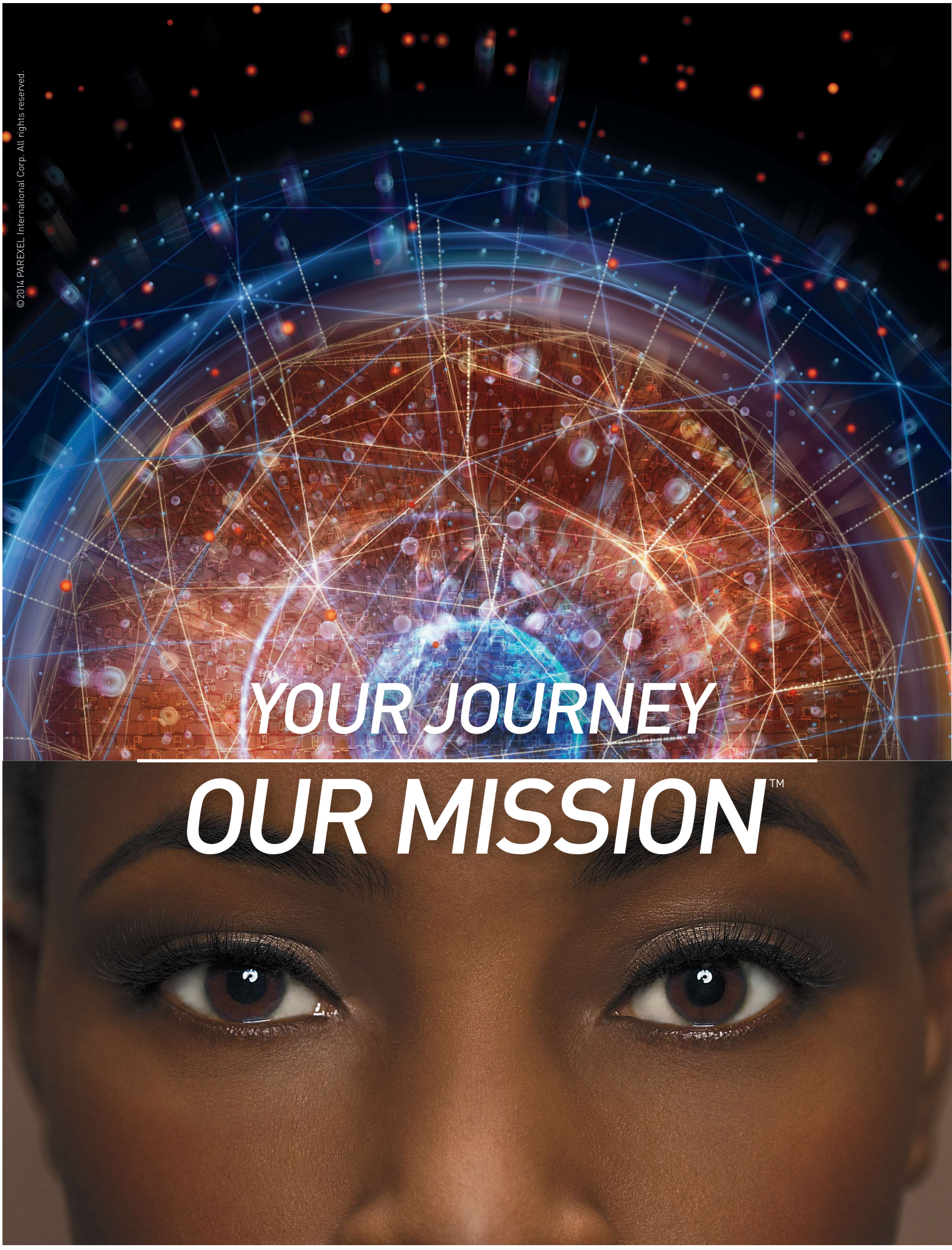

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My first tweet at this year's JP Morgan Healthcare Conference was, "Interesting Celgene bases forecasts on 'operational momentum' not pending clinical trial results."

It was far from the only place the word momentum appeared at the conference; for the key question on everyone's mind was how much the stunning surge in IPOs and other funding for small life sciences companies in 2013 would carry over into the new year. If I had to hazard a description of the consensus answer, it would be, "No more boom, but no bust either."

It hardly made for a comfortable feeling. The companies that attracted big dollars last year were overeager to justify the trust put in them. Other small companies occupied another notch up on the anxiety scale, lest they miss out on the high funding tide — one still rising, but whose ultimate crest remains unknown. The large companies, for their part, ranged from defensive but determined, to self-congratulatory. On balance, however, general optimism overcame uncertainty and generated great energy at the event, buoying up the mood of the crowd to match the sunny vista of Union Square outside the St. Francis.

Energy is good. Energy plus data is better. Although I agree companies should not project value or growth on what might happen in clinical trials, the acid test for any company pitching its concept is solid, preferably human, data. That axiom applies especially to the current race for accelerated review at the FDA. Another principle that boiled up again and again at the event: Business models matter. There is no stage too early to define one. When a company creates a new platform or product, it should ask itself, "How will this work in the patient/practice setting? Who will be willing to pay for it, and how much? How will we make the product, distribute it, and ensure its safe supply?"

Thus, when **Novartis** said it was feeling good about the potential breakthrough drugs in its pipeline, giving honorable mention to its CART (chimeric antigen receptor therapy) project with the University of Pennsylvania, my tweeted comment was, "I still have doubts on CART biz model — cell manipulation unwieldy." My doubts do not concern CART's basic viability but the issue of practical limitation — how widely can such a complicated procedure be applied? For example, even after decades of use and improvement, blood stem-cell transplants have never become commonplace.

Any successful immunotherapy helps prove we can employ the immune system to fight cancer and perhaps other diseases, but the challenge is to do it with the most practical, cost-effective treatment forms and delivery means possible. If not oral drugs, then injectables or even IV formulations would seem, at least at this point, superior to cell transfer.

But who am I to argue with Novartis? The company reached the traditional Big Pharma double-digit growth levels in 2013, reporting a third-quarter rate of 17 percent. Nevertheless, Novartis also declared a new level of introspection: Get ready for some business-unit divestitures, central-procurement and manufacturing-quality initiatives, and increasing emphasis on productivity in 2014 to overtake patent and revenue losses.

BIG PHARMA EDGES BACK IN

During the conference, Chief Editor Rob Wright and I met with, or simply met,

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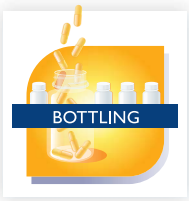

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At this year's JP Morgan Healthcare Conference, *Life Science Leader* hosted an off-site, private roundtable of small-cap CEOs and investment experts.

a number of small companies and even held a private roundtable of small-cap CEOs and investment experts off-site. Much editorial will flow from those encounters over the months ahead, but here I will focus a bit more on the large pharmaceutical companies that are trying to retain, or restart, their own momentum this year.

Roche, like its neighbor on the Rhine, had good news to declare. It touted its sales growth and pipeline rebound in the past few years and said it flirted with double-digit growth and margins in 2013. Roche has certainly pumped up its oncology pipeline with a number of candidates for single or combination immunotherapy.

On the other end of the teeter-totter from Novartis and Roche was Lilly, whose CEO John Lechleiter displayed extraordinary patience in the breakout as he and his team tackled sometimes picayune queries about the company's pipeline. Setbacks in clinical trials, of which Lilly seems to have had more than its share, put the company in the sights of more than one questioner eager to score sardonic points.

Why do disappointing trials still surprise us? Doubtless, Lilly needs some successes, but I can see no reason to believe at this point that its remarkable but largely unremarked crop of candidates will yield worse results than other companies' pipelines, in the long run. If Lilly has problems in R&D, they are likely similar to what you would find on close inspection among its peers. Some Big Pharmas obviously have a higher rate of success in picking winners from the well of life sciences discovery. But if companies are now competing as well on clinical trial design and execution or operational excellence in general, none has made an obvious leap ahead of the pack.

Lilly is pinning more immediate hopes on its Novel Basal Insulin Analog product, which would be consistent with its history of leadership in diabetes. If the product launches as hoped in 2016, it will employ much of the company's underused manufacturing capacity. Productivity improvements have lowered Lilly's R&D costs, despite creating the biggest pipeline in its history, the company reported. Successful launches of its oral diabetes 2 drugs will give the company a good shot at expansion in the primary-care market, it said.

As Lilly was open, **AstraZeneca** was particularly opaque, even in the breakout, and no amount of quibbling queries could roll back the company's official cover. "Why ask such detailed questions about AZ's pipeline when they won't share anything not already disclosed?" I tweeted. "The only novel information companies and their chief executives disclose are insights into their strategic thinking in answer to insightful questions." It was difficult, however, to see anything beyond AZ's single, monolithic strategy these days, which I described as, "Be into everything, overwhelmingly, and you're bound to win more than lose."

Merck (MSD), on the other hand, was trying its best to be transparent. CEO Ken Frazier stressed "accelerated strategic actions for growth," but unfortunately he was playing against the backdrop of clinical setbacks and patent losses, accenting how good times for the company now appear to lie only in the past or in hopes for the future. It seems Merck still struggles with the integration of Schering-Plough, which forced the company to make hard decisions about products and therapeutic areas that would remain in the combined pipelines. Whether Merck made the right choices will only become obvious over time. The more failures it has coming out of the clinic, the greater the pressure on management to reconfigure the pipeline yet again, at least by acquiring some relatively low-risk products.

Meanwhile the other Merck, aka **Merck KGaA** or **Merck Serono**, is looking and sounding more and more at home in the larger world. When I first visited the company in Darmstadt in the early 1990s, it could at best aspire to regional expansion beyond Germany and the EU. Now, thanks to Serono's previous foothold in the United States and market growth since the merger, the company has successfully reoccupied territory it lost to reparations after World War I. It was modest in its disclosures at the conference, however, citing sales growth and gross margin "in line" with its peers while also noting below-benchmark spending in R&D and SG&A (selling, general, and administrative).

Look for more biosimilars and fewer specialty drugs in this Merck's future, as it tries to squeeze still more productivity out of R&D. But the company will also continue to innovate in its strong areas, such as endocrinology, and in new ones, such as combination cancer immunotherapy.

Takeda is another company leaving regionalism behind, and over time, it is becoming more global than Japanese in management, strategy, and culture.

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"What we may be witnessing is a race among companies to set the gold standards for clinical data at both the investment and regulatory levels."

The company plans to promote its new COO, ex-GSK exec Christophe Weber, to the CEO position after current President and CEO Yasuchika Hasegawa becomes chairman in June. Both men participated in the company's breakout session, and they left the strong impression the transition would happen soon.

Hasegawa told me the company has become steadily more diverse through the years and will become more so as new leaders emerge from its international operations and acquisitions such as Millennium (though Weber "parachuted in" from GSK last November). Takeda's top financial and strategic goals for 2014 come right out of the Western playbook: efficiency, productivity, globalization of operations, procurement, integration of R&D, and intellectual property protection. In the GI therapeutic area, as others' patents expire, the company aims to claim the territory as global number one.

GlaxoSmithKline's CFO, Simon Dingemans, may have coined a new industry euphemism in saying the company had encountered "unexpected headwinds" in 2013. Beyond its bribery scandal in China, however, the company news was mostly good: "We put growth back in the system," said Dingemans, as shown by a modest but positive rise in sales of 2 percent. Still, GSK has also trimmed down — simplifying its business portfolio to just pharmaceuticals, vaccines, and OTC medicines. The restructuring delivered billions of dollars in savings, but the company is now looking at cost-of-goods and the supply chain for more weight reduction even as it bulks up its sales volume and lifts new revenues. In fact, Dingemans said the company wants its EPS to grow faster than sales.

GSK's R&D delivered five new products in 2013, but the products are "still in their early days." Likewise, the company expects an "interesting wave" of Phase 3 data in 2014, but Dingemans downplayed any excitement about the late-stage pipeline. Following a noticeable trend among the big companies, GSK ended the year with a large share buy-back, explaining it wants to "keep the balance sheet tight" but with plenty of room for investment opportunities.

CARPE DIEM FOR THE SMALL-CAPS

Those investment opportunities for GSK and its industry peers lie mainly in the small-cap life sciences sector, of course, which is increasingly active in the small-molecule side as well as biotech. But there was a palatable change in the air this year. Even though the past year's IPO boom may be behind us, the momentum it has created now sustains a new level of confidence among the smaller players. Undaunted by the continued coolness among VCs, the small-caps now have somewhere else to turn besides Big Pharma to fund drug development, as well as the potential for regulatory relief from the costs of late-stage trials.

The IPO attrition in the new year has been visible, at times dramatic, but somehow optimism has persisted. Though my imagination may be fooling me, I sensed greater pride and confidence among the small-company execs encountered at the conference — as well as a more solicitous attitude toward them by the big companies.

If any company could be expected to douse cold water on its sector, it would be one like **Ariad**. Only a few months before the end of 2013, Ariad was a darling of Wall Street. With its leukemia drug Iclusig (ponatinib) on the market thanks to an accelerated review by the FDA and Phase 3 trials under way that would have greatly expanded Iclusig's market, the company sported an extraordinary market cap of about $4 billion.

Then last fall, serious safety problems suspended the product's sales and the clinical trials. Although Iclusig has returned to the market for a narrowly targeted patient group in CML (chronic myeloid leukemia), its future is, to understate the matter, highly uncertain. At the conference, the most the company could say about the product was that it appears to stabilize patients in its current use. Interestingly, though, Ariad has generally traded up since its big fall in October, and it has not dragged the sector down as some predicted.

I am going to hazard a highly speculative theory to explain the case: However much investors may reward or punish a single company, they appear ready to learn from the experience rather than run from it. What we may be witnessing is a race among companies to set the gold standards for clinical data at both the investment and regulatory levels. Even though Wall Street and the FDA have opened new routes for Phase 2-based entries, they will base their criteria on a comparison of different companies' data, creating a natural selection mechanism and inevitably raising the general standard for IPOs and for accelerated reviews.

Now, if only the life science investors of 2013 could also acquire a more long-term perspective, their optimism would not wane, however, their realism could sustain them. Rougher, discouraging times will come again, and the historical volatility of the stock market in the sector may stimulate but can never maintain the momentum of small-cap innovation. For the needed change to happen, naïve investors must grow up to become wise investors. By next year's JPMHCC, we shall no doubt see which way the wave breaks: Will small-caps be forced to turn once more to Big Pharma with hat in hand, or will the latest crop of life science investors develop some staying power? L

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How Rare Disease Know-how Can Shape Big Pharma Clinical Trials

NICK TAYLOR Contributing Editor

When Andy Lee joined Genzyme from Pfizer, the differences between the companies were staring him in the face. Walking the corridors around his new office, Lee passed artwork by rare disease patients. This was a different sort of drug development organization. Even the building was patient-centric.

Lee, now senior VP and deputy head of clinical sciences and operations at Sanofi, recounts this tale while talking about the experience of going from Big Pharma to biotech and back again. While Lee has nothing but good things to say about Pfizer, it is clear the 18 months he spent at Genzyme before its acquisition by Sanofi reshaped his thinking, particularly regarding how the industry runs clinical trials.

"The classic clinical trial asks 'what does the sponsor want and need?'" says Lee. Everything is focused on delivering the data the sponsor needs, with little consideration given to the two stakeholders intimately involved with generating the results — investigators and patients. This attitude manifests in many ways, such as with electronic data capture (EDC) tools designed more for the sponsor than the user, clinical study nurses, and doctors.

Of course, the irony is that the sponsor-centric approach has done little to benefit Biopharma companies, which are paying more and more to run ever-larger trials that nonetheless still fall short of expectations. Activating a trial site costs up to $35,000, yet many never recruit a single patient. Equally, activating the trial sites and building other aspects of a clinical infrastructure takes time, pushing back drug approval dates.

Tufts Center for the Study of Drug Development calculated that between 1999 and 2005, the average length of a clinical trial increased by 70 percent and the burden on study staff rose by 67 percent. At the same time, enrollment fell 21 percent and patient dropout rates grew 30 percent. Lee saw the model was unsustainable for sites, patients, and pharma, and set about adopting lessons learned at Genzyme to change the paradigm at Sanofi.

LEARNING LESSONS FROM RARE DISEASE TRIALS

The different approach taken at Genzyme was borne out of necessity. Biotechs, even those that grow as big as Genzyme, are used to running trials on a tight budget. Splurging $350,000 on 10 clinical trial sites that never recruit a patient is an unacceptable use of limited resources. The nature of the drugs developed by Genzyme, which target rare diseases, increases the likelihood this scattergun approach will fail, too.

Around 6,000 people in the United States have Type 1 Gaucher disease, the genetic disorder targeted by Genzyme's blockbuster biologic Cerezyme. There are 4,300 times as many patients with diabetes. When designing a clinical trial for an orphan drug — the term for treatments targeting rare diseases — companies must think how this massive difference in prevalence affects their patient recruitment strategies.

"Finding a rare disease patient is like predicting the next lottery winner," says Lee. Instead of simply activating sites in metropolitan areas and waiting for patients to arrive — the flawed "if you build it, they will come" strategy — rare disease drug developers must take a more nuanced approach. It is no use activating trial sites in the 10 biggest cities if the only patients you can find are in rural areas of Brazil or Montana.

Consequently, Lee and Genzyme design studies that build support, capacity, and infrastructure around the patient long before the trial begins. This reverses the traditional model and takes the trial to the patient wherever possible. Instead of telling a patient to travel to a trial site, a nurse visits the person's home to do the infusion. When travel is unavoidable, the sponsor helps with logistics. "It's not rocket science. It's just about making things easier for the patient and site," says Lee. The process starts upstream in the study designs, where the input and engagement of patients and advocacy groups is essential.

Technology can facilitate this approach. Lee is particularly effusive about the potential for telemetry innovations to

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MATERIALS INNOVATION

enable remote data capture, severing the link between a patient's location and their ability to join a study. While such technology is already creeping into the consumer space in self-tracking devices, it is still on the cusp of acceptance in clinical trials. Lee is on a mission to accelerate adoption.

The potential is massive. Take the transdermal monitoring patch in development at Sano Intelligence, a start-up backed by seed fund Rock Health. Sano is trying to create a patch that continuously monitors glucose levels, kidney function, and electrolytes. Others, like Imec, are working on electrocardiogram patches. For trials, these patches could yield unprecedented insights into the health of participants between site visits.

HOW TO BRING BIOTECH IDEAS INTO BIG PHARMA

It is one thing to talk up an innovative prototype or novel methods used by a biotech in a rare disease trial, but quite another to implement experimental strategies at a Big Pharma company. The scale of Big Pharma companies necessitates reliable, industrialized development processes. Moving away from established methods is a risk. Yet, as these processes are failing, maintaining the status quo is a risk, too.

Lee, who is tasked with bringing innovation into the workings of Sanofi, grapples with these issues on a daily basis. Having the support of management helps. Lee says Sanofi's leaders are keen to adopt a culture of "open innovation" and establish a "biotech" mentality to help drive productivity and develop new medicines. Recently, this has led to the company implementing ideas from rare disease trials.

Instead of simply activating lots of sites and hoping patients show up, Sanofi is working more strategically with key research institutions from around the world. The strategy has reduced the overall number of sites needed in a given study. Together, Sanofi and the sites are trying to understand how and where patients access clinical trials, as well as ways to reduce the burden of their protocol designs. Through these partnerships, investigators and study nurses are able to provide Sanofi with real-life clinical perspectives as part of program and protocol development.

"This type of advice allows us to design studies void of challenges that could otherwise prevent some patients from participating, and it allows research sites to recruit more individuals in a given study," says Vicky DiBiaso, head of investigator and patient networks at Sanofi. The site-focused method should also cut down on turnover of investigators — a major problem for efficiency and quality — while reducing the proportion of locations that never recruit. Lee has been thinking about this model for years. In pharma, it takes time for ideas to come to fruition.

New technologies also go through a long gestational period. EDC, for example, was available for years before becoming mainstream. For Big Pharma, these gradual, phased introductions allow for the testing of innovative technologies without disrupting the running of vital clinical machinery. Lee is taking this stepwise approach at Sanofi, using post-authorization safety studies as a proving ground for new tools.

If successful, widespread use will follow quickly. Sanofi is looking to pilot iPad technology for informed consent, replacing bulky, paper-based, 20-page documents with interactive electronic forms. By allowing patients to give consent at home, a less stressful, time-pressured environment than the clinic, and using video "explainers," Sanofi is trying to make the process more informative and less daunting. In the future, sites will also benefit when new versions of the consent form are administered and tracked through electronic updates, eliminating the risk of using outdated documents.

CREATING AN ENVIRONMENT FOR INNOVATION

Shire is also trialing iPad e-consent, and Lee is pleased other companies are tackling the same problems. In presentations, he quotes Steven Johnson, an author who popularized the theory that innovations stem from the collision of small hunches. The more people who are thinking about a problem — and sharing

ANDY LEE
Senior VP & Deputy Head Of Clinical Sciences And Operations at Sanofi

their thoughts with like-minded individuals — the greater the chance they will hit upon a real breakthrough.

Biopharma as an industry clearly contains lots of people who are thinking about how to improve clinical trials. What is more questionable is the extent to which they are discussing their hunches with peers. In the past, Biopharma companies have been reticent to share their thoughts with competitors. In Johnson's model, this isolation of ideas slows the rate at which small hunches turn into full-blown innovations.

Lee sees these walls between companies coming down. Last year, 10 Big Pharma companies, including Sanofi, founded TransCelerate BioPharma to collaborate on overcoming their shared problems, such as sourcing comparator drugs and communicating with trial sites. If Johnson is right, the creation of a space in which ideas from different firms can mingle should spawn innovative solutions to pharma's problems.

At the very least, banding together could help overcome one of the obstacles to adoption of novel tools. "There's a fear of going alone and falling afoul of regulators," says Lee. By approaching regulators up front as a collective, the risk of trying something new is shared. Regulators also benefit from having one point of contact, instead of dealing with multiple firms running similar projects. This simplifies communication.

TransCelerate has already expanded beyond its 10 founding companies, adding another 8 members in its first year. The very existence of the organization shows companies are rethinking which of their functions give them a competitive edge and which are better handled collaboratively. With all five of TransCelerate's initial projects focusing on trials, it is clear that operational aspects of human studies are classed as precompetitive.

As Lee puts it: "It's expensive, and it's broken for all of us. To borrow a JFK quote, 'a rising tide lifts all boats.'" L

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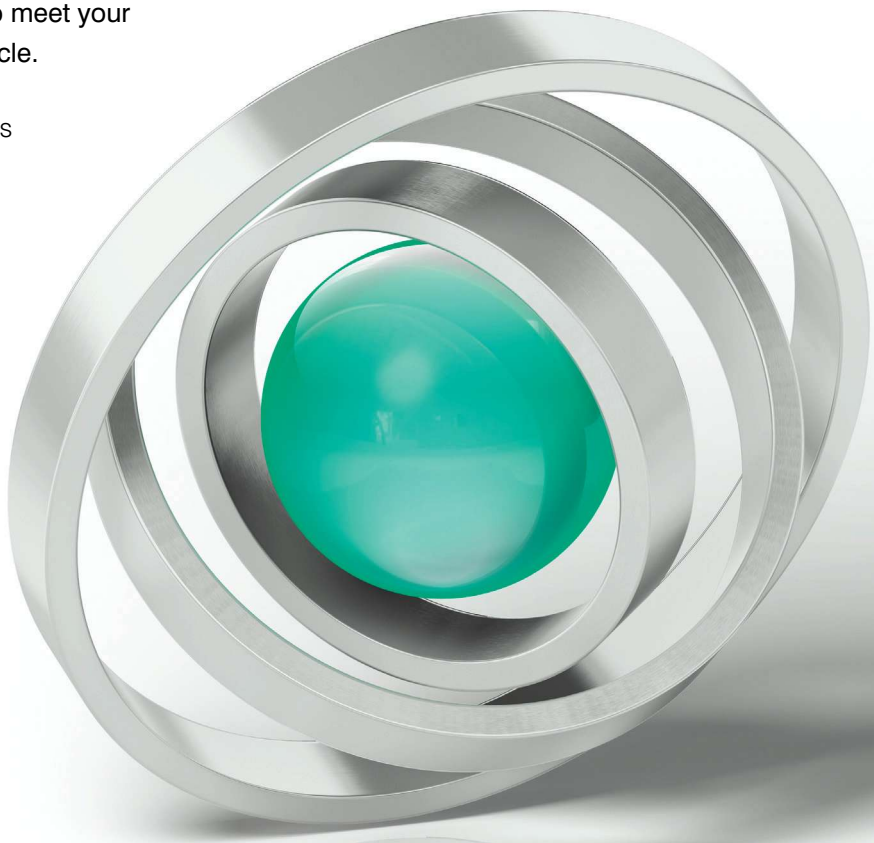

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Embracing M2M Technologies To Transform Clinical Trials

MUKHTAR AHMED

In late 2013, the FDA issued its long-awaited final guidance for mobile medical application developers. The agency announced that it will pursue limited regulation of health and wellness applications that help patients manage their conditions. Instead, the FDA will focus efforts, including the application of risk-based standards, on diagnostic and quasi-medical device applications.

The recent ruling provides important clarity for organizations that look to use innovative machine-to-machine (M2M) technologies to significantly improve the efficiency and accuracy of clinical trials — a perennial quest for many health sciences organizations.

Nearly every day we hear of exciting new uses for M2M solutions in the health and fitness realm. For example, M2M technologies are offering new insight into the prevention and treatment of traumatic brain injuries. With nearly 4 million mild traumatic brain injuries reported annually due to sports and recreational activities, the health community is excited at the prospect of using helmet sensors that collect immediate and accurate data on the severity and history of impacts a user experiences. The information enables real-time assessments that can protect the athlete from further potential harm. Another M2M solution is helping healthcare providers assess the severity of concussions, and patient progress after one occurs, with a device and iPad application that tracks a patient's dynamic vision reflexes, motor skills, balance, and more.

Life sciences organizations are equally eager to embrace emerging M2M technologies, especially in their clinical development programs. M2M solutions have the potential to transform many clinical programs — from patient recruitment and retention, to data collection and accuracy, to safety and pharmacovigilance. The possibilities are exciting and endless.

ACCURATE AND IMMEDIATE DATA DRIVES INFORMED, PRODUCTIVE, AND TIMELY STUDIES

Health sciences organizations and their CRO partners have long been focused on improving the productivity of clinical trials by boosting data collection and management efficiency. As a result, electronic data capture solutions have become the industry standard. We've made much less progress, however, improving the fundamental quality of clinical trial data. This is where M2M technologies will prove their true potential.

M2M technologies enable continuous patient monitoring, which can deliver several important and long-term advantages to research teams. First, researchers can collect more types and higher volumes of data than ever before. Traditional clinical trials typically rely on patient journals and intermittent exams. With M2M sensors and telemetry connectors — whether the patient wears them or digests them — researchers can collect continuous data on patient vitals, medicine intake, activity levels, and more. With these real-time statistics, trial managers can gain key insight into efficacy not possible with traditional trial methods.

Additionally, M2M enables an immediacy of data collection that was previously impossible to achieve, and which can have important implications for clinical trial safety. Solutions can deliver data automatically and instantly, without human intervention, to researchers, who can then identify potential adverse events sooner to improve safety as well as accelerate the overall pace of data collection, all helping to speed time to data lock and regulatory submission.

With any clinical trial or data collection situation, the accuracy and quality of the data is extremely important to the end result of the research. M2M solutions enable trial sponsors to collect higher volumes of information and an expanded array of data types to support more exhaustive analysis and insight. Another benefit of continuous data capture is that the risk of human error with manual data entry is removed.

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Protocol compliance, medical adherence, and patient engagement remain significant challenges for clinical programs. A study published in the New England Journal of Medicine notes that clinical trials report average adherence rates of only 43 percent to 78 percent among patients receiving treatment for chronic conditions. Another example of protocol adherence challenges comes from a double-blind outpatient study examined by the NIH, in which only 39 percent of patients met 100 percent compliance on all visits.

Low patient engagement can have a detrimental effect on the economics of clinical trials and ultimately the success or failure rate of the trial as a whole, potentially wasting time and money.

Continuous monitoring, made possible through M2M technologies, can enable researchers to confirm treatment adherence with near absolute certainty, which we could not do before. As a result, study sponsors and managers can more accurately determine efficacy as they filter out nonadhering patients.

Continuous monitoring with M2M technology can also facilitate subject recruitment, and help sites optimize their performance by focusing on the science, simplifying unnecessary trial complexities, and ultimately shortening the length of a trial. Trial managers could identify nonadhering patients quickly and make faster decisions about whether to remove them from the study or focus resources on boosting adherence. This capability also provides better insight into how many subjects will be required to complete the trial, and more importantly, it can help reach key decisions concerning the validity of protocol amendments and the progression to latter stages of clinical development.

Further, M2M solutions can help improve participant retention because recording critical data and adherence would be automated and, therefore, more convenient. In addition, the ability to automatically upload data to the clinical data management system would eliminate manual input into an electronic case report form — driving new levels of study efficiency.

IMPROVING TRIAL SAFETY THROUGH REAL-TIME DECISION MAKING

M2M technologies enable continuous monitoring that can have an immediate positive impact on patient safety. With vast and accurate information streaming in real time, researchers can quickly identify potential adverse events or side effects such as changes to heart rate, heart rhythm, blood pressure, or sleeping patterns, after prescribing a medication or therapy, and they can take action to intercede. This capability also has promising application in post-market surveillance.

As important, access to real-time information can support adaptive trials, providing early indications of changes that might need to be made to protocol, sample size, or trial scope. Similarly, trial sponsors can have earlier insight into a therapy that is performing better than expected, which would accelerate the delivery of life-saving treatments to market.

M2M TODAY

We are just beginning to get a glimpse into the exciting real-world potential of M2M technologies in the clinical realm. For example, we are seeing the emergence of surgical instruments equipped with imaging telemetry sensors that support four-dimensional (4D) visualization and predictive simulation modeling. For therapies that have a surgical component, these smart surgical instruments capture and process rich data, which can then be used to build a real-time visual model of the specific patient's anatomy as the surgeon conducts the procedure. The data from the surgical procedure can provide significant real-time insight and guidance for the surgeon and the operating theater team. This critical physiologic data can also be transmitted to researchers to yield greater insight into outcomes and potential adverse events.

Another example is Proteus Digital Health's FDA-approved ingestible sensor, designed to work together with a wearable sensor to capture precise information about medication ingestion, dose timing, physiologic responses, and other behaviors, sending the digital health information to a patient's smartphone.

The ingestible sensor sends a signal containing a unique identifier recording the time the patient took a pill. A wearable sensor worn on the skin captures continuous readings of the patient's heart rate, temperature, activity, and rest patterns. The solution can collect more than 5,000 data points per minute.

BECOMING EARLY ADOPTERS

Challenges — whether regulatory, technological, or ethical — are to be expected with the maturation and adoption of any revolutionary technology. M2M is no different. However, it is important to note that the challenges are far from insurmountable.

Safety is paramount in the health sciences, and the FDA guidance will help bring structure and process to the development and testing of M2M technologies designed for the medical sector. Security of confidential and protected health information is a constant concern, as are regulatory policies regarding the use of such information technology in medicine. Regulatory policies are being created to not only promote innovation and adoption of technologies such as M2M, but to also protect patient safety and security.

The influx of massive volumes of data emanating from M2M applications can also present a Big Data challenge for study sponsors and their CRO partners. To realize the true potential of M2M technology, and transform clinical trials, organizations must be able to rapidly analyze and act on the vital information gathered in real time.

Forward-looking health sciences organizations can position themselves to rapidly reap the benefits of M2M by building a foundation for adoption in the short term. Many of the core technologies — including data repositories, analytics, and integration technologies — are already in place at health sciences organizations today, and we can learn a lot from other industries progressing rapidly toward greater use of M2M technologies.

Mukhtar Ahmed has been the vice president of product strategy for Oracle Health Sciences for more than two years.

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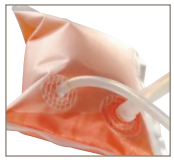

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SUZANNE ELVIDGE Contributing Editor

Since the discovery of penicillin in 1929, the birth of the antimicrobial era meant the beginning of a brave new world, where people no longer died from common bacterial infections, and surgery could be approached with confidence.

However, it didn't take long for the shadow of drug-resistant infections to creep in, and drug developers and physicians have been fighting what is now a losing battle against drug-resistant bugs.

Unfortunately, creating more antibiotics, whether broad- or narrow-spectrum, is unlikely to solve the problem, as resistance is virtually inevitable. However, the search for a solution in the form of new nonantibiotic-based approaches is providing a new opportunity, particularly for biotechs and for their future pharma collaborators and partners. These tactics include bacteriophages (bacteria-killing viruses), and non-bacteriophage proteins, from companies such as Novolytics, AvidBiotics, AmpliPhi Biosciences, and Pherecydes Pharma.

FROM ANTIBIOTICS TO THE POST-ANTIBIOTIC ERA

In early 2013, Professor Dame Sally Davies, the chief medical officer for England, stated that the danger presented by the growing resistance to antibiotics should be ranked alongside terrorism as a threat to the nation. However, this threat isn't unique to the United Kingdom. In 2013, the first case of a totally drug-resistant infection was discovered; a New Zealand teacher was found to have a bacterial infection resistant to all known forms of antibiotic, probably picked up while teaching overseas.

What will this mean? There could be deaths from infections following routine operations, especially in the very young and very old, and in people with compromised immune systems. Furthermore, it could result in no organ transplants or chemotherapeutics that suppress the immune system.

"Broad-spectrum antibiotics have been critical for most surgical procedures and many medical interventions. They have saved many lives and limbs since their launch. However, antibiotic resistance has emerged and has now become rampant worldwide," says David Martin, CEO and cofounder of AvidBiotics, a company that generates nonantibody therapeutic and prophylactic proteins that specifically target bacteria.

So, if the old antibiotics don't work, then surely the solution is simply to develop new ones, right? Unfortunately, this hasn't worked so far, as shown by the lack of new classes of antibiotics since 1987 when oxazolidinines were introduced. The first of these, linezolid, was discovered in the 1990s and launched in the U.S. in 2000 by Pfizer. However, there were reports of resistance as early as 1999.

"The antibiotics industry is well established, but over the last two to three decades the amount of research effort placed behind new antibiotics has tailed off. Evidence for this comes from the fact that between 1983 and 1987 the FDA approved 16 new antibiotics, but between 2008 and 2012 they approved just two," says John Hardcastle, CEO of Novolytics, a company working to combat antibiotic-resistant bacteria using bacteriophages.

Besides the inevitability of resistance, economic forces are also likely to be behind this reduction in antibiotic R&D. Infectious diseases generally require a short course of treatment, compared with statins or antihypertensives that are used lifelong. And payors expect infectious disease treatments to be low cost. Because resistance can set in quite quickly, antibiotics also have a limited life.

"For good commercial reasons, drug companies have become more focused on chronic diseases, such as depression, cardiovascular disease, diabetes, and cancer, which is reflected in the top 10 drug revenue statistics published each year," says Hardcastle.

Another black mark against broad-spec-

trum antibiotics is that they damage the balance of the natural microbiota (the naturally occurring population of bacteria in the gut, vagina, mouth, and skin). This can have a negative impact on health.

CREATING AN OPPORTUNITY OUT OF A PROBLEM

These issues all make the market dynamics of creating new antibiotics less attractive. This void is being filled by companies creating nonantibiotic antibacterial agents that can target specific antibiotic-resistant and antibiotic-sensitive bacteria, and that are less likely to encourage resistance or to affect the overall microbiota profile. Because these nonantibiotic agents can destroy resistant bacteria, they could also have potential in tandem with antibiotics, which may even reduce the development of resistance. While the initial development of antibiotic alternatives is largely in the hands of small biotech companies, pharma companies are likely to take an interest in the outcomes of research, maintaining the prospect of future support and collaborations.

PHAGE THERAPY: COMBATING MICROBES WITH MICROBES

A bacteriophage (more commonly just known as a "phage") is a naturally occurring virus that has evolved specifically to target bacteria, with no impact on other cells or organisms. Physicians in the former USSR have used phages to treat bacterial infections for almost a century. However, other than a brief time in the early 20th century when they were sold as treatments in the U.S., they have been regarded with some suspicion.

"Phage cocktails were sold in the 1920s and 1930s by a number of well-established Western pharmaceutical companies. However, unfortunately they were sometimes sold inappropriately, partly because

"Antibiotic resistance has emerged and has now become rampant worldwide."

DAVID MARTIN
CEO & cofounder
of AvidBiotics

of a lack of understanding of the basic molecular biology," says Hardcastle. "For example, phages were sold as a therapeutic for polio and influenza [both of which are caused by viruses not bacteria]. Consequently, people began to question their efficacy. Once penicillin was discovered and we learned how to make it in large quantities, phage therapy was con-

signed to the history books, at least in the West," says Hardcastle.

But now phages are attracting the attention of the West again as the fear of drug resistance rises. However, while there is animal data available from work in Western labs, the human data generated by the old Eastern bloc countries isn't acceptable to the regulatory authorities, largely because of the manufacturing conditions under which the cocktails are manufactured and the lack of rigorous double-blind clinical trials.

Phages have a number of advantages over antibiotics. They are dosed "live," and will continue to replicate and attack bacteria until the infection is cleared. In contrast with small molecules and vaccines, which target one particular pathway or antigen, phages can be dosed as a cocktail attacking different targets on a specific bacterial pathogen of interest. This future-proofs the treatment against changes in targets on the bacteria's surface, thus reducing the risk of driving resistance to the phage treatment.

Novolytics' lead product, NOV012, is an example of a phage in development against resistant bacteria. It's a topical gel formulation of a bacteriophage cocktail targeted at methicillin-resistant Staphylococcus aureus (MRSA). The company has completed preclinical animal toxicity tests of NOV012 with no adverse outcomes, along with in vitro studies showing equivalent or better efficacy against MRSA compared with Mupirocin. Novolytics is planning a Phase 1/2 clinical trial for the nasal decolonization of MRSA as a prophylactic in carriers, and NOV012 also has potential as a therapeutic in wound care management. In mid-2013, Novolytics signed a manufacturing deal with Cobra Biologics to support GMP manufacturing, and is seeking further partnerships to drive development of both the therapeutics and diagnostics.

AmpliPhi Biosciences, another biotech company focused on developing bacteriophage-based antibacterial therapies to treat antibiotic-resistant infections, has a number of collaborations supporting its research. Those include an R&D agreement with the United States Army to develop phage therapeutics to treat Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa infections; a collaboration with Intrexon to develop phage-based therapies to target specific antibiotic-resistant infections; and most recently, an agreement with the U.K.'s University of Leicester to license a number of phages with activity against Clostridium difficile.

French company Pherecydes Pharma is developing phages targeted against E. coli, Pseudomonas, and Staphylococcus, and has seen efficacy in animal studies with no toxicity. The French government's defense procurement agency has invested €0.9 million ($1.2 million) into the PHAGOBURN project to create a product to use on infected burns. Other projects are underway for respiratory, bone, and joint infections, and Pherecydes Pharma is seeking partners to support the clinical development of its phages and the associated companion diagnostics.

PRECISION MEDICINE DRIVEN BY PROTEINS

Other approaches to antibacterial therapy include nonviral therapeutics, which do not include genetic material and cannot replicate. One company taking this route is AvidBiotics, which is developing Avidocins (R-type bacteriocins). These are reengineered forms of bacterial defensive proteins that target surface molecules on the bacteria. They lock onto specific receptors on the bacteria's surface and physically punch holes in the cell envelope. AvidBiotics' molecules successfully treated E. coli O157-induced diarrhea in rabbits and Pseudomonas aeruginosa peritonitis in mice.

"We are starting with Clostridium difficile, the number one urgent threat to U.S. citizens, according to the CDC," says Jim Knighton, president and cofounder, AvidBiotics. "If we kill only Clostridium difficile, this could eliminate selective pressure for the spread of drug resistance and leave unharmed the insensitive members of the microbiota. Our approach could change the practice of medicine."

According to Martin, around 3 percent to 11 percent of people going into the hospital carry Clostridium difficile. When these people are treated with broad-spectrum antibiotics, which kill most if not all of the sensitive bacteria, the resistant forms of the bug can recolonize the gut, leading to C. difficile-related diarrhea, which kills around 14,000 people in the U.S. every year.

"The antibiotics industry is well established, but over the last two to three decades the amount of research effort placed behind new antibiotics has tailed off."

JOHN HARDCASTLE
CEO of Novolytics

THE CHALLENGES

Obviously, precision medicine is better for everyone — patients, physicians, and payors. Specific agents like these bacteriophages and nonphage proteins will need accurate and rapid diagnostics that can be deployed at the bedside or in the emergency room, and this creates another challenge, or perhaps another opportunity, for the originator companies and potential partners. Another challenge for these new approaches, which is similar for any first-in-class project, is reeducating the stakeholders, including physicians, payors, regulators, and health technology assessment bodies such as NICE (National Institute for Health and Clinical Excellence) in the U.K.

If these challenges can be overcome, phages, antibacterial proteins, and other nonantibiotic therapeutics and prophylactics could provide a new way to tackle the old enemy of bacterial infection, moving medicine on from the threat of the post-antibiotic era. L

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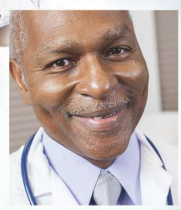

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Patient-centric Design: The Next Frontier In Drug Delivery

ED MISETA Contributing Editor

Patient-centric is one of those terms we suddenly seem to hear mentioned often. Everyone in pharma wants patients to know that it's their comfort and well-being that are always at the forefront of development efforts for medicine and delivery devices.

But true patient centricity is not about saying the right things at the right time. Nor is it thinking about the patient only when it comes time to present a product to them. Rather, it involves thinking of the end user at the very beginning of the discovery process, and keeping them in focus throughout the product development cycle.

Ralph Lipp, president and CEO of consulting firm Lipp Life Sciences LLC, has been advising clients on the importance of a patient-centered approach for years. He believes that when developing novel drugs, it is even more important to keep the patient in mind, as that focus will drive everything else involved in the drug development process.

"When it comes to patient-centered drug delivery, topics like safety, minimization of side effects, and efficacy are all important topics in the development process," he says. "But some in the industry fail to understand that portability, social acceptability, and a good understanding of how patients interact with the delivery device are topics that must also be considered. A better understanding of patient-centric drug delivery will lead to better patient outcomes, which is clearly the overall goal of what we do."

Lipp defines patient centricity as thinking of the patient at each and every phase of the development process. It involves moving beyond the most basic patient needs of safety and efficacy, and thinking about the entire spectrum of patients who may be using the drug, and what their needs are. When dealing with medicines that must be self-administered, the human factor will have to play an even greater role in the area of drug and device development. Easier self-administration will lead to greater patient adherence, which in turn will significantly support reaching the ultimate goal of improved patient outcomes.

ADHERENCE EQUATES TO SUCCESS

The advantages of patients being able to self-administer a drug are many. First, it will cut down on the amount of time a patient must spend in a hospital or clinic. Patient-friendly devices mean medicines can be administered at home, whether by the patient or a nurse or home care professional. For example, Kurt Nielsen, CTO and SVP of R&D at Catalent, notes being able to self-administer an anticoagulant at home can knock two days off a five-day hospital stay, resulting in a savings of thousands of dollars.

Nielsen also believes a significant value of the patient-centric approach lies in adherence. "If patients understand why they need to take medicines, they are more likely to take them," he says. "Only then is the magic of the drug able to happen. The more difficult the process of self-administration, the less likely it is to happen. And when patients stop taking their medicines, the magic can't happen."

To increase acceptance, there are several factors to consider. Lipp starts with invasiveness. "Users will more readily accept a medicine that is administered via a device that is comfortable to handle and easy to self-administer," he says. "With age, self-administration becomes one of the greatest challenges patients face. In addition to dexterity issues caused by the onset of arthritis in some patients, there will be challenges created by the deterioration of vision in other patients. Packages and devices with small writing and multiple steps that need to be performed will result in lower acceptance rates."

When developing the device and the

labeling, Nielsen recommends catering to the lowest common denominator. For example, if a portion of the target audience might have difficulty reading, that factor has to be considered when designing the instructions. "There is not a lot of customization for the different patient populations," he says. "I have yet to see anyone produce a pen for a patient in their 20s and another one for patients in their 60s. We may see more of that in the future when companies get more involved with addressing patient subpopulations, but until then we need to do whatever possible to minimize side effects and maximize adherence for all potential patients."

START THINKING ABOUT PATIENTS EARLY

To ensure patients are a primary concern throughout the development process, they should be a consideration from the very start. "Depending on where a drug is in its life cycle, decisions on technology design should be part of the initial drug development strategy or as soon as the need for reformulation is identified," notes Robert Becker, chief research officer for Aptalis Pharma. "Of course, we need to ensure a drug is effective and tolerable, but if it can't get to where it needs to go because patients can't tolerate it, or it is delivered in an inefficient dosage form—it is not going to achieve its intended clinical goal."

When it comes to decisions about drug delivery technology, time is of the essence. Becker believes incorporating the most appropriate drug technologies from the start also helps optimize life cycle management, making the most of the drug at every stage. "Ultimately, this will enable the drug to bring more value to the patients who use it and greater profitability to the company that makes it," he adds.

One way to make sure all patient considerations have been taken into account

"A better understanding of patient-centric drug delivery will lead to better patient outcomes, which is clearly the overall goal of what we do."

RALPH LIPP
President and CEO of
Lipp Life Sciences LLC.

> *"There is enough risk in showing the safety and efficacy of a drug. For many executives, laying an additional layer of risk on top of that goal would be a step in the wrong direction."*
>
> **KURT NIELSEN**
> CTO and SVP of R&D at Catalent

is to prepare a list of questions to be asked throughout the process. The first question should obviously ask what patient population will be using the device. Once that is known, determine if there is already a device on the market that is appropriate for that population and is readily available. "You can't use a pen that was designed for diabetics needing insulin and expect it to be used by an elderly patient with rheumatoid arthritis," says Lipp. "However, if there is already a device available tailored to the needs of arthritis patients, it would make sense to use that device. Then you can build on it going forward if you believe there are improvements that need to be made. Of course if a device is not readily available and the target population cannot easily handle a prefilled syringe, then a more sophisticated device should be considered."

GO TO MARKET OR WAIT?

A dilemma faced by many pharma companies is whether to get a drug to market as quickly as possible or wait until a better delivery device is developed. If a medicine can be put on the market quickly, it is good for patients who need the drug, and it provides a quicker economic return for the firm. But releasing the drug with an inappropriate delivery device could also cause the whole effort to backfire.

This is a decision moment that must be considered, and there are two schools of thought. "If there is a similar drug already on the market with a sophisticated device, are you willing to go into that market with a new biologic and an inferior delivery device?" asks Lipp. He recommends taking a close look at the market to see what medicines are already available, along with the devices available to deliver them. One should only go ahead quickly if the new biologic/device combination-product offers patients advantages over already existing combination-products, otherwise one should consider further investment into device optimization.

Unfortunately, this approach may also create additional risk. Nielsen believes many manufacturers will have a different perspective. "When you are in clinical development, the goal is to demonstrate the safety and efficacy of the drug; everything else is secondary to that," he says. "Once you launch it and get some clinical experience with it, only then will most companies look at the product to consider how they can make it better. Companies have a lot to worry about when submitting a drug for FDA approval. Once they prove the safety and efficacy of the drug to the FDA and payers, they may go back and make incremental improvements or breakthroughs with the device, but not until after the approval."

Including the device design step into this process, and proving that it works in a clinical study, certainly entails taking on an additional risk. According to Nielsen, that is a risk 9 out of 10 companies would likely not want to take. "There is enough risk in showing the safety and efficacy of a drug," he adds. "For many executives, laying an additional layer of risk on top of that goal would be a step in the wrong direction."

WILL THE PAYERS BE WILLING TO PAY?

Even if you develop a safe and effective drug in a delivery device appropriate to your patient population, there is no guarantee insurance companies will be willing to pay for it. Becker believes payers in the U.S. and around the world are looking for measurable improvement in patient outcomes as the criteria for new device acceptance.

"The trend among payers is to look more comprehensively at the range of benefits a drug provides to the health of patients and the economic impact of a disease," he states. "If we are improving adherence to a drug with our technologies, patients can better manage their conditions, and the cost of care goes down. Insurance companies want to be able to measure that improvement. If we can show them how much of an impact patient-centric dosage formulations can have, they will be more apt to reimburse more of the cost. They just need to recognize the value the medication and the delivery method brings."

Nielsen agrees payer coverage is an industry concern. Still, he believes it can be easy to overcome. "If patient adherence is 50 percent when using a prefilled syringe, and your studies show adherence to be 80 or 90 percent with a new device, that will cause the payers to take note," he adds. "Payers will ultimately benefit from the patient having fewer relapses, fewer emergency situations, and fewer hospital and home care visits. If the device costs an additional $5 or $10, but the savings to the insurer is in the hundreds or thousands, that is something you can quantify. It is an economic argument that is easy to make, but you need to have the data to prove it. Managed care is built on the premise that if you have the right interventions with physicians and are taking medications, symptoms can be alleviated without hospitalization or emergency care. That is the primary reason for having devices patients can use to self-administer, and which they will continue to use in the future." L

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Serialization – Pharma Faces 2015 Deadline

GAIL DUTTON Contributing Editor

Pharmaceutical executives are hustling to finalize plans to implement the Drug Quality and Security Act, which became law last November. Although that law was seen as allowing extra time to serialize packaging lines, it actually moves up some deadlines and adds additional requirements that are causing pharmaceutical companies to adjust their serialization strategies and implementation timelines.

"The industry is uncovering a lot of unexpected complexity that may have a dramatic effect on manufacturers," says Rob Young, Accenture's life sciences North America lead for serialization. Compressed timelines are the biggest concern, followed by added requirements.

For example, the California Board of Pharmacy requirement — the de facto U.S. standard before the federal mandate was enacted — called for complete unit-level traceability for dispensers in 2017. The new federal mandate extends that deadline to 2023, but requires product identifiers to be added to each package and homogeneous case of product by November 2017. It also adds interim steps, so that the first deadline manufacturers must meet is Jan. 1, 2015.

By 2015, manufacturers must incorporate product transaction data into a single document that is available, either electronically or on paper, each time ownership is transferred. This document must include transaction data listing lot-level information, a complete transaction history, and a transaction statement and must be maintained for six years after the transaction. By November 2017, that information must be available electronically, and the product identifier must be affixed or imprinted on the label at the product and case level.

In light of these changes, "Big companies are moving faster now. They recognize they have only a limited time in which to get things done," Greg Cathcart, CEO of Excellis Health LLC, says. "They can't slow down."

While the federal mandate avoids a state-by-state legislative patchwork, it extends serialization requirements to entities that otherwise would not have been affected. As an example, Cathcart cites large and regional wholesalers that could manage the California requirement by deploying solutions to sites that shipped to that state, but which now must deploy solutions for their entire networks. "In some cases, this will increase the number of sites affected by as much as 75 percent," he says. Healthcare providers unaffected by the California mandate now must develop track-and-trace plans for their inventories. Some regional healthcare providers, for example, have more than a dozen pharmacies they must prepare for serialization.

PHARMA FOCUSES ON NEAR-TERM REQUIREMENTS

"At Pfizer, we've been preparing for the California mandate for several years, so we are able to leverage that work to prepare for the federal mandate," says Peggy Staver, director, product integrity. The Pfizer team is continuing to deploy serialization throughout Pfizer packaging lines and is building out a cloud-based IT solution that integrates with the company's contract manufacturers to ensure Pfizer meets the November 2017 compliance deadline for lot-level serialization.

"For the pharmaceutical industry to meet the 2015 deadline, there's a great deal of work that must be done in a short time frame," Staver says. "Within Pfizer, there are some near-term requirements we need to work toward. We're moving forward with the development of our IT enterprise solution and are reassessing the effects of the new law on our packaging lines' serialization plans. While some capital investments required to meet the 2023 deadline may be deferred, we're not slowing in any way."

Stephen Kovary, senior director, operational excellence in supply chain and technical operations at Daiichi Sankyo, Inc., says Daiichi's approach to serialization and data aggregation hasn't been affected. However, he adds, "We have reevaluated our implementation schedule and have delayed some of those activities based on meeting the new federal legislative date of November 2017, versus the California Board of Pharmacy dates of January 2015 and January 2016. Our focus has shifted to the federal lot-level pedigree requirement, which has a January 2015 due date."

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"To meet lot-level pedigree compliance, companies have 13 data elements that must be incorporated," Cathcart points out. "These elements include the name of the authorized reseller, product quantity, lot number, and container size. The information must be stored and made available to the FDA within 24 hours." That means a database of authorized trading partners must be developed, he adds.

"Additionally," Cathcart says, "wholesalers must be able to receive the data, make it available for FDA audits, and send it with their sales information downstream to their customers. However, the FDA guidance interpreting these requirements isn't due until Nov. 27, 2014," one month before mandatory implementation.

"A wait-and-see approach will not leave us much time to implement a proper solution," Kovary says. Daiichi is assessing the requirement and identifying options now.

Hussain Mooraj, global managing director, life sciences supply chain and ERP (enterprise resource planning) for Accenture, cautions, "We expect this lot-based regulation to potentially disrupt the industry by forcing manufacturers to divide their resources between this requirement and maintaining momentum for unit-level serialization."

THIRD-PARTY ISSUES INVOLVED

The federal mandate also includes a provision to deal with suspicious and illegitimate products. It calls for quarantine, an investigation with trading partners, FDA notification with 24 hours, and, by November 2017, the ability to verify the product at the package level with a standardized numerical identifier. For some, that's a backburner issue that will be addressed in concert with their third-party distributors.

Pfizer is engaging with the FDA and industry to better understand the requirements regarding suspect and illegitimate product. "To some degree, we have a system in place," Staver says. "For example, today if a pharmacy sees a suspect product, it phones us to check the lot number, discuss any recent packaging changes, and determine appropriate next steps." To implement the new approach, the FDA must provide additional guidance regarding identification and disposition of suspect and illegitimate product by May 2014. That leaves manufacturers only a few months to implement compliance strategies, she points out.

Another challenge, according to Young, is that the FDA now has oversight of processes and operations in which it may not have deep experience. "Therefore, companies may be forced to spend extra resources to make their processes more straightforward and consistent (both in-house and with the industry). For example, in the logistics and supply chain space, many organizations — especially the smaller ones — haven't thoroughly documented their processes. So, when FDA regulators ask for details of a particular process, like they do for manufacturing, many companies may not be ready to reply. Therefore, life sciences companies must become more vigilant [about documenting their supply chain processes]."

USE SERIALIZATION TO INCREASE VISIBILITY

Mooraj encourages companies to look beyond the deadline and focus upon the opportunities serialization offers. "The companies that will succeed are those with concurrent strategies to meet the requirements and to extract value by increasing visibility into the global supply chain," he says. "Don't lose sight of longer-term efforts. Think about ways to extract value from these investments."

The data required for serialization should be in demand throughout the supply chain. The level of tracking enabled by serialization enables forward-thinking companies to use that data to gain more comprehensive understanding of the entire supply chain and, for example, minimize distribution bottlenecks and more tightly target recalls. Additional uses may be identified once the FDA guidelines are developed.

The immediate challenge, Kovary says, is determining how best to collect and move this data while meeting the yet-to-be-established FDA requirements. "While we can't predict the exact FDA requirements, in today's sophisticated electronic world, this hopefully would be nothing more than determining what data to extract and what report format to use."

> *"To meet lot-level pedigree compliance, companies have 13 data elements that must be incorporated."*
>
> **GREG CATHCART**
> CEO of Excellis Health LLC

INCORPORATE A GLOBAL APPROACH

Traceability is a global need, and "The U.S. serialization law lags behind those of other countries," says Michael Lucas, president and founder at Frequentz, a track-and-trace technology specialist. Given the global proliferation of serialization regulations, "This law has marginal to no impact on the overall global traceability requirements and planning efforts. Serialization laws and regulations have already been piloted, if not fully executed abroad."

Serialization requirements are in various stages of development in the EU and in its member nations, as well as in Turkey, India, China, Brazil, Argentina, and Korea. The most recent change occurred in Brazil, which in December published RDC 54/2013, specifying track-and-trace requirements. According to that document, manufacturers must provide serialization and tracking data for three batches of products by Dec. 10, 2015. All pharmaceuticals must be serialized and tracked by Dec. 10, 2016. "For a growing market, that's a critical milestone," Young says. The first public hearing discussing implementation was held Jan. 23, 2014.

With so many different reporting requirements throughout the world, one-size-fits-all responses are inadequate. "You have to take a harmonized approach to compliance," Young says. "Think from a global perspective, and then break the program down for specific countries."

As implementation deadlines approach, "There's no more breathing room," Mooraj adds. "Manufacturers need to get this right." L

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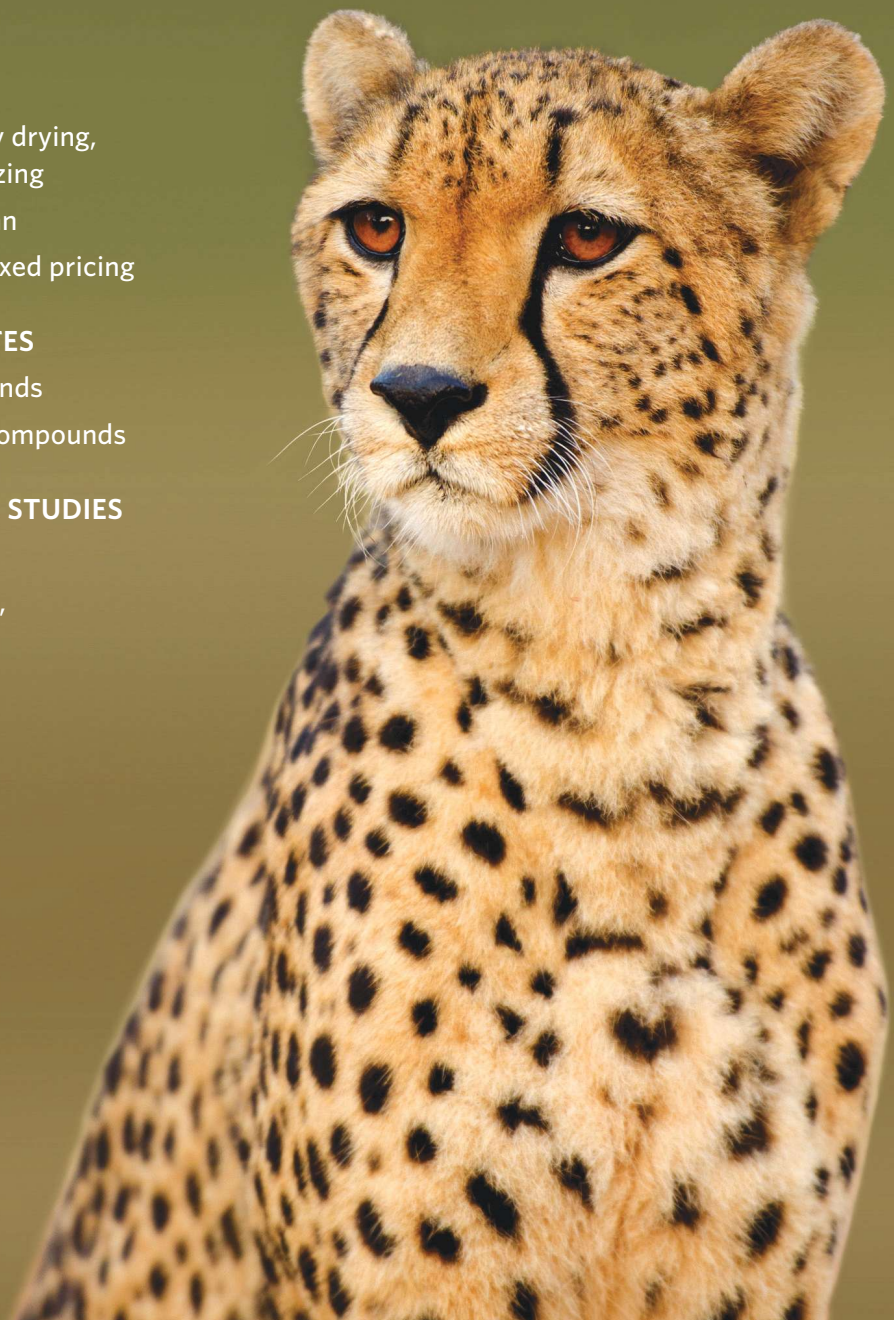

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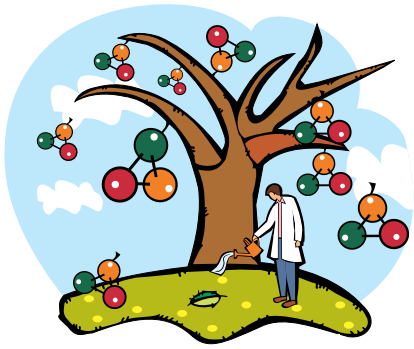
Evolva Turns Around Its Business Model: Swiss Biotech Opts Out Of Drug Development

K. JOHN MORROW JR., Ph.D. Contributing Editor



Drug development is a tough proposition for the biotechnology industry. The targets today are complex disease conditions whose molecular bases may be poorly or not at all understood. Potential pharmacologic agents that inhibit critical metabolic pathways will frequently generate unanticipated and life-threatening side effects.

Preclinical screening of drug candidates may yield encouraging results based on data from lab animals and cell cultures that cannot be substantiated in clinical trials. And in Phase 1 studies on very small numbers of human subjects, positive data is often not confirmed in expanded, double-blinded Phase 2/3 trials on large, randomly chosen populations.

With so many barriers to achieving a successful new drug entry, it is hardly surprising that some biotechs have looked for alternative directions for their technological base. Evolva, a Swiss-based company, has turned from drug development to making ingredients of industrial and culinary value. Mr. Neil Goldsmith, CEO, explained that the company started with a traditional focus on drug development, but three years ago switched gradually to nutritional biotech, aiming at high-value food ingredients such as flavorings and spices that cannot be produced through synthetic chemistry in a cost-effective manner. Evolva's technology is also being applied to the search for cosmetic components, such as natural pigments and colorants, yet the company still maintains a toehold in its original pharma commitments.

EVOLVA'S STRATEGY FOR MOLECULAR DEVELOPMENT

Evolva uses a yeast-based procedure to optimize the pathways for expression of small molecules. This approach is quite different from the conventional tactic that dominates the pharmaceutical and chemical industries. The Evolva technology uses yeast cells programmed with gene libraries in which billions of combinations are expressed. These combinations can be tested by subjecting cells to a selective process in which the most efficient biosynthetic pathway for producing the target is favored. The rare cells that produce the desired compound or ingredient most readily can be detected by fluorescent reporter signals, and hundreds of these candidates can be set aside and the process repeated.

Goldsmith explained Evolva's decision to move in the direction of nonpharmacological molecules. At the company's inception, the focus was on various drug candidates, and nonpharma compounds were not a high priority. "However, we received a lot of interest from companies outside the pharma sphere, notably a small company, Abunda," he stated. "Initially we viewed these inquiries as tangential to our main mission of drug development, but then we realized that what they were proposing would fit our technology better. There are no risks brought about by an adverse clinical outcome, there is a much shorter timeline of three to five years, and the cost to market is considerably less. So based on these factors, we decided this was a better business proposition. But it did not arrive as an overnight revelation; we started several years ago talking about what other ingredients we might go after."

In considering the last few years of gradually turning the company in a new direction, Goldsmith continued, "In retrospect, reinventing the company looks obvious, but it didn't look obvious at the time, and it certainly didn't look obvious to our investors, so we had to persuade them that this change of direction was appropriate."

"It was a very big decision. I am amazed that we were able to pull it off. We had to convince a number of people that we weren't completely mad, but rather the original thesis was flawed and we needed

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- Solid Dose Antibiotics
- Sterile Antibiotics
- Solid Dose
- DiffCORE®
- Liquids Dispensing Technology
- Inhalation
- BioPharm
- Foams
- Liquids
- Topicals
- Suppositories

North America

1. US: Solid Dose, DiffCORE®, Inhalation, BioPharm
2. Canada: Clean Liquids, Solid Dose, Foams, Liquids,Topicals
3. Mexico: Solid Dose Antibiotics, Solid Dose, Liquids

South America

4. Brazil: Solid Dose, Liquids,Topicals
5. Argentina: Solid Dose, Liquids,Topicals

Europe

6. Ireland: API
7. UK: Antibiotics API, API, Steriles, Clean Liquids, Solid Dose Antibiotics, Liquid Dispensing Technology, Liquids, Topicals
8. Spain: Clean Liquids, Solid Dose, Inhalation
9. France: Solid Dose Antibiotics, Inhalation, Liquids
10. Italy: Steriles, Sterile Ampoules, Clean Liquids, High Containment Solid Dose, Sterile Antibiotics
11. Poland: Oral Solid Dose, Topicals, Suppositories

Middle East & North Africa

12. Algeria: Solid Dose

Asia & Australia

13. Singapore: Antibiotic API, API
14. China: Solid Dose Antibiotics, Solid Dose, Liquids
15. Japan: Solid Dose
16. Australia: API, Inhalation

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to change it. So we built our arguments based on financial markets and technical analysis. Because we had already negotiated deals in the space, we were able to reassure skeptics that there was genuine interest in the specialized nutritionals marketplace. The fact that companies such as Nestlé were making moves in this direction helped to show that very large corporations were comfortable with this concept. Other companies, including DSM and Unilever, are moving in that direction, but as a Swiss-based company, it is fair to say that Nestlé had the most impact on our thinking."

Another problem that Goldsmith had to confront was the mindset of many venture capital investors and some members of his board. "Because it's conventional wisdom that the money for biotech is in therapeutics, and that was the space most of them knew, they were pretty uncomfortable with the change. Their argument was, 'Why plunge off into an unknown area which would appear on the face of it to have much less blockbuster potential?' Fortunately we had people who knew and understood this commercial landscape. Convincing the staff to adopt the concept was the easy part, because we didn't have to develop new technology."

"During the interim, we inevitably looked a bit muddled. So we talked to a cross section of people, including customers and industry consultants over an extended time frame to stress-test our ideas. We accomplished this by constructing best case/worst case scenarios for various outcomes on both our current and new strategies and looked at what it took for one to beat out the other."

Goldsmith believes that while the newly designed game plan won't yield multibillion dollar drugs, the company will achieve a high level of consistent success and return on investment.

EVOLVA CONSIDERS A RANGE OF POSSIBLE MOLECULES

One of Evolva's major projects is Stevia, a plant that produces a popular sugar substitute. Although economic considerations are fundamental for any profit-based enterprise, Goldsmith said the company is also committed to generating products that have direct benefit to humanity. "One of the most important conversations we had in the midst of this transition was explaining to our employees that getting Stevia to market would have a major impact on world health, affecting millions of people through improved nutrition."

In addition to Stevia, the company is pursuing a number of food components including saffron, vanilla, resveratrol, and pomecin. When asked how the company decided what products to go after, Goldsmith replied, "We built a standardized assessment plan to match the products to the demands of the marketplace. An internal team contributed to building the criteria. With this accomplished, we implemented it by prioritizing all potential projects against these criteria using the usual market and technical analyses. Some of these, however, are proprietary, and I'm not able to provide additional details at this time."

IMPLEMENTING A NEW STRATEGY

Goldsmith stated that the pivotal point in deciding to move the company away from pharma products occurred when Evolva acquired Abunda, a San Francisco-based company funded through venture capital. Abunda developed food ingredients, taking advantage of biochemical analysis of their nutritional components. The company's long-term aim was to push forward unmet global needs in dietary management.

Evolva and Abunda had collaborated since 2009. One part of this partnership, using Evolva's proprietary technology, succeeded in making the key components of Stevia via fermentation in yeast. This process bypasses the complex needs associated with the traditional cultivation, processing, and refining of Stevia plants and allows the Stevia glycosides (the chemical substances responsible for the plant's sweetness) to be produced directly.

The value of the global sweetener market is currently estimated at $78 billion, with sugar far and away the dominant component, commanding approximately 85 percent of sales. Within this commercial space, Stevia-based sweeteners are the fastest-growing segment, reflecting increasing consumer demand for health food products that are low-carbohydrate and low-sugar. By enabling the introduction of new sweetener products with compelling benefits for consumers, pure fermentation-derived Stevia components can dominate an important part of the overall sweetener market.

NEIL GOLDSMITH
CEO of Evolva

The original Stevia products had a bitter, licorice-like aftertaste which can be eliminated by selecting the appropriate glycosides. So by producing the individual components, Evolva can generate a much better-tasting sugar substitute that will fulfill the needs of the consumer.

While it is clear that the public will not accept veggie burgers or other poorly made, ersatz food substitutes, Evolva may be on the wave of a revolution in food production. In recent months PayPal cofounder Peter Thiel's company, Hampton Creek Foods, has developed plant-based substitutes for meat and eggs that are realistic enough to attract funding from Bill Gates, among others.

Much of Evolva's future will depend upon existential considerations, such as the public's willingness to accept innovative approaches to nutrition, over which the company has no control. Goldsmith considered the long-range implications of his company's transition. The value of Evolva shares suffered during 2011 and 2012, possibly a reflection of the market's apprehension of a unique business model applied to a distinctive market.

But he is sanguine: "During 2013 they have recovered to the point where we are back above the price at which we went public. And I think this is in large part because investors eventually have come to understand the change we have made. We'll see what the future holds." L

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How Patent Translation Can Affect Your Bottom Line

MATTHIAS STEIERT

Matthias Steiert is cofounder of Afaf Translations specializing in language services to the pharmaceutical industry. He holds a Ph.D. in biochemistry from the University of Basel, Switzerland.

On average, more than 750 patents are granted each day, or about one patent every 2 minutes, and of those, more than half are of non-U.S. origin. The number of U.S. patents granted to foreign inventors has increased by nearly 10 percent per year during the past two decades. Every country has different patent laws and patent application requirements, so inventors must apply for a separate patent in every country in which they intend to make, use, or sell their product, or simply to maintain IP protection. The World Intellectual Property Organization (WIPO) reports that in 2012 global patent filings increased at their strongest rate in nearly two decades — growing at 9.2 percent. China topped the ranking for both the source (filings by China) and destination (filed in China) for the four types of IP (copyrights, trademarks, patents, and trade secrets).

Since many patents these days are filed in many countries, they need to be translated. With more than 5,000 patents being filed every day, companies need to find an efficient and cost-effective way to assure quality and quick turnaround of the patent application/translation process.

IMPROVED TRANSLATION TECHNOLOGY = SAVINGS

By improving technology that helps the translators do their work, patents can be turned around faster. One significant source of savings stems from technology that enables translation companies to charge less based on repeated text. At first glance, the idea that repeated text is a notable factor in the cost of patent translation may seem irrelevant. After all, inventions are supposed to be unique. One might guess that the text supporting the patent would be as unique as the invention itself, making cost savings from repeated text marginal. However, since companies frequently file multiple patents pertaining to the same industry or product area, these filings often use similar wording. Patents also have boilerplate statements, meaning there is some repeated text. Even if previously translated material comprises only a small fraction of the translation, those fractions add up to a substantial amount, especially for translation projects that can cost millions of dollars.

Translation technology is useful not only for improving cost efficiency, but also for managing terminology. Proper management allows for the consistent use of correct terminology by all translators, enabling many people to work on a project and still maintain the same degree of accuracy. During translation, technology can pull terminology from predefined lists and present these translated terms to translators, thus improving productivity. The automated use of those terminology lists greatly contributes to the linguistic quality of the project by helping translators be more consistent not only within one project, but also from one project to another.

Moreover, translation memory technology aids the preservation of formatting codes and layout information, reducing the time a desktop publisher needs to ensure that the translated document looks like the source document. When skillful translators use this technology, their clients reap the benefits of a more accurate translation.

STREAMLINING TRANSLATION SERVICES

Often, companies don't want to separate patent translation from patent filing. They want a more streamlined process that includes one — preferably smaller — invoice and less of a workload for internal staff. Consequently, some translation companies are now subcontracting with patent agents who take care of the filing.

The translation industry is not done evolving; new challenges are already on the horizon. Patent offices around the world are trying to find ways to make patent filing less expensive and more efficient. This has led to the London Agreement. Under this agreement, companies in certain European countries are allowed to file patents in English. This agreement has resulted in decreased patent filing costs. Although similar agreements could spread to other countries, it took more than 10 years for the London Agreement to become a reality, and there are still many European countries, such as Spain and Italy, that are not willing to relinquish their rights to require patents in their own language.

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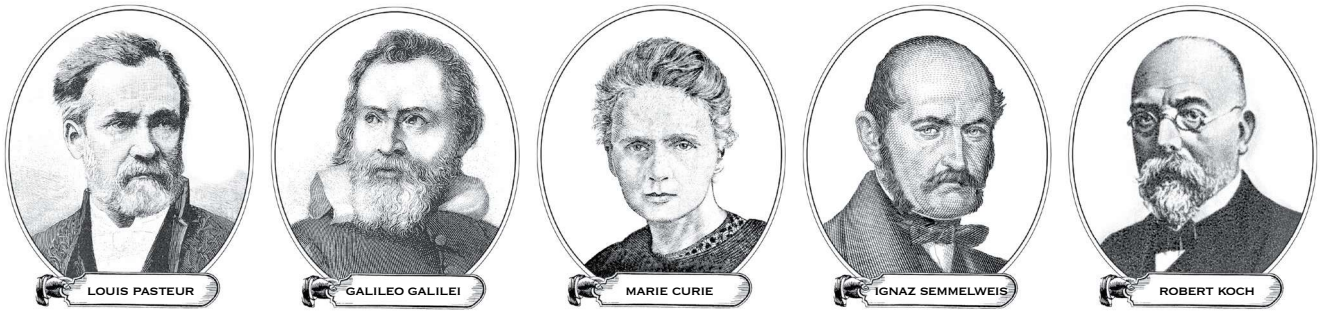

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Contact Frauke Schorr at frauke@centeredleadershipinstitute.com.

4 Power-Thinking Strategies Of Centered Leaders

FRAUKE SCHORR, Ph.D.

The life sciences world has enjoyed many decades of solid success, manifested in a culture of a fairly stable, predictable environment. Unfortunately, pace and predictability in the industry are changing significantly, challenging also the typical work culture. We are looking at leaders within companies to change the communication culture among their teams to become more efficient and agile in decision-making processes, exchanging information, and moving things forward at an increased pace.

This is a challenging endeavor, as leaders often grew within the industry and found comfort with established ways. The most powerful step toward cultural change, however, is for leaders to change their own behaviors.

We conducted an eight-year study based on observation and interviews of successful entrepreneurs and leaders. The study showed specific thinking habits that are indicators for the success of these people. It has been said that "Successful people are simply those with successful habits." Understanding the success patterns of others helps us to review and start applying the same thinking habits ourselves. The insights from this research, coined as "Centered Leadership" principles, may give leaders in the life sciences sector a new mental and behavioral approach for their organizations:

1 Expertise Vs. Curiosity

When a large number of highly educated people work together, it can often create a culture of demonstrating expertise rather than displaying curiosity and a willingness to grow and stretch. Centered Leaders ask: "What can we learn, and what else is possible?" rather than "What can I teach?"

2 Attachment To Outcome Vs. Present-Moment Focus

In a very science-oriented environment it is not unusual to focus on the end goal and try to draw a line toward the outcome. Yet, in a fast-changing environment, this can lead to missed opportunities. Centered Leaders in the study first ask, "What is needed right now?" and only then do a directional check, "Does this align with our overall goals?"

3 Leading From The Head Vs. Head-Gut Alignment

In the business world in general, and especially in a culture that is heavily rooted in logic and science, decisions are often solely made from a rational standpoint based on hard evidence. Centered Leaders say, "Decision making is certainly important from logic. But it is also important from your gut. Often logic gives you the answer, but your gut makes you stop and analyze deeper. For best decisions, head and gut need to be aligned."

4 Clarity Of Personal Strengths And Passions & Leveraging Others To Offset Limitations

Successful leaders in the study had a high level of clarity about what they are good at, what they care about, what gets their energy moving, as well as their weaknesses. They consciously position themselves to leverage their team members' talents, knowledge, and interests to complement their own skills and create sustainable success.

Adopting thinking patterns of highly successful leaders can help pharmaceutical and biotech leaders to model more efficient ways to deal with an increasingly fast-paced environment for themselves and their teams. Reviewing your own thoughts and beliefs, and adopting proven successful ones as needed, are powerful steps toward change.

Change is inevitable. Leaders cannot just demand it from the organization, they have to embrace it for themselves to truly lead.

Frauke Schorr, Ph.D., is founder and principal at the Centered Leadership Institute, a firm that helps leaders and teams gain high performance skills. She can be reached at frauke@centeredleadershipinstitute.com.

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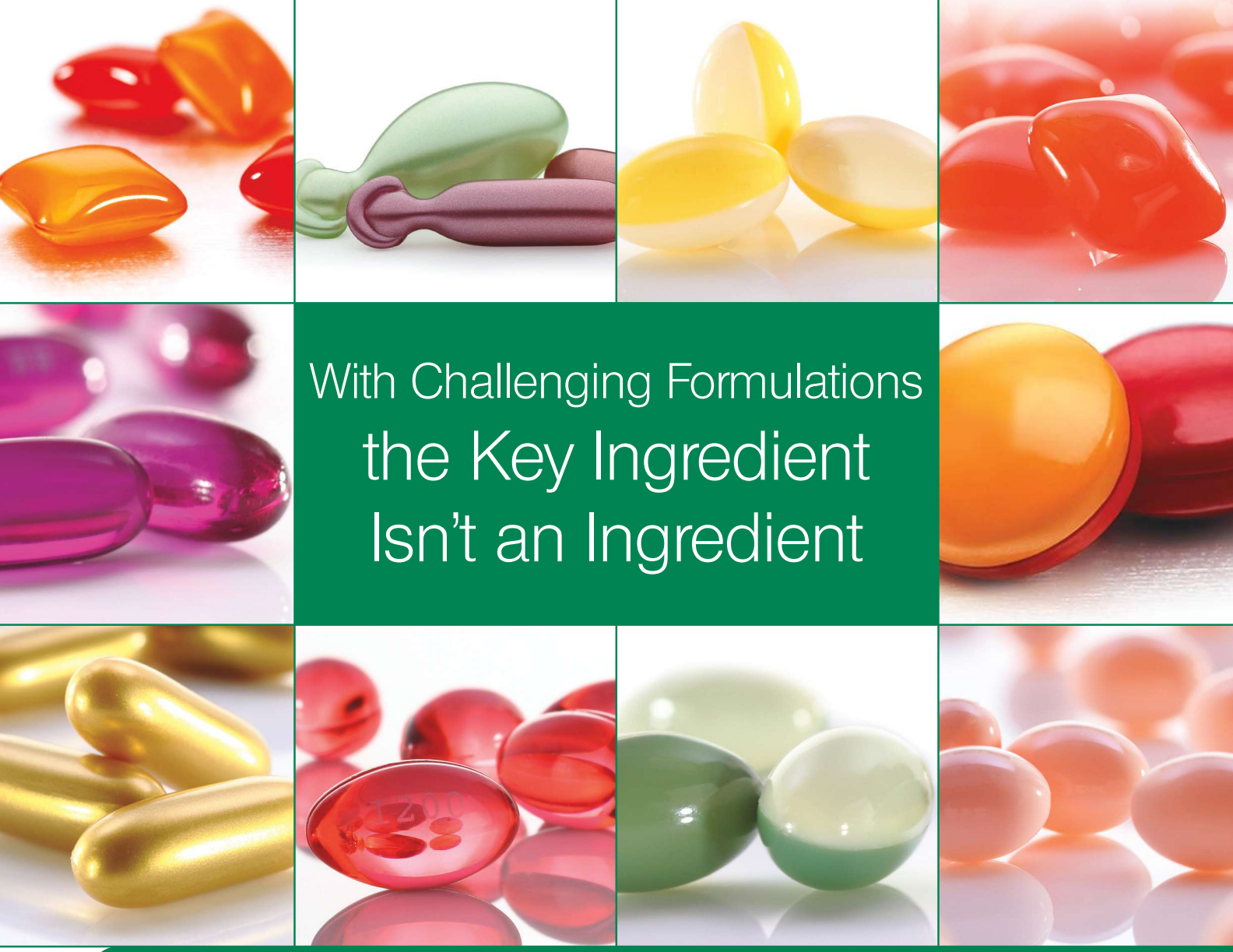

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