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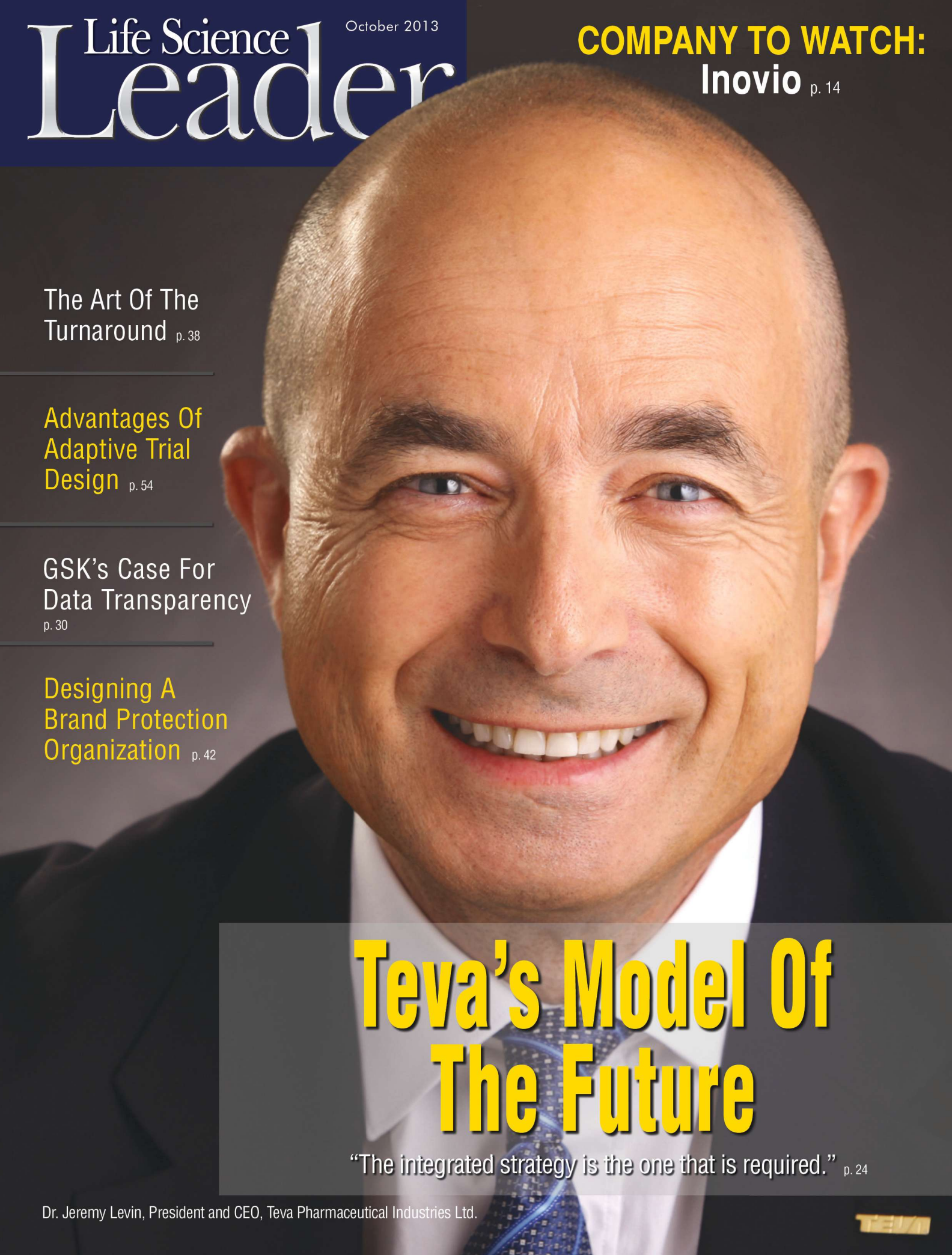

Teva's Model Of The Future

"The integrated strategy is the one that is required." p. 24

Dr. Jeremy Levin, President and CEO, Teva Pharmaceutical Industries Ltd.

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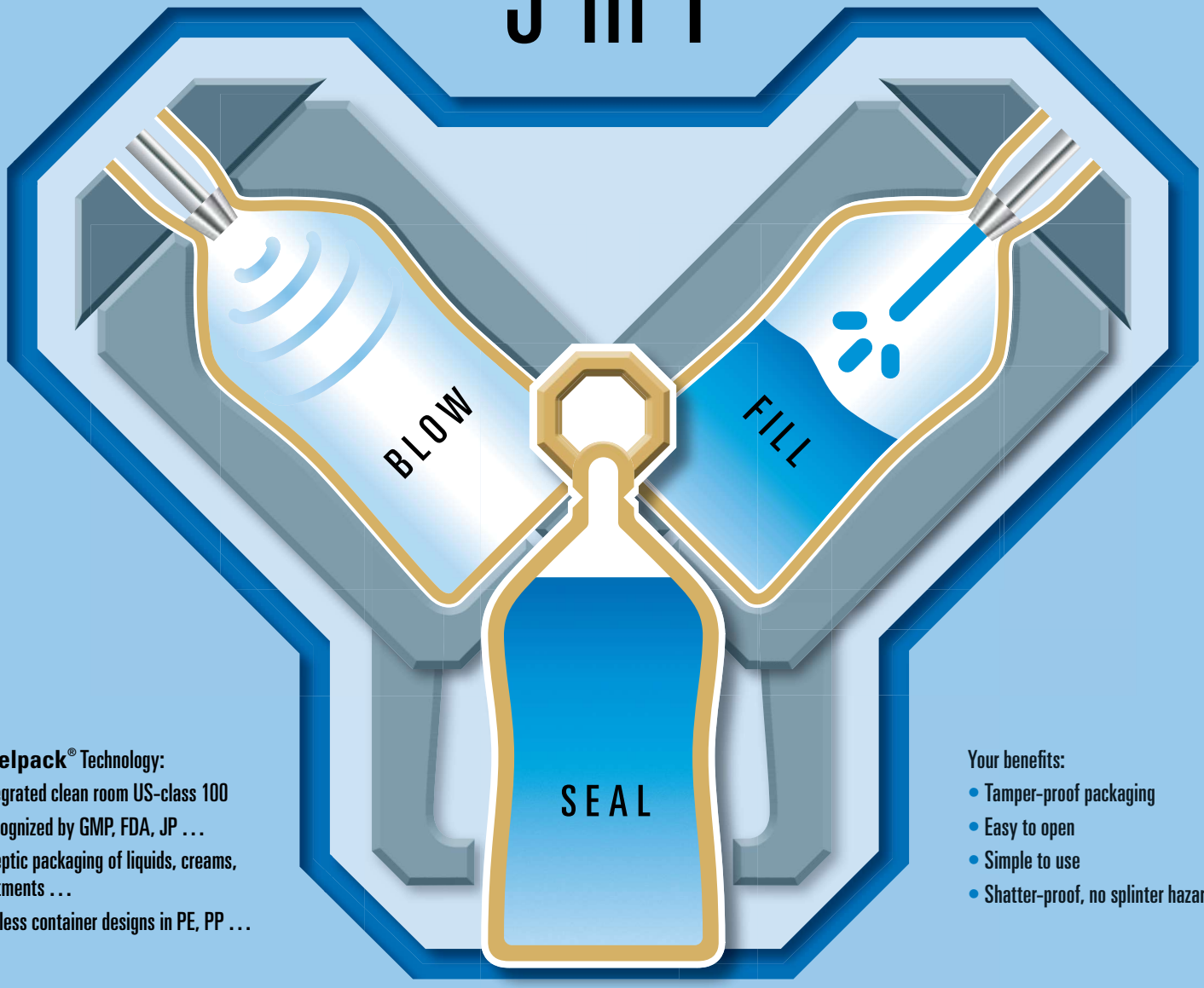

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24 FEATURE: TEVA

An instructive view of Israel's global powerhouse in traditional pharma, generics, and "special generics" at a critical time for the company and its leader, Dr. Jeremy Levin, president and CEO

October 2013

DEPARTMENTS

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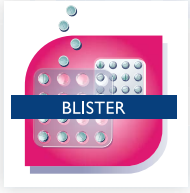

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EDITOR'S NOTE

Drug Take-Back Programs – Coming To A Municipality Near You

The drug industry is already the primary funder of the FDA's operational budget through the payment of user fees. The FDA's proposed 2014 budget, a whopping $4.7 billion, includes a proposed increase of $821 million, 94 percent of which is to be funded by drug companies. While some believe self-funded regulatory agencies to be a good thing, others feel it allows industry to have major leverage over FDA policy decision making. My concern — what precedent does this set for state and local governments to create similar self-funded regulatory initiatives?

In July 2012, Alameda County, CA, passed an ordinance making manufacturers responsible for unwanted medicine collection. Just under one year later, California regulatory lawmakers moved forward with making the practice a statewide initiative. The idea is to prevent unused drugs from endangering children from accidental overdose, to prevent the potential of drug abuse, as well as to decrease the likelihood of these medicines getting into the waterways and environment by being flushed or thrown away. The bill (SB-727) introduced by Hannah-Beth Jackson (D) would require drug companies to fund the collection, transportation, and disposal of unwanted medications from residential sources. If passed into law, the "Medical Waste: Pharmaceutical Product Stewardship Program," as it is formally called, would require pharmaceutical manufacturers selling drugs in California to launch by January 2016 either an individual or joint collection program with enough drop-off locations so residents never have to travel more than 10 miles to rid their medicine cabinets of unwanted pharmaceuticals. Further, drug companies would not only pay all operational costs, but would also pay a fee to the California Department of Public Health to finance the program's oversight and law enforcement. Finally, the law would prohibit manufacturers from passing the cost onto consumers. I understand the importance of environmental and consumer safety. However, I don't understand why the pharmaceutical industry has to create, let alone fund, an infrastructure when one already exists in the form of your friendly neighborhood pharmacy.

Estimates place the number of pharmacies within the United States at 67,000, with more than half of these being located within other facilities, including grocery and department stores. California has the most pharmacies of any state (5,560). Doesn't it seem fairly reasonable that if consumers are capable of picking up prescription medications, then they would be just as capable of dropping off a few unwanted medications? Not according to U.S. District Judge Richard Seeborg. On Aug. 29, 2013, Seeborg ruled in favor of Alameda County, on a lawsuit brought forth by the pharmaceutical industry claiming the drug take-back ordinance as being unconstitutional. I fully expect industry to file an appeal. In the meantime, perhaps PhRMA, BIO and the Generic Pharmaceutical Association (GPhA) should take a page out of the battery industry's playbook and develop its own take-back initiative.

A nationwide approach to taking back medications, proactively managed by the pharmaceutical and biotech industries, could prevent companies from having to embark on the daunting task of trying to fund and manage possible drug take-back ordinances developed by even the smallest form of local government.

Rob Wright
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Want to find out what's on the mind of our chief editor, Rob Wright? Check out his blog on our website where he writes about a variety of topics such as recent shows attended, conversations with industry experts, and irritating business buzzwords.

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ASK THE BOARD

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Q: What market trend do you think will accelerate single-use manufacturing adoption?

The bioprocessing industry continues to expect better control and connectivity over its single-use devices. Standardization is a broad theme in bioprocessing that will facilitate segment growth through plug and play operations and will reduce worries over getting stuck with a sole supplier. Standardization also will permit sensors and software to effectively monitor, communicate, and automate to optimize the process. This will simplify the regulatory process. Most suppliers are already working on elements of these problems. It will take time to adopt an industrywide, open-architecture format and design process while also facilitating cross-industry agreement. Our research indicates that 44 percent of decision makers are demanding better bags and connectors. Nearly 40 percent want improved sensors for bioprocess monitoring. Sixty-four percent fear getting stuck with a single vendor due to the inability to connect devices. Lack of standards for testing is a key factor holding back adoption.

Eric Langer
Langer has over 20 years' experience in biotechnology and life sciences international marketing, management, market assessment, and publishing. He has held senior management and marketing positions at biopharmaceutical supply companies.

Q: What are some pitfalls to avoid when conducting a clinical trial in a developing market, e.g. Africa?

Clinical trials in any country with underdeveloped healthcare delivery systems can require upgrading your lab and clinic infrastructure, training personnel in good clinical practice, and designing creative data management and storage processes. Labs with skilled personnel and expertise in specific clinical-specimen testing protocols are frequently in short supply. Consistent electricity (and backup sources) for clinical study product and specimen storage is a problem in rural sites. Telephone/fax lines and Internet service in many rural areas are often absent or unreliable. Transportation is usually required to bring product in and samples out of field locations, as well as to bring study subjects to the site. Site personnel should have no language barriers with either subjects or study sponsors and should understand the true meaning of "informed consent." Everyone should be aware of (and respect) local customs and practice.

Carol A. Nacy, Ph.D.
Nacy is CEO of Sequella, Inc., a private company that develops new anti-infective drugs. She was formerly CSO at Anergen and EVP/CSO at EntreMed. Prior to her business experience, Dr. Nacy directed research in tropical infectious diseases at Walter Reed Army Institute of Research.

Q: How will the Supreme Court decision that naturally occurring genes are not patentable impact the development of precision diagnostics?

This decision was seen as good news by many. It may open up new clinical testing options and allow companies that had been precluded from offering tests using patented genes to now step in. The public may benefit with lower-cost products as competition and limiting pricing pressure increase. There are early signals that prices may already be falling. Lower prices may enhance insurance coverage for genetic tests and increase access to important precision diagnostics. However, the court ruling also noted that synthetic cDNA (complementary deoxyribonucleic acid) can be patented (a synthetic version creates something novel), and it cited the importance of "methods patents" in providing protection. How much this will amount to is unclear as many gene patents are set to expire soon anyway.

Mark Pykett, Ph.D.
Pykett, is the president and CEO of Navidea Biopharmaceuticals. Previously, he has held numerous senior executive positions at both public and private companies.

"We needed a high-quality pharmaceutical checkweigher to present data sync on our demo line; we chose Thermo Scientific's Versa Rx to demonstrate this critical capability."

- Glenn R. Siegele, President
Omega Design Corporation

Scan to see what else Glenn said...

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When it came to finding the right partner for integrating key checkweighing equipment into their pharmaceutical demo line, Omega Design Corporation chose Thermo Fisher Scientific. Omega Design's dedicated serialization lab required a reliable solution to demonstrate data sync on their line; Thermo Fisher Scientific rose to the challenge, delivering a reliable, accurate solution.

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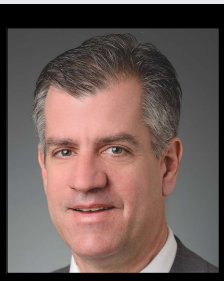
Raising Co-Pays On Low-Income Beneficiaries' Drugs Not A Solution

Raising the cost of a good or service results in less consumption of that good or service. That fundamental economic principle makes it hard to understand why the Medicare Payment Advisory Commission (MedPAC), which advises Congress on Medicare payment policy, has recommended increasing cost-sharing on low-income Medicare beneficiaries for their brand name drugs dispensed through the Part D program.

MedPAC proposes doubling co-pays for preferred brand name drugs from about $3 per prescription to over $6, on the argument that low-income subsidy (LIS) beneficiaries – those with incomes below $17,000 — do not have sufficient incentives to choose generic drugs. But that premise is unfounded: Generic utilization between LIS beneficiaries and non-LIS beneficiaries is similar — 75 percent versus 79 percent in 2011 (the most recent year data is available). And generic utilization has soared for both groups since the inception of the Medicare drug benefit.



John McManus,
The McManus Group
jmcmanus@mcmanusgrp.com

The real impact would be less patient adherence to needed drugs that do not yet have a generic substitute on the market. Harvard economist Michael Chernew (now vice chairman of MedPAC) published a study a few years ago that demonstrated medication adherence is more likely to decline when co-payments increase for individuals in low-income areas. Since considerable research suggests that adherence to medications is an important driver of good clinical outcomes and key driver of total costs, for patients with chronic diseases, Chernew concludes that "increases in patient out-of-pocket expenditures for prescription drugs is likely to exacerbate health disparities."

Even small increases in cost-sharing can significantly reduce prescription drug adherence for low-income beneficiaries for two reasons:

1. Low-income beneficiaries tend to be sicker and therefore need more prescription drugs.
2. Any cost increase for patients with very limited resources makes it much more likely they forgo their prescriptions because they are least able to afford them.

Whether patients should be dispensed a generic drug when a physician prescribes a substitutable brand-name drug is not really in debate. A more complicated challenge is whether a patient should be coerced into taking a generic drug in a therapeutic class when the prescribed brand-name drug has no generic available.

For example, although most drug classes for treating psychiatric conditions include generics, beneficiaries with these conditions are particularly vulnerable to treatment disruptions. A study by Morden et al. published in *Health Affairs* found that "In treating mental illnesses, patients and physicians typically work through trial-and-error processes to identify the best medication or medication combination." As such, formulary enforcement that requires patients to be switched off a brand-name drug that is working for them to a chemically different generic drug would create serious safety and efficacy concerns.

For decades the Congressional Budget Office (CBO) adopted a static view of preventive benefits when evaluating the fiscal impact of legislation. For example, CBO only counted the increased costs of covering prescription drugs when Medicare Part D was enacted and making preventive benefits free when the Affordable Care Act was enacted. The reduced costs or savings from keeping patients on drug regimens and out of hospitals and other acute settings was not considered.

A sea change occurred in November of last year, when CBO released a pivotal white paper which acknowledged that a 1 percent increase in the number of prescriptions filled by beneficiaries would cause Medicare's spending on other medical services, such as hospital care, to fall by roughly one-fifth of 1 percent. Conversely, a policy that resulted in a drop in prescriptions filled would result in a medical cost increase of the same proportion. The estimate applies only to policies that directly affect the quantity of prescriptions filled.

Raising co-pays on low-income beneficiaries for their brand-name prescription drugs should certainly trigger this more dynamic view of the world! Thus, increasing LIS co-payments would not only put safety of low-income patients at risk but result in higher medical spending per Congress' official scorekeeper.

WHAT ARE THE ALTERNATIVES TO PRODUCE SAVINGS FROM DRUGS PROVIDED TO LIS BENEFICIARIES?

The Obama Administration has proposed applying Medicaid rebates to drugs provided to LIS Medicare beneficiaries. As

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I detailed in a previous column, this would undermine the market forces that have successfully controlled cost in Part D, result in pricing distortions and cost-shifting to employers, veterans, and other groups, and could result in shortages seen in other parts of Medicaid.

A preferable solution to either higher cost-sharing for LIS beneficiaries or Medicaid rebates on that population would be to strengthen the competitive forces that have already contained costs in Part D.

Currently, Part D plans receive a full subsidy up to the average bid of all plans in a Part D region. That means plans can maximize their revenue if they bid at or just below the average. They lose potential revenue if they bid below the area benchmark and lose their opportunity to cover these beneficiaries if they bid above the benchmark. But this formula has resulted in shadow pricing, where plans bid as close to the benchmark as possible without exceeding the benchmark.

Congress could make the LIS program far more efficient if it rewarded plans for bidding low. For example, it could auto-assign more LIS beneficiaries to the plans with the lowest bids; e.g. 50 percent for the cheapest plan, 30 percent for the second cheapest plan, and, 20 percent for the third cheapest. Presently, beneficiaries who do not affirmatively select a plan are auto-assigned randomly, and there is little incentive to bid low and deliver healthcare more efficiently.

The old ways of approaching healthcare policy no longer work. Conservatives generally would like to impose more cost-sharing so there is more "skin in the game." Liberals look to price controls, such as arbitrary Medicaid payment rates (i.e. rebates).

Competition is a better solution. Congress should be more creative in unleashing competitive forces so that beneficiaries and taxpayers alike can benefit from a more efficient system.

1% increase in number of prescriptions filled = 0.2% reduction in Medicare spending on medical services

CBO: Rx Use Reduces Healthcare Spending

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

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By Wayne Koberstein, executive editor

Inovio

A "breaking news" partnership deal with Roche highlights the stakes for this key player in DNA vaccines, as well as presaging the role of combination cancer immunotherapies.

SNAPSHOT

Inovio is developing DNA-based vaccines and its Cellectra Electroporation Delivery Technology platform in multiple disease areas — therapy for cervical, prostate, breast, and lung cancers and Hep B & C; and prevention of HIV, flu, and malaria — with the combined support of the U.S. government, the stock market, and numerous research grants.

LATEST UPDATES

- Sept. 10, 2013: Announces Research Partnership with Roche worth up to almost $0.5B
- Summer 2013: Positive results from animal studies for vaccines and electroporation in HIV, malaria, tumors, and influenza

J. Joseph Kim, CEO

WHAT'S AT STAKE

On the eve of this report, Inovio announced its massive partnership with Roche, giving us a special opportunity to spotlight a company at a major juncture. I had already initiated an exchange with the company's CEO, J. Joseph Kim, when the announcement came, so I quickly added some questions related to the partnership and its implications for the development path of Inovio's DNA therapeutic vaccines and electroporation delivery platform. Landing a deal of this magnitude with a Big Pharma raises the question: What is so special about this vaccine company?

"We have generated best-in-class immune responses in both animal models and humans," says Kim. "These are highly competitive, large market areas in which we have developed a potent and safe platform of clinical products, that based on our data to date, would be competitive with any other approach to immunomodulation."

Those same areas have also defeated many other contenders. But Kim gains confidence from the immune response, specifically T-cell response, to Inovio's products and platform, as well as from the "validation" represented by the many grants and investments supporting the company, now capped by a partnership bound to capture much awe and respect. The delivery platform addresses a common failure point for DNA vaccines — overcoming millions of years or so of evolution in cells' ability to resist entry of foreign materials into the nucleus — with proprietary intramuscular and intradermal electroporation devices.

Kim says the company has carefully selected the many areas and indications for which it is developing vaccines, based on the absence of existing or alternative treatments. For example, the lead program, VGX-3100, addresses cervical cancer, an HPV-associated disease where no other option exists but a surgical procedure. "As a science-based company, the science told us that developing a vaccine against HPV-associated diseases is a viable path."

Inovio has managed the risks and costs of development by "establishing a broad portfolio of vaccines and immunotherapies," Kim says. "Our platform allows us to pursue both antibody targets and T-cell targets across a broad range of diseases and conditions. We might be the only immunotherapy company that is pursuing both sets of targets — and that spreads risk across a broad and diverse portfolio."

To what extent will the Roche partnership constrict development plans for the affected prostate cancer and Hep B programs? Kim says only that the deal terms specify "conventional development-based regulatory and commercial milestones." But the partnership also reveals Roche's strategic recognition that the future of cancer immunotherapy depends on combinations of multiple agents.

"Past successes for drug treatments for HIV and HCV suggest that a combination therapy might be the best strategy for an effective cancer immunotherapy," says Kim. "Early results from the checkpoint inhibitor studies demonstrate that taking the brakes off the T cells is an important step to an effective cancer immune therapy. However, 25 years of T cell immunology studies support that active immune therapies to accelerate the specific production of T cells using a therapeutic vaccines approach could further enhance the impact of cancer immune therapy. Inovio is leading the path for the latter part of this winning formula."

VITAL STATISTICS

- Employees: 60; Headquarters: Blue Bell, PA
- Finances: Cash, cash equivalents & short-term investments: $23.6M; Additional cash raised: $11.4M; NYSE Listing: Issued & outstanding shares: 190.8M (Recent $2.55/share); Market Cap: $486.5M
- Research partnership funding: Roche $412M license for prostate cancer and hepatitis B DNA therapeutic vaccines.
- Other partners: Merck, NIH, NCI, HIV Vaccines Trial Network, U.S. Military HIV Research, U.S. Dept. of Homeland Security, PATH Malaria Vaccine Initiative, and Universities of Pennsylvania, Southampton, and Manitoba.

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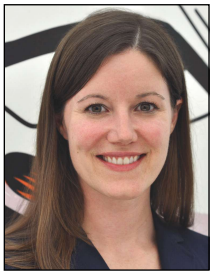

OUTSOURCING INSIGHTS

API Manufacturing: Strategic Partnering Preferences With CMOs Vary Among Small-Molecule, High-Potency And Biologic API

By Kate Hammeke, director of marketing intelligence, Nice Insight

Research from Nice Insight's pharmaceutical and biotechnology outsourcing survey has shown that buyers of outsourced services have differing viewpoints when it comes to strategic partnerships. In previous columns, we've explored how company type (Big Pharma vs. biotech) and phase of development (CRO activities vs. CMO activities) factor into a buyer's desire to form a strategic partnership. In addition to these factors, we've observed from the data that the type of manufacturing project also impacts strategic partnering preferences.

Nice Insight compiled the data collected from strategic partnering surveys over the past year that relate to outsourcing commercial-scale drug substance projects in three categories — small-molecule API manufacturing, high-potency API (HPAPI), and biologics (large-molecule API) — to see if there are any noteworthy differences in how these buyers think about strategic partnerships with contract manufacturers.

Across all three API manufacturing categories, buyers of CMO services iterated that roughly one-quarter (26 percent) of outsourced projects are allocated to strategic partners. Despite expressed interest in forming strategic partnerships, the bulk of projects are still allocated to tactical service providers (37 percent to 40 percent), followed by preferred vendors (34 percent to 37 percent). Interestingly, respondents showed higher levels of interest in forming strategic partnerships with high-potency API and biologics manufacturers than they did with small-molecule manufacturers (36 percent and 35 percent very interested as compared to 25 percent, respectively).

There was some correlation between a buyer's interest level in a strategic partnership with an API manufacturer and the likelihood that a tactical provider would advance from tactical to preferred provider and then strategic partner. Just as a higher percentage of respondents were interested in forming strategic partnerships with high potency and biologics API manufacturers, these types of CMOs were more likely to move up the ranks in outsourcing relationships. Sponsors indicated that HPAPI manufacturers had the greatest probability of moving from a tactical provider to a strategic partner, with 81 percent stating it is likely a tactical HPAPI CMO will advance to a preferred provider, and 84 percent stating it is likely a preferred provider of HPAPI will become a strategic partner.

As interest levels in forming strategic partnerships varied by the type of API manufacturing outsourced, it makes sense that the fundamental attributes that influence CMO selection varied somewhat as well. The attributes that are quantifiable or measurable in nature, such as geographic location or manufacturing capacity, fall under the umbrella of "hard traits." These attributes are not easily changed, nor can they be quickly changed in order to win a project. The top three hard traits that sponsors desire in a small-molecule API manufacturer are improved quality/regulatory positioning, experience, and timeliness. For HPAPI manufacturers, experience takes the top position, followed by timeliness and the CMO's financial stability. Sponsors looking to engage a CMO for biologics manufacturing prioritize experience, followed by improved quality/regulatory positioning and, in third position, timeliness.

In the research, respondents are also asked about soft traits that influence CMO choice. "Soft" traits describe the less-quantifiable characteristics that one can't necessarily provide a set of measures to assess; rather they are the attributes that relay the dynamic of the working relationship. Similar to the hard traits, there is overlap across the group, but slightly different prioritization of qualities. Good communication and an understanding of the customer's requirements were prioritized in the top three across all three API categories. High-potency and biologics outsourcers placed good communication first and understanding of the customer's requirements third, whereas small-molecule outsourcers placed understanding of the customer's requirements first and good communication second. A "willingness to go the extra mile" prioritized in the top-three soft traits for both small-molecule and biologics outsourcers (third and second positions, respectively), while high-potency buyers valued a company's reputation (ranked second) over willingness to go the extra mile.

As more API manufacturing is moving offshore — India and China currently supply more than 40 percent of the API used in the United States — knowing which qualities to look for in a supplier will help in finding the right CMO for your API manufacturing project, whether the company is in an established or an emerging market.

Outsourcing Practices		Small-Molecule API	High-Potency API	Large-Molecule API / Biologics
% of Projects Allocated to Each Type of Outsourcing Relationship	Tactical Service Provider	37%	40%	38%
	Preferred Provider	37%	34%	36%
	Strategic Partnership	26%	26%	26%
Interest in a Strategic Partnership with...	Very Interested	25%	36%	35%
	Interested	59%	52%	53%

What is the likelihood that a CMO...		Very Unlikely	Unlikely	Undecided	Likely	Very Likely	Top Box
Small-Molecule API	Who started off as a tactical service provider will become a preferred provider?	1%	4%	20%	60%	16%	76%
	Who is a preferred provider will become a strategic partnership?	1%	2%	23%	42%	31%	73%
High-Potency API	Who started off as a tactical service provider will become a preferred provider?	0%	5%	14%	62%	19%	81%
	Who is a preferred provider will become a strategic partnership?	0%	3%	13%	48%	36%	84%
Large-Molecule API	Who started off as a tactical service provider will become a preferred provider?	2%	4%	18%	56%	20%	76%
	Who is a preferred provider will become a strategic partnership?	1%	3%	21%	45%	31%	76%

Survey Methodology: Nice Insight Strategic Partnering Surveys are deployed on behalf of Nice Insight clients to a targeted group of outsourcing decision makers. The surveys are comprised of ~40 questions geared towards understanding current outsourcing practices, present and future expectations from outsourcing partners, and which traits contribute to successful partnerships. The above data includes the combined results from six studies, two in each API manufacturing category. [n=200 per study]

Walker

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

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BIO INNOVATION NOTES

Innovation In Alternative Chromatography

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

For years, many biopharma industry manufacturers have said the use of Protein A chromatography for purifying biologics (a mainstay process) isn't broken, so why fix it? However, Protein A media remains a major thorn in the side of operators due to its high cost, as well as the cost of recycling and cleaning/validation. Alternative technologies for purification of antibodies have been and are being developed with longer lifetimes and therefore, lower cost-per-unit of protein produced.

The industry continues to show significant interest in alternatives to Protein A this year, although that interest appears to have waned somewhat from prior years. Results from our 10th Annual Report and Survey of Biopharmaceutical Manufacturers (see www.bioplanassociates.com/10th) indicate that 33 percent of the industry is considering alternatives to Protein A for new production units. That's a significant step back from a range of 51 percent to 61 percent expressing such an interest in the four previous years.

Furthermore, this year 1 in 10 respondents "agreed" or "strongly agreed" that they are considering alternatives to Protein A for existing production units. Consideration of alternatives for existing production has been on a decline for four consecutive years, down from 27.1 percent expressing interest in 2009.

While fewer respondents this year claimed active consideration of alternatives, the proportion planning to move away from Protein A for existing scale-up or commercial production units over the next 12 months has remained steady. This year, 14 percent of respondents indicated that to be the case, double last year's percentage, but more in line with results from 2011 (15 percent) and 2009 (12 percent).

It should be noted that, this year, very few noted that they "strongly agree" with the statements. So, respondents don't appear to have very committed views in this area. As downstream operations improve, the industry is recognizing that, while it is open to considering Protein A alternatives, this isn't a burning topic. In addition, few viable alternatives are currently available or at least proven and documented to be cost-effective at large scale. Thus, most of the industry has not yet formed strong opinions and are sticking with Protein A products for lack of better, cheaper alternatives. The prevailing opinion, then, seems to be that Protein A works well enough.

MANY HAVE INTEREST; FEW MAKE THE SWITCH

The gap between interest and behavior when it comes to Protein A alternatives is evident in other results from this year's study. In our in-depth exploration of downstream operations, we asked respondents to indicate the various activities their organizations have engaged in to improve downstream purification operations.

Tellingly, while about one-quarter (23.8 percent) of the respondents claimed to have investigated alternatives to Protein A, just 4.8 percent said they had actually switched to alternatives. That follows a pattern seen in past years: in 2012, 21 percent indicated they had investigated alternatives, while 10 percent had made the switch; in 2011, the figures were 31 percent and 11 percent, respectively.

Aside from demonstrating that far fewer respondents switch to Protein A alternatives than investigate them, the results also show that the percentage who have switched to alternatives is in the midst of a multiyear decline.

That may not change soon. That's because CMOs appear to have less interest in switching to Protein A alternatives than innovators. This year, while a relatively equal percentage explored alternatives (23 percent for biomanufacturers, 25 percent for CMOs), no CMOs reported switching, compared to 5 percent of biomanufacturers who did so. Given that other results from our study suggest that CMOs tend to be leading indicators of future innovator trends, there's reason to believe that developers won't be flocking to alternatives anytime soon.

There are also some fascinating differences when sorting the responses into three geographic regions: the United States, Western Europe, and the rest of the world (ROW). Among U.S. respondents, one-quarter claimed to have investigated alternatives to Protein A in order to improve downstream operations, although none switched to alternatives. By contrast, while fewer European respondents explored alternatives (14 percent), a significant 7 percent switched. And finally, respondents from the rest of the world were both most likely to have investigated alternatives to Protein A (30

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percent) and to have switched to alternatives to Protein A (15 percent).

This may be due to the construction of newer ROW facilities that have enabled them to consider alternatives to legacy purification processes. Or, perhaps, ROW respondents simply have less need or concern regarding meeting major market cGMP and major market regulatory standards, with Protein A long the standard for initial mAb capture, which has allowed them to more quickly consider and adopt alternatives. But contrary to this finding, overall, ROW facilities are doing much less investigation of bottlenecks and adopting of alternative downstream technologies.

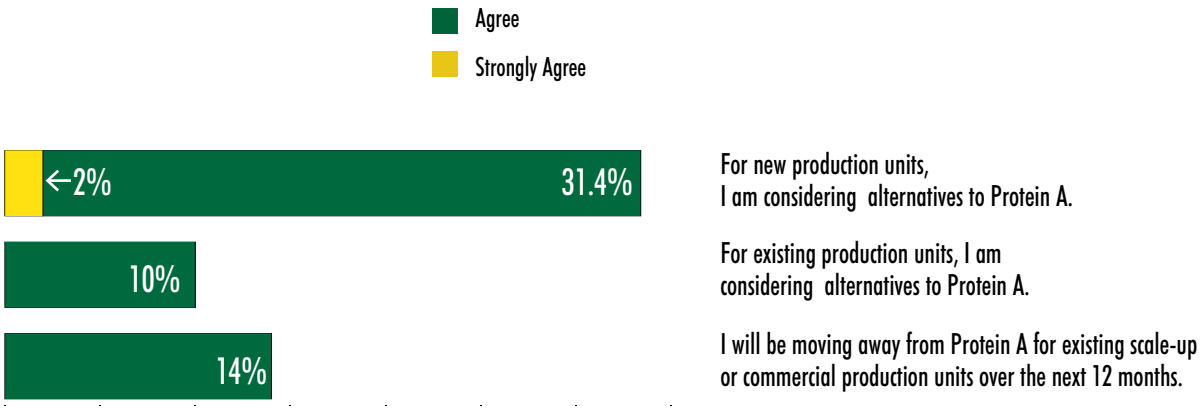
WHAT'S TO COME?

This year, we continue to see a decrease in the percentage of biomanufacturers indicating that they expect to move away from Protein A. Thus, the current dominance of Protein A products for initial mAb capture can be expected to continue. We can expect the market for Protein A products to remain stable in the near-term, other than shifts and increases associated with new major commercial products coming online.

Those products also may take some time to develop. Perhaps in response to lessening demand on the part of end users, fewer suppliers are working on Protein A alternatives, according to our study. Indeed, only 15 percent of supplier respondents cited "chromatography, alternatives to Protein A" as a top-new technology or new product development area their company is working on in biomanufacturing. That figure is down from 19 percent last year and 23 percent the year before. What's more, the $12,000 to $15,000 per-liter cost for Protein A and its recyclability makes disposable options for current products unlikely.

It's worth noting that the introduction and adoption of recombinant Protein A products in recent years in place of legacy nonrecombinant Protein A products may be contributing to a less perceived need to adopt Protein A alternatives. There's reason to believe that the industry will continue to seek alternatives to Protein A: A recent survey we conducted among a panel of hundreds of biotechnology experts found alternatives to Protein A emerging as a key micro-trend to watch. In the end, though, it seems simply that while many firms would like to avoid the high cost of Protein A affinity resin, most are reluctant to make changes to existing processes, particularly as there continue to be few, if any, proven alternatives.

Figure 1: Issues Regarding Protein A In Downstream Purification



Survey Methodology: The 2013 Tenth Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production yields a composite view and trend analysis from over 300 responsible individuals at biopharmaceutical manufacturers and CMOs in 29 countries. The methodology included over 150 direct suppliers of materials, services, and equipment to this industry. This year's study covers such issues as: new product needs, facility budget changes, current capacity, future capacity constraints, expansions, use of disposables, budgets in disposables, trends in downstream purification, quality management and control, hiring issues, and employment. The quantitative trend analysis provides details and comparisons of production by biotherapeutic developers and CMOs. It also evaluates trends over time and assesses differences in the world's major markets in the U.S. and Europe.

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

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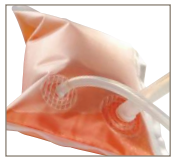

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Dr. Jeremy Levin, president and CEO, Teva

Photos by Reuven Kapuchinski

Teva Explores the Common Ground of Follow-On and Innovative Pharma

An instructive view of Israel's global powerhouse in traditional pharma, generics, and "special generics" at a critical time for the company and its leader

By Wayne Koberstein, Executive Editor

No other company could reproduce the unique history and market range of this one; the circumstances of Teva's birth and growth have been as entirely novel as its location at the commercial crossroads of Europe, Africa, and Asia. Current headlines suggest the scope of its story — everything from closed plants and massive layoffs to executive compensation "secrets" and a key patent expiration — yet the reports shed little light on the company's inner workings and new management thinking. Teva was relatively new on the scene in North America at the turn of the millennium, when I had already been covering the industry for 15 years. To many, it was the company that appeared in the top 20 pharma lists seemingly overnight.

It speaks volumes that Teva, which first grew large selling and manufacturing drugs other companies had introduced, will now be judged on how well it survives a key-product patent expiration. Fortunately, the company has since pioneered new ground that encompasses both sides of the old follow-on and innovator dichotomy. The same wave of patent expirations that threatens Teva, as it does most Big Pharmas, brings many new opportunities to this uniquely diverse company. Teva has also appointed new president and CEO Jeremy Levin, a physician and innovative pharma veteran. Levin explains the company's future lies not in producing more traditional, "Paragraph IV" generics, but "high-value generics" and innovative treatments in CNS, respiratory, and other areas. Teva is expanding its OTC products in a joint venture with P&G, and it is applying the Teva-coined, but now more widely adopted concept of "new therapeutic entities" (NTEs) — novel formulations or combinations of existing drugs designed to improve compliance and, hence, patient health.

Most of the press coverage on Teva has focused on whether it will find new drugs to replace older products in its branded portfolio. But here we look more closely at the company's strategy for dealing with a much greater and comprehensive set of changes in business and healthcare.

GROWING BY LEAPS

Levin spoke with me by phone from the company's headquarters in Petah Tikva, modern Israel's first new town, after responding to my July 2013 article, "GDUFA Sheds Light on Industry's Common Ground." In his initial note, he said, "I was particularly struck by the convergence that you described and, indeed, the thinking which articulates some (but not all) of the conceptual underpinning for Teva's transformation. At the end of the day, there is one clear imperative — the production and provision of superbly high-quality and effective medicines." Teva's "transformation" into an originator company is actually the latest in a long history of seismic changes the company has undergone since its

founding 110 years ago.

Teva's first original product to go global was Copaxone (glatiramer acetate) for multiple sclerosis (MS), launched in 1996. Copaxone may lose IP protection as soon as May 2014, and the company also faces patent losses on other branded products it markets. Levin, who joined the company as CEO in May 2012, has been under pressure from analysts and shareholders to boost the pipeline and cut costs simultaneously, speeding up the one while deepening the other. They would like to see him repeat his celebrated "string of pearls" strategy at Bristol-Myers Squibb, bringing in new products through partnering and acquisitions.

Though seemingly two different issues — industry's innovator-generics convergence and Teva's against-the-odds growth strategy — a common challenge unites them. Put simply, the industry and Teva have met at the crossroads of medical need and industrial invention. In Teva, you can see the industry's uphill struggle to bring new therapeutics into the world that help patients and give vitality to the enterprises that develop and supply them. And you can see the wide range of approaches this company is taking to meet its humanitarian and business challenges.

> **"Teva's approach to specialty products is industrial scale. You need to produce them consistently and in an industrial fashion."**
>
> Jeremy Levin, CEO, Teva

Levin gives positive credit to conventional generics for greatly widening patient access to critical medicines and lowering the cost of care. He views low prices as a key benefit of follow-on medicines and the original Paragraph IV process — by which generics makers must seek to invalidate originators' patents — as a necessary, even heroic mechanism for healthcare progress.

"America's pharmaceutical landscape was historically driven by large, high-priced drugs. Companies that introduced generics were not well-thought-of, and the large pharmaceutical companies battled against them. But in effect, the penetration of generics was initially very minimal," he says. "Now it's 83 percent, and generics have had a huge, multibillion-dollar effect in reducing healthcare costs. Today, generics are part of our life, and they will be forever."

Indeed, that seems to be the case — even if generics will not forever be the same. Levin says two main developments are forcing changes in the generics business model: greater challenges with the character and reproducibility of molecules coming off patent, and a steep decline in the value of Paragraph IV products, with dozens of companies now typically sharing marketing exclusivity for a single drug.

Both factors encourage the emergence of "high-value" generics, follow-on versions of complex medicines, and improved versions of standard medicines. Complex generics — such as injectable, liposomal, long-acting release, nasal, patch or device-delivered drugs — present real development challenges, Levin says, because it may be difficult to engineer the optimized molecule, formulate the API, or overcome other technological barriers. An essential ingredient of the new business model he describes is a company's ability to develop and manufacture complex and special products in a broad variety of types and at a scale sufficient to keep costs for company and customers as low as possible.

"Whether it's a simple generic or a complex one, high-value or otherwise, integrated generics companies like Teva are all working toward the same end — we're all basically bringing greater competition that will ultimately lead to more patient access for critical medicines," Levin says, in what he calls his "apple pie" statement. His main point highlights an objective change in the pharmaceutical/biopharmaceutical business model: Products will no longer compete only upon price, in generics' case, or upon first-to-market in the case of the original patent holders, but also upon finished-unit quality.

Levin cites Teva's "capabilities in formulation" as one of the areas where it has stepped ahead of traditional pharma in manufacturing. Advanced formulation allows the company to explore a nontraditional but medically needed form of innovation. Rather than drawing on drug discovery, it puts products through a rebirth. Its NTEs, siting on proven targets with known efficacy and safety profiles, improve on the original products with optimized formulations, new delivery technology, or even repurposed applications to address unmet patient needs.

The company's first initiated NTE project deals with HIV, where it aims to improve adherence by significantly reducing the pill burden for patients. Other targets of Teva's NTE focus include prolongation of drug half-life to reduce frequency of administration, modification of pharmacokinetic profiles to reduce side effects, converting drugs from parenteral to oral or other favorable routes of administration, drug delivery systems for special patient populations, such as children and the elderly, and drugs developed for new indications. "The model of the future is managing complexity; we can create better and better medicines which improve compliance, rather than relying on small Paragraph IV products."

So, does the new model predict the demise of the traditional mom-and-pop generics company that plowed the first ground in this field? "I believe the integrated strategy is the one that is required," says Levin. "Some individual companies will be able

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to produce a single product at a very low cost because that's all they do. The question is, will they be able to deliver high quality at the high volumes the FDA and customers demand, and can they ever do a high-complex product? It will depend on their ability to finance quality capabilities to support FDA regulations, whether they produce in the United States or import from foreign countries — that will be an essential requirement of all great producers of medicines in the future."

Teva's entry into specialty pharma also begs the question of whether smaller specialty companies will survive the competition from larger players. "Specialty companies have a very important role. Small companies and large companies can now explore alternative forms and uses of medicines in a way that hasn't happened before. But Teva's approach to specialty products is industrial scale. You need to produce them consistently and in an industrial fashion. Then you can select them from an array of choices in your armamentarium based on whether you'll get a reasonable return, have the technological capability to produce them, and know they'll benefit patients and payers."

"We globalize certain functions such as compliance, finance, legal, procurement, and R&D. We've also globalized our whole specialty medicine franchise and capabilities," says Jeremy Levin, CEO, Teva.

Levin says the company has a system for selecting and assembling a portfolio of drugs and advancing them through NTE development. It has promised to deliver 10 NTEs into the pipeline every year and, he says, will end this year well ahead of that number. "Our pipeline includes some potential blockbusters, in terms of both their value to us and their value to patients. Success in meeting our targets for the number of new pipeline projects we add each year will rapidly build a multibillion-dollar opportunity for the company, by virtue of having many different products that we know are successful, we know their pharmacological capabilities, and we know what they do for patients."

COST CONSCIOUSNESS, FLOOR TO CEILING

With all the talk about high-value, complex, and special generics, it is fair to wonder whether the sector could move away from its original cost-saving mission. Is this a bit like new cancer medicines, vaccines, and orphan drugs growing in sophistication but with price tags that empty pocketbooks and strain payer budgets?

Levin's answer is an unequivocal no. "That is why a large fundamental capability is important," he says. "You cannot raise the cost, developing more and more complex products at higher and higher prices. You must maintain access at the most affordable prices. If you don't do that, you run into a major problem. That's why I believe that scale matters. Scale matters a lot."

In addition to scale, Teva epitomizes the aggressive adoption of advanced manufacturing technologies now gaining momentum among generic drug producers to ensure product quality and gain efficiency. Levin believes the generics industry is catching up with Big Pharma on the manufacturing front and, in Teva's case, often surpassing it.

"The standards and capabilities and skills inherent in a pharmaceutical operation are now the same ones required for generics — and this is all to the good," Levin says. "I view Teva as a natural partner of the pharmaceutical base because we manufacture."

Everything said so far about branded or originator versus generic medicines applies mainly to only one market, albeit a large one, the United States. Travel outside its borders, and the clear distinction between the two nearly fades away. So when I ask Levin whether the Big Pharma execs still give his company the cold shoulder over its generic roots, although the company's business is far broader now, his response reflects a much larger, global, and historical picture of the dichotomy.

"The original antagonism that existed between the pharmaceutical industry and the generic industry was based on directly competing business models. The pharmaceutical industry had every interest to protect their franchises, whereas the generics companies were specifically attacking those franchises. But for Teva, and from my point of view, our interests have become more and more intertwined. The lack of sustainable franchises and the social pressure around healthcare economics in the United States gave us one enormous shared interest — to retain public confidence in our medicines across the board. Having spoken to the more thoughtful leaders in the pharmaceutical industry, I believe we are seeing a convergence."

TEVA'S TEAM RESHAPES

Tooling up for its innovation initiatives has affected more than technology at Teva. According to Levin, operations and management

structures have taken on new shapes to execute the new strategies.

"We globalize certain functions such as compliance, finance, legal, procurement, and R&D. We've also globalized our whole specialty medicine franchise and capabilities, but we've stayed local where local matters, with local commercial capabilities in different countries, and we've stayed regional where it's important. The United States is one big market, but once you get to Europe, you're dealing with tens of different markets and many different kinds of players."

Although Teva went through a long period of growth by acquisition, Levin says those days are over. "I am convinced the only sustainable way to grow is through internal growth — organic growth driven by great products. Targeted acquisitions can supplement that, say, to help build a portfolio in a key therapeutic area or to enter a new country, but they should not have the main role for growth in the future."

The "constellation strategy" is the term coined for Teva's supplemented organic growth approach, as Levin explains. "We weave together transactions, small acquisitions, internal programs, and alliances with other companies to create a strong arena where we will see growth in our core area of respiratory or in our core area of CNS."

Outsourcing has limits as well. Levin says the company aggressively searches for suppliers that satisfy two criteria: "They can do it better than us, and they can do it cheaper. But they must start with the better. I want high-quality outsourced capabilities across the board." He says the company does about $9 billion in procurement of outsourced programs per year, "and we've hired some of the best procurement people in the world to do it." Teva has brought in outside experts in manufacturing, especially in quality assurance and control.

A GROUNDED STRATEGY

Outside the company, opinions about Teva's future remain mixed. If you concentrate on the branded side of the industry or otherwise don't buy the argument that high-value generics can share the playing field with patented originals, you'll keep looking for the company to pull a mega-blockbuster out of the hat. If your focus is generics, you have more to hope for in Teva.

Analysts who have looked beyond the company's IP predicament or blockbuster potential generally give it high marks for basic soundness and steady growth, with a wealth of products and a thriving API business. If I were an analyst, I would render an opinion one way or the other. But I'm not.

"Observers say we are focused on the right things, but want to see how the strategy unfolds," Levin adds. "In today's world, we will seek solutions that rely on telemedicine — smart devices, smart diagnostics — and integrate them into one total picture of care. The new team at Teva is aiming for cures to diseases not yet curable, solutions that make quality of life better, and therapies that leverage our understanding of genetics and can slow down the progression of diseases like Huntington's."

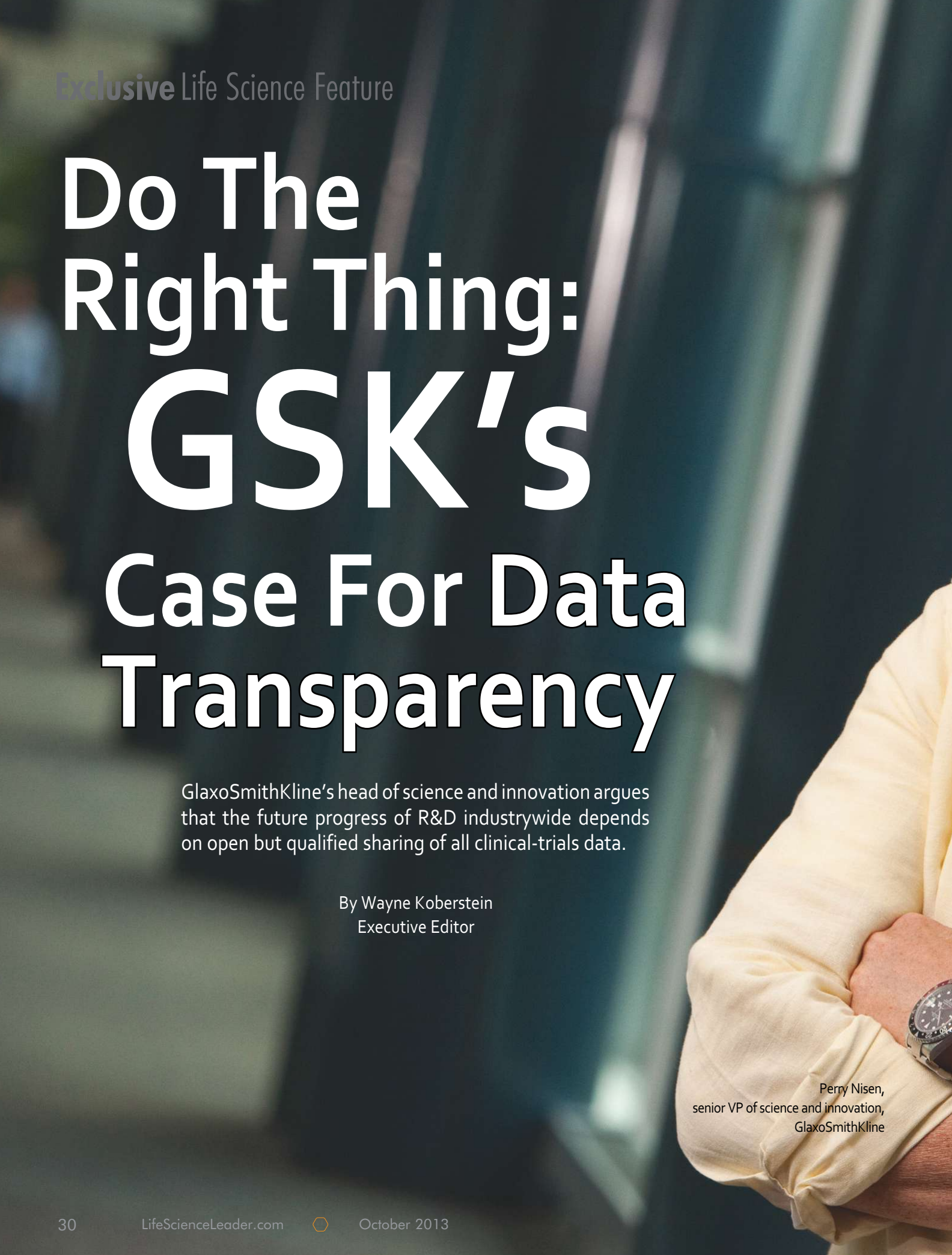
A key growth driver will be the NTE strategy, which has shown early success but is not yet proven on the industrial scale that Teva is planning. Other major drivers include emerging business areas like consumer health and a stronger footprint in new markets. Levin is still relatively new to the company, and he is still proving himself as a CEO. He has not yet revealed his full strategy as the company adapts its portfolio to the changes in the healthcare market.

One of the most interesting aspects of this story is the dramatic tension of a company in transition, largely into unknown territory and against fluctuating odds. Although that unexplored region may be the industry's most promising common ground, where the branded and generic businesses converge, it now seems wild, untamed, and excitingly unpredictable.

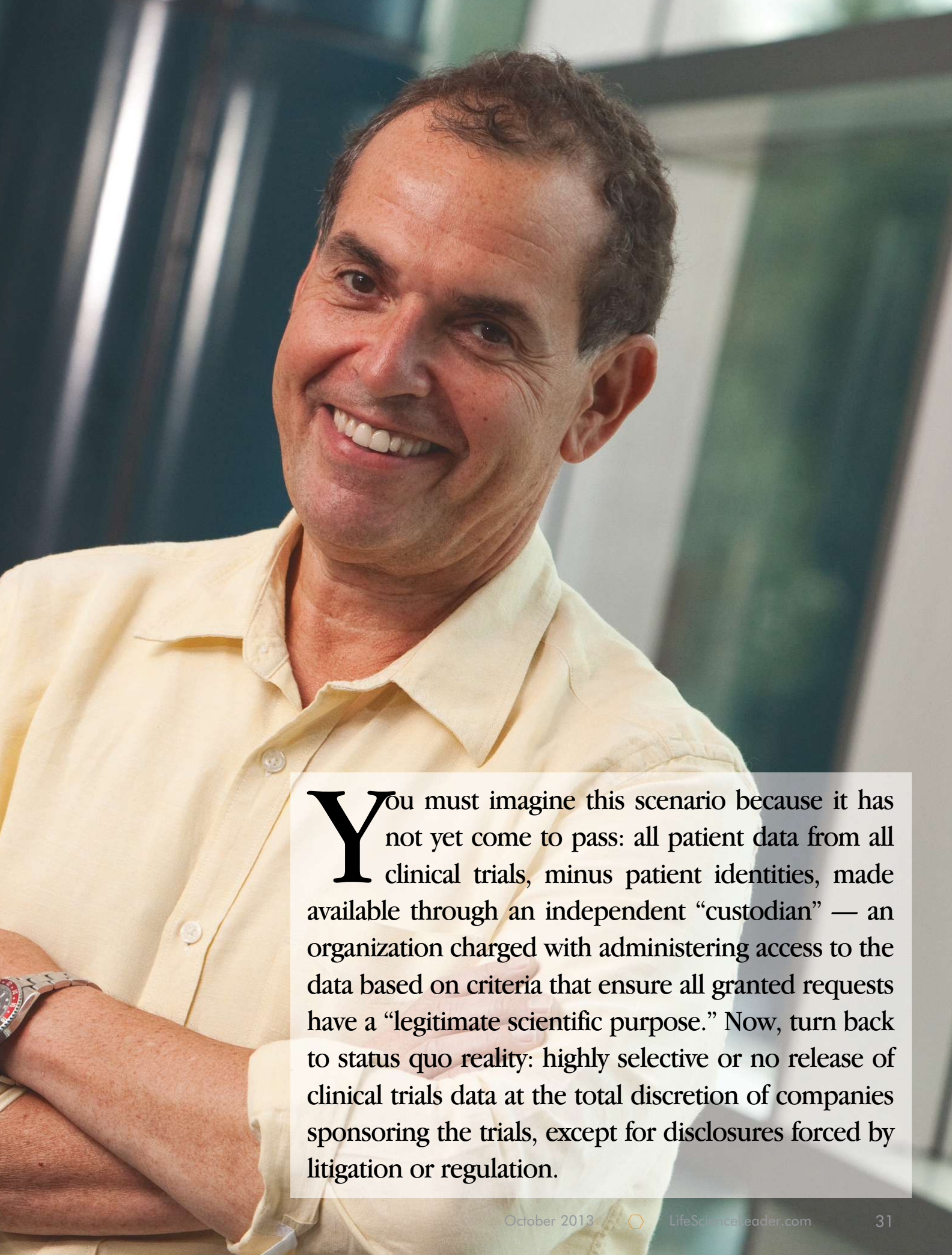
Do The Right Thing: GSK's Case For Data Transparency

GlaxoSmithKline's head of science and innovation argues that the future progress of R&D industrywide depends on open but qualified sharing of all clinical-trials data.

By Wayne Koberstein
Executive Editor



Perry Nisen, senior VP of science and innovation, GlaxoSmithKline



You must imagine this scenario because it has not yet come to pass: all patient data from all clinical trials, minus patient identities, made available through an independent "custodian" — an organization charged with administering access to the data based on criteria that ensure all granted requests have a "legitimate scientific purpose." Now, turn back to status quo reality: highly selective or no release of clinical trials data at the total discretion of companies sponsoring the trials, except for disclosures forced by litigation or regulation.

Compared to such a reality, the imagined scenario amounts to data transparency. It may not be the naked transparency sought by Internet hackers and activists, where any person could obtain clinical data like readers of Gutenberg's Bible received scripture. Quite frankly, the custodial model of transparency serves the industry's interests in avoiding the chance that someone could wildly misinterpret such data to suit a nonscientific agenda, a distinct and even inevitable possibility. Yet the model, as expounded by Perry Nisen, senior vice president of science and innovation at GlaxoSmithKline, actually seems to give sponsors no real place to hide when science calls for a reexamination of the data generated in their human trials — an amazing change of climate for the industry should it become the new reality.

A basic rationale for the data transparency movement is that the data summaries published by sponsors do not always accurately reflect the underlying data. But if sponsors can distort the data in summary, why cannot their critics do the same? Therein lies a key argument for the independent custodian.

> **"I've always been struck by the duplication and inefficiency in clinical development."**
>
> Perry Nisen, senior VP of science and innovation, GlaxoSmithKline

Nisen's argument for a custodian does not rest solely on the question of summary error or bias, but also on the idea of refereed access to a massive data pool from which researchers can draw great power in their quest for safer and more-effective medicines. The custodian's role thus becomes more a facilitator of research than a simple gatekeeper — ensuring shared data goes to qualified scientists on bona fide scientific quests, rather than amateur sleuths with axes to grind.

An article published in the Aug. 1, 2013 edition of NEJM gives a detailed account of GSK's current and planned data-sharing program. Here, we are more concerned with the "why" than the "what" of the company's data-transparency initiative. Why would a single company, acting on its own, go against the industry grain to push for transparency?

TRANSPARENCY, RIGHT VS. WRONG

Ben Franklin believed in "doing well by doing good" and suggested it is not enough to do good; you should be seen doing good. Similar practicality and honesty combine to explain GSK's reasons for advocating and implementing the industry's first company-initiated system for voluntarily disclosing patient-level data from its clinical trials.

"I've always been struck by the duplication and inefficiency in clinical development — the inability to analyze in a meaningful way such a rich and deep source of data," Nisen says. "We were getting ourselves organized to meta-analyze information, to validate methodology, to interrogate, and explore everything from placebo data to signals we would see in unexpected ways. But it was frustrating not to have access to the data in a straightforward way because of varying data standards, multiple databases, and so on."

Although GSK has worked for years to establish standards that enable internal company access to patient-level data, Nisen says it still lacked an integrated sense of all the relevant data generated outside the company. Access to the universe of scientific information from outside trials was becoming essential, he says, particularly at the broader management level such as the company's safety board, which he co-chairs.

On the other side of the equation, it became apparent that the often negative and poor-quality meta-analyses of GSK's trials by people outside the company suffered from lack of data it controlled and traditionally held confidential. Custodial transparency appeared to be the only logical solution.

"We have an obligation to share our data," asserts Nisen. "Even back in med school, I saw how powerful and useful a clinical trial with large data sets could be, as well as impossible to duplicate. To generate such magnificent amounts of data and not have a means for investigators and scientists to explore it in all kinds of ways seems so misguided. So here at GSK, one of the issues that especially matters to me is data transparency — making anonymized patient-level data available, ultimately in the interest of society — because it's the right thing to do."

A FEEDBACK OF BENEFITS

Three main reasons may justify the adoption of data transparency from the industry's perspective: the potential for validation by multiple analyses of original observations or interpretations, the unleashing of data resources for researchers, and the advancement of evolutionary improvements in future clinical trials and data. Without such access to clinical trial data, each trial remains a closed book, locking up a wealth of irreplaceable information. "How many times can you reproduce a large clinical Phase 3 trial that involved 38,000 people? It's not a doable thing," says Nisen. "Companies are unlikely to repeat trials, especially the larger, late-stage clinical trials, just because of the enormity of the investment to generate that data in the first place."

But if data transparency is the answer to how companies can have their trials and use them, too, it raises many other questions. Nisen

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says GSK's goal is to publish all of its past trials, going back even before its merger — but how feasible is the goal? "The further we go back, the harder it is because of paper patient report forms and the ability to just track down all the bits of data and get them in shape to anonymize them," he replies.

Similar limits apply to how far back in development data transparency may reach. "In the discovery space, we and all other sponsors have a way to go in making data available. Arguments could be made for sharing a lot of our validation work," says Nisen. "With how much we all invest separately to validate and revalidate preclinical data, we could pool our results — and then let the winner get ahead with the best molecule, the best studies, and the best indications."

On the clinical side, Nisen says companies could share a treasure trove of data about placebo effects, ranges of normal variation, validating methodology, and so on. "It is a shame we don't make such data more available to investigators."

The payoff for doing so, he says, could be nothing less than a leap in drug safety and efficacy. "Increasing benefit to risk, understanding disease, understanding the range of normal response — all that and more is possible once we unlock the data. We could apply signals, measures, and even methodology that could assess human response using biomarkers, *in vivo* or *in vitro* models, or other predictors of toxicology and efficacy."

Companies could do a lot together to reach the goal, and some efforts are under way to set up "cloud sharing" and other cooperative programs for exchanging commonly useful data. But Nisen makes the point that the issue of transparency is not restricted to pharma-company sponsors. "There are lots of studies undertaken in academia where we should be able to see, cross-analyze, and interrogate the data." An independent custodian would maintain a platform for the broadest possible inclusion of all sponsors' data, he believes.

"We hope to move to a situation where an independent custodian would have oversight of which academia and sponsors could make their data available, preserve anonymity of patients, ensure a reasonably legitimate scientific question is being asked, and verify the research teams are equipped with the necessary IT and support to handle and analyze the data. Without those protections, one of the risks is nonqualified people using our data to make nonscientifically valid assertions about benefit and risk," he says.

GSK BLAZES THE TRANSPARENCY TRAIL

According to Nisen, the company began it efforts toward data transparency prior to his arrival in 2001. Frank Rockhold, now senior vice president, drug development sciences, and others inside the company started to work internally and externally on establishing a common database and standards and dealing with issues such as patient privacy and informed consent. Actual sharing of data began in the same time frame with GSK trials of medicines for developing-world diseases such as TB and malaria.

Finally, last May, the company made anonymized patient-level data available from more than 200 studies "within certain boundaries" on the GlaxoSmithKline Clinical Study Requests website (https://clinicalstudydata.gsk.com), and Nisen says it will continue to expand its program, doubling the number of studies available by the end of the year. GSK has also committed to publishing clinical study reports (CSRs) of its marketed and terminated/failed medicines and the detailed summaries and interpretation of results from its clinical trials. Beginning in December, more than 1,500 reports will be made available over a two-year period. "It started in Europe, and by December we'll be putting out thousands of the clinical summary reports."

Meanwhile, the company has been working with SAS to build the analytical system where this patient-level data can be made available on a central hub database, along with a deployed model where outside investigators can have access to data, once their request has been approved by an independent panel.

GSK's first step toward implementing the broader custodial idea was to establish its own

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But to establish an independent custodian would require an industrywide effort. GSK's vision of the custodian is an organization modeled on the Structural Genomics Consortium, formed initially by reaching out to all the key constituents and structured to represent all of their interests. "Once we work out some of the issues for ourselves, hopefully a few other sponsors will join in, and we will make some adjustments to accommodate their expectations. And presumably, that will help GSK create a movement to start making the consortium happen," Nisen says.

"One of the only ways to get around antagonisms and distrust is to just start making our data available and let others then affirm or refute the conclusions that we've made," says Perry Nisen, senior VP of science and innovation, GlaxoSmithKline.

GSK may have some competition in influencing the form data transparency eventually takes. The EMA (European Medicines Agency) is preparing to advance an entirely different approach, in which the agency would be the central arbiter of data release and publication for trials in its jurisdiction. And activist proponents of total transparency would be loathe to surrender the initiative to any company they consider responsible for secreting the information in the first place.

Academic institutions may find it particularly difficult merely to participate in a data transparency system, partly because they typically lack the institutional history of open research, but perhaps more importantly because of the costs involved. Nisen says the resources needed to put clinical data into an analytical form according to a common data standard are expensive and perhaps impractical in such institutions, considering the high turnover among their investigators.

In the face of those and other issues, Nisen is philosophical, but determined to push ahead. "One of the only ways to get around antagonisms and distrust is to just start making our data available and let others then affirm or refute the conclusions that we've made. At the end of the day, there will be a benefit, predicated upon data generated to the best of our ability, along with the best analysis possible. And the more we can do that, the more acceptance we will win. We will also have less waste in generating and regenerating data."

Nisen says the company is now in related discussions with a few other pharma sponsors about joining its transparency initiative. "I am cautiously optimistic that we'll move forward and they, too, will start contributing." He says GSK has also spoken with "independent parties who could potentially function as independent custodians."

OPEN DATA, INNOVATION, AND TRUST

Well done is better than well said — according to another Franklin maxim. Inside GSK, Nisen and his team turn words into action, coordinating a flexible group of personnel largely drawn as needed from the company matrix. "We receive team support, policy support, and operational support from the company," he says. "We can put enough resources behind any particular project to make it work. And we have a commitment to data transparency as a high priority from the top of the organization down."

One of the ongoing responsibilities of Nisen's group is to use data sharing as a tool for clinical trials improvement. To start with, it teaches investigators in new trials how to prepare the clinical data they help generate for future sharing, including publications. But data transparency also molds the operations, regulatory routines, policy development, and overall planning of trials — essentially forcing an innovative approach to the clinical development.

Outside GSK, however, the people running small development companies may well wonder, Why should I add this to my plate? Why should I make my data transparent? "For all the same reasons that we do — to leverage the opportunity to cross-analyze and harmonize the information," answers Nisen. "If you move to common standards, you have to give a little to get more back, on some level. But it will not be so easy for small companies to do that unless, from the inception, they adhere to a common standard and leverage the information to model and simulate what they want to do. It might make for much better studies on their part as well, I would think."

It would also not hurt the partnering prospects of small companies to be a part of an industrywide collaboration or consortium in data transparency. Doing good, being seen doing good, plus doing what you say should be done — not a bad equation for entrepreneurs out to change the world. If nothing else, joining the data transparency movement will help remove the stifling insulation that all too typically surrounds young companies.

Nisen cites the company's chief executive to summarize why GSK has chosen transparency as the right thing to do. "One of the fundamental pillars that Andrew Witty has articulated from the very beginning was building trust. And one of the key ways to build trust, I would say, is to be transparent, to make our data available — just walking the talk." The rationale of trust seems sound for any clinical trials sponsor, no matter how large or small.

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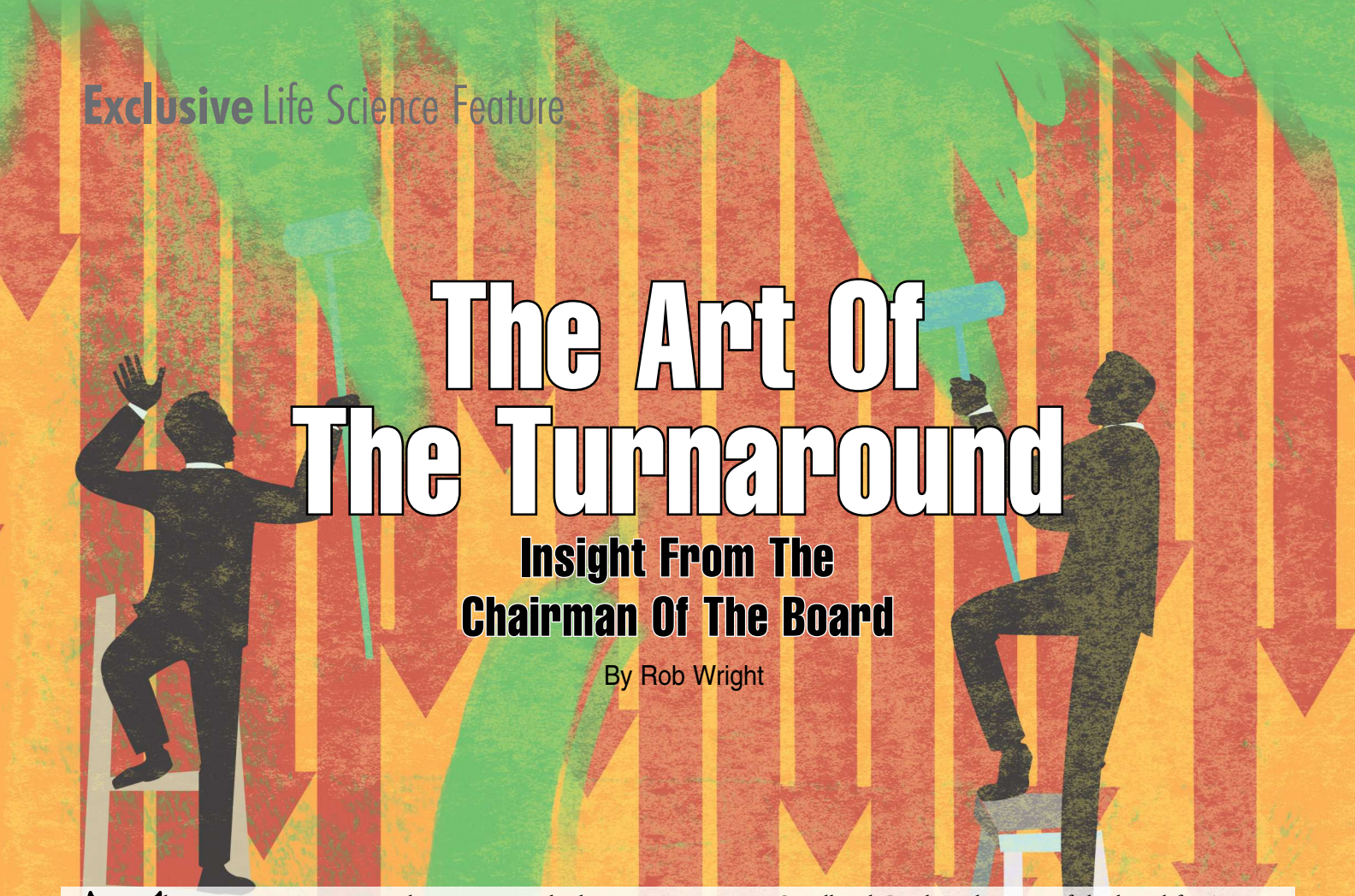

The Art Of The Turnaround

Insight From The Chairman Of The Board

By Rob Wright

There are many reasons and motivations why business leaders decide to start a pharmaceutical company — make money, gain prestige, leave a legacy, etc. Or perhaps they do this simply because of a desire to fill a perceived market need and help people. For Leonard Jacob, M.D., Ph.D., it was the desire to link science to medicine and business. By the age of 34, Jacob had risen to the position of worldwide VP of pharmaceutical development at SmithKline & French Labs (now GlaxoSmithKline). A mere five years later, he had had enough of Big Pharma. "What you have is a bureaucracy where there is constant review, prioritization, and reprioritization, resulting in a management fiasco of private teams making decisions without the line authority to fund them," he states. To realize his desire to link science to medicine and business, he felt he would have to do so in an entrepreneurial venue and exit the security of Big Pharma. Since that day, the 35-year industry veteran has cofounded a pharmaceutical company that was eventually dissolved, founded another that was acquired for $190 million, and served as the chairman of the board of two publicly traded companies — Bradley Pharmaceuticals (acquired by Nycomed and subsequently acquired by Takeda) and Antares Pharma (NASDAQ: ATRS), a specialty pharmaceutical company created through the merger of Permatec and Medi-Ject Pharmaceuticals. What he has learned through these experiences is how to go about assessing and fixing a troubled company.

ASSESS THE PRODUCT FIRST – THEN THE LEADERSHIP

Shortly after leaving his position as chairman of the board for Bradley Pharmaceuticals in 2006, Jacob received a call from Jacques Gonella, Ph.D., then chairman of the board for Antares Pharma. "He was in Africa and called me in a panic, saying, 'Len, I need you to be chairman, and I need you to be chairman now,'" Jacob recalls. Gonella had founded Permatec, which merged with Medi-Ject Pharmaceuticals to form Antares. Jacob joined the company officially in 2007 and took over as chairman of the board in 2008. When he received that phone call from Gonella, the company's market value was around $29 million.

Jacob believes that when assessing a company for growth, although the management team and financials are two common factors to consider, the most important is product opportunity. "If you look at the core principles — good technology, good products, good patents — you can't take those away. If companies have good products, they should generate revenue. If they aren't generating revenue, 9 times out of 10, it's people performance."

According to Jacob, commercial failure is often the result of a breakdown between linking the bench to the bedside. To build value in a company, you need the commercial element that comes not only from having good products being developed at the bench, but from understanding how to link that science to how a patient will actually use the product. "In order to do so, you can't hire physicians who are merely clinicians and don't understand the science," he states. "Conversely, you can't have scientists developing products who have no experience with how the patient will actually use it."

If a company has good products (which Jacob determined Antares had), you next need to look at the leadership. To do this, Jacob tapped into his past experience as a CEO of InKine, a company he founded in 1997 but eventually sold since he realized he

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didn't have the commercial skillset to make it successful in the GI space. He says learning those types of tough lessons about his own capabilities as a leader (see sidebar, "Lessons Learned From Failure") has helped when he has to assess if a company's executives can grow the business.

One of the biggest problems Jacob sees when he evaluates a CEO is that many of them lack the vision to recognize problems that may occur in the next three to six months. "They are so immersed in meeting the revenue challenges of today they actually don't pause to say, 'Here are the things in the future that can end up biting me in the behind.' When I come in as a chairman of the board to try to turn around a company, this is something I look for immediately." When Jacob joined Antares, he determined the CEO at the time was too much of a financial person in a technology-driven company. "He was counting dollars while there was nobody really being a champion around some very impressive formulation and device-engineering work," he attests. Jacob also quickly recognized there was a cultural disconnect throughout the organization. Eventually, the CEO and the company parted in an amicable way. "I elected, with our board, to appoint Paul Wotton, Ph.D., an actual board member, to be the new CEO. He had been the CEO of a Canadian company, Topigen Pharmaceuticals." Prior to Wotton taking over in 2008, the company was replacing the top spot on an average of every 3.5 years. Having a CEO carousel is not the best approach to create a consistent culture, let alone fix the cultural disconnect he had uncovered, which became the next task on Jacob's agenda of turning Antares around.

INTEGRATING CULTURES NECESSITATES TOUGH DECISION MAKING

Because Antares was formed from the merger of two companies, the company had a device facility located in Minneapolis, a corporate office in Ewing, NJ, and a research arm in Allschwil, Switzerland. "When you have a market value of $29 million and you are running out of money, you had better start changing the culture of the enterprise," Jacob states. "What that meant was Paul had to build a team and integrate the three locations so they were all stakeholders, working on one project, and that project was making Antares successful." Jacob and the leadership team quickly recognized Switzerland was a problem in trying to bring the business together. "We elected very rapidly to close down the Swiss research center, a decision that was tough, economic, and strategic." In a brilliant move, the company signed a simultaneous license-and-asset purchase agreement with Ferring on Nov. 11, 2009. In the deal, Ferring obtained the rights to certain IP relating to Antares' proprietary transdermal gel delivery technology, agreed to purchase the research equipment, and assumed responsibility for the Antares leased development facility in Switzerland. In addition, a majority of the current employees of the facility became employees of Ferring. The agreement didn't impact any of Antares' current licenses, minimized the financial impact that results from

LESSONS LEARNED FROM FAILURE

According to *Business Week,* the average life expectancy of a multinational corporation is between 40 and 50 years. Research conducted by Bradley University and the University of Tennessee this past July revealed 25 percent of U.S. start-ups will fail in the first year, and 71 percent will have failed by their tenth year of operation. Leonard Jacob, M.D., Ph.D., knows firsthand the pain of creating a business only to watch it fail. In 1989, he cofounded Magainin Pharmaceuticals and served as the COO until 1996. "The company was focused on isolating antibiotics and anticancer agents from frog skin," he recalls. In 1999, the FDA rejected the company's small antibacterial peptide it had been working on for the treatment of diabetic foot ulcers. The bad news resulted in its cofounder and discoverer of the peptide, Michael Zasloff, M.D., to leave the company and return to an academic position at Georgetown University. Two years later, the company changed its name to Genaera Corporation. In 2009, the company filed a certificate of dissolution having never brought a drug to market.

Though the experience was financially successful for Jacob personally, the fact that he left the company, which eventually went belly up, places it in the failure category. The role being played by the company founder is a valuable lesson he learned from this experience and something he applies when evaluating companies as to their potential success as a turnaround. "I will support founding scientists in their labs and universities," he affirms. "However, I want no founding scientists in my building." According to Jacob, the brilliance of founding scientists functioning as the CEO of a company can be a problem. "They're brilliant. This causes them to think they are smart in every aspect of our business, such as drug development and marketing, even though they may have had no experience in these areas." Founding scientists have powerful personalities, which can destroy the culture of a company. "To truly have a successful company, the CEO has to build a culture within the company that is motivating, rewarding, and kind, so people don't look at their watch and say, 'It's 5 o'clock. It's time to leave'," Jacob says.

Though Jacob experienced butting heads with a company founder in his own business, he also experienced it when he became chairman of the board at Bradley Pharmaceuticals, a public company being run as a private business by a very dynamic CEO who was also the company founder and chairman of the board — the late Dan Glassman. When Jacob joined the company, Glassman had to give up some power. "Giving up authority is very difficult for a company founder to do," he states. "However, as a public company, you are ultimately responsible to the shareholders." According to Jacob, when you have a founder who is not willing to do what is necessary to turn around a company in decline, the only way out for shareholders is to find a company willing to purchase it at a premium. This is what happened in the case of Bradley. When Jacob had joined the company and was subsequently named the chairman of the board, the stock was trading around $6 to $7 a share. In 2007, Nycomed purchased the company for $20 a share. Jacob describes the process of supplanting a founder to be a difficult situation from a governance perspective. To maintain the best interest of the shareholders, Jacob believes company founders of publicly traded companies should not hold the positions of both CEO and chairman of the board.

*"When you have a market value of $29 million and you are **running out of money**, you had **better start changing** the culture of the enterprise."*

Leonard Jacob, M.D., Ph.D.

closing a facility, minimized the loss of jobs, and allowed Antares to jettison a cultural integration challenge.

With that behind them, leadership could then focus on putting more support behind the Minnesota device area, which was producing patents around autoinjectors and needle-free injectors. To do this, the company needed more revenue and sought to develop some strategic partners, which required the chairman and CEO to work hand in glove. For example, Wotton and Jacob met with the CEO of Teva North America over dinner. In 2009, Teva (NYSE: TEVA) received FDA approval to market the Antares needle-free injector with the hGH product in the U.S. Antares also created partnerships with the biggest of Big Pharma, Pfizer (NYSE: PFE), in 2011, as well as another top 50 pharma company, Actavis (NYSE: ACT), formerly Watson Pharmaceuticals. Antares continues to expand its IP portfolio with 43 patents filed and 9 patents issued in the past 18 months. It also has two potential blockbusters in the works -- OTREXUP, a patented auto-injection system that works in combination with methotrexate to help rheumatoid arthritis (RA) sufferers, and a combination testosterone drug-delivery system for hypogonadism. OTREXUP is currently under FDA review with a potential approval as early as October; the second drug has entered clinical trials.

The Antares model is to take generic drugs and link them to a patent-protected device system with a clear safety or efficacy benefit. This model builds extensions through a product's life cycle, creating additional exclusivity. With a market cap of just over half a billion dollars, Antares has analysts like The Motley Fool taking notice of its successful turnaround -- something Chairman of the Board Jacob describes as less of a science and more of an art.

Designing A Brand Protection Organization

by Ron Guido

In recent years, many life sciences companies have formalized their processes and expertise to combat counterfeiting through the establishment of a relatively new business discipline known as brand protection. Of course, the first two questions that come to mind are "What is brand protection?" and "Why is it important?" The answers to these questions lie in three value generators that are emerging within brand-protection-savvy companies. Concerned executives are taking a proactive approach to elevate anticounterfeiting activities from a "see-and-treat" mentality (i.e. security breaches) to a more strategic role within the organization.

WHAT IS BRAND PROTECTION?

Simply stated, brand protection is the collection of capabilities and activities conducted by a company and its stakeholders to help prevent unauthorized use of intellectual property and/or commerce associated with that company's brands and trademarks. In today's world of global trade and complex supply networks, brand protection is not a luxury; it is a necessary core competence for any organization that commercializes popular brands.

Like all well-established business functions that incubated from unstructured beginnings, the work of protecting brands originated in the trademark law group, supported by corporate security, quality, compliance, supply chain management, and, of course, brand management. Brand protection is still a nascent function in corporate society, emerging from and nurtured by the wisdom of these important supporting functions. However, as the discipline matures, even if brand protection continues to exist as a virtual function, the major differentiating element over traditional ad hoc working teams is the creation of a sustainable learning environment dedicated to preventive measures.

WHERE BRAND PROTECTION RESIDES

Assuming your company decides to coalesce its focus against counterfeiters within a dedicated organizational unit, the next decision to be addressed is where should the brand protection function report. This will depend upon a number of factors related to the structure of your corporate footprint with various legal and commercial entities and how centralized or decentralized your structure has become. It also depends upon the roles and responsibilities embodied in your business alliances and comarketing partnerships, as well as your level of contracted manufacturing and distribution.

Having said this, because brand protection must become a featured "discipline" for your company to realize its full value and since such a discipline will strongly promote best practices across the business, an enterprise-based organization makes the most sense. By reporting up to a centralized function, brand protection will command the influence across organizational lines necessary to effect important operational changes. The goal is to rapidly shift the culture from one that responds to incidents as a set of uncoordinated events to one that takes a strategic position against brand attacks and supply chain integrity issues. Furthermore, a single "voice" on brand positions and policies is important in communicating with affiliated organizations, the public, and the industry at large.

Specifically within an organization, the brand protection role functions well when operationally aligned with supply chain management, quality/regulatory/compliance, and legal or strategic marketing. Of these, supply chain management is perhaps the best nest for brand protection expertise, since a large portion of preventive best practices apply to the core supply chain functions of plan, procure, make, ship, and service.

THE VALUE OF A BRAND PROTECTION FUNCTION

As mentioned above, the primary thrust of brand protection is prevention. Sustained preventive measures lead to the single greatest value driver of this work — patient safety. We can stop here because there is no call to action more significant than a life protected or assuring a life-enhancing medicine is safely delivered to a patient in need.

Yet to help appreciate the full value proposition of brand protection, it is important for business-minded leaders to know that such an investment in resources can yield significant returns for the company, even establishing brand protection as a profit center.

Agreed, it is extremely difficult to quantify the business impact that counterfeits and illegal diversion have on our operation and subsequently calculate the cost/benefit of countermeasures. This dilemma is largely attributable to the obscurity of

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illicit trade, the complexities of international supply chains, and the many interconnected business factors that contribute to supply-demand variability.

In some respects, the aggregate activity of all counterfeiters that target your brands is best viewed as an unethical competitor, one which attacks your market share, disrupts your brand equity, creates pricing instability, erodes confidence in your products, and disregards your intellectual property. Placing counterfeits on this level allows us to cast the countermeasures in a business perspective, leading to the proper focus on supply chain integrity as part of your annual process of setting goals and objectives.

In this business context, the level of counterfeit trade can be estimated based upon analyses of market share, demand patterns, average selling price, and most importantly, accounting for total supply. Such considerations should include qualitative assessments of risk, liability claims, the impact on future competition, especially in emerging markets, and quantitative analyses of the loss of revenue and the impact to brand value. While we are primarily driven by the urgent need to reduce risks to consumers' health and safety, monetized impact analyses are important to set business priorities and to allocate funds to those programs that most effectively drive risk mitigation and revenue recovery.

Brand protection value creation, therefore, is generated from successful achievement of three business objectives:

- recovery of revenue lost to counterfeits and diversion (lost demand and price)
- brand equity enhancements from consumer protection and IP rights enforcement
- collateral benefits from applying security measures to supply chain management

The first value-creating objective, revenue recovery, is perhaps the most tangible when field actions result in seizures of in-transit goods or raids on rogue manufacturers. In such cases, the market value of the confiscated products can be registered and then extrapolated over a logical period of time to record a credit to the overall anticounterfeiting effort. The greatest opportunity for recapture, though, comes from systemic improvement in practices, policies, and processes that prevent fakes from entering the normal supply chain and help eliminate unauthorized trade of genuine goods.

The second category of value creation, brand equity preservation, is related to the negative impact that counterfeits or tampered and mislabeled goods can have on the reputation of your brands and your companies. There are financial models that can be applied to estimate the reduction in brand equity (or market share) that results from a publicly communicated breach of the supply chain (i.e. recall, cargo theft, tainted product, or discovery of counterfeits in the marketplace). Brand equity can also become compromised by undetected counterfeits influencing consumer behavior. Some of the negative implications to brand equity that can result from the presence of counterfeits in the market are:

- increase in brand awareness, but only in terms of bad outcomes
- reduction in perceived quality
- reduction of brand association with high status and value
- interruption of brand loyalty
- reduction in average selling price due to buyers unknowingly substituting genuine goods with lower-priced fakes

The third objective, collateral benefits, is an interesting means of justifying investments in supply chain security because, when many safeguards are implemented, they actually manifest as improvements in the efficiency and effectiveness of the company's routine operations. Thus, the benefits of applying best practices exceed the costs of implementation.

Collateral benefits are defined as secondary benefits to the company (beyond the cost avoidance of trade interruptions) resulting from investments in secure supply chain practices. These benefits are derived from creating new or improved business capabilities, access


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to information, more efficient processes, or an enlightened business environment. For example, many companies are beginning to experience the operational benefits associated with unit serialization of finished goods, as required by new track-and-trace regulations. As companies continue to wrestle with traditional business tasks, such as recalls, returns, chargebacks/rebates, expired products, supply/demand balancing and new-goods monitoring, the increased supply chain visibility that is attainable from unit serialization can translate into increased operational efficiency and inventory reductions.

Companies with advanced brand protection programs have developed internal financial scorecards to revenue recovery, cost avoidance, and efficiency gains from anticounterfeiting activities. Such metrics will be further discussed in the next article in this series on brand protection.

THE ELEMENTS OF A BRAND PROTECTION PROGRAM

As introduced above, brand protection should be charged with becoming the center of excellence for the enterprise in matters of best business practices to help prevent (1) fake goods from entering the legitimate supply chain and (2) genuine goods from being diverted into unauthorized (gray market) channels.

In order to meet this challenge, the brand protection team must mobilize the people, processes, and technologies that sustain core operational and commercial tasks. Toward this end, the function must serve several key roles, including that of an internal best practices consultant, a trainer, an auditor, and a purveyor of innovative technology.

There are seven core elements of work and expertise that are foundational to a broad-based organizational model for brand protection:

1. Incident Management. Aggressively investigate, record, and analyze each incident for root-cause factors, capturing key data relative to principals involved and interpreting forensic results. Classify incidents as to source, product category, location, and harm caused. Establish a culture of civil litigation in addition to criminal penalties. Apply advanced analytics to help identify the behavior and affiliations of the perpetrators.
2. Market Monitoring. Proactively examine internal commercial information for abnormalities possibly attributable to illicit trade. Includes incident reporting, Internet monitoring, customs collaboration, field audits, product purchases, supply/demand patterns, and sales/pricing information.
3. Community of Knowledge. Awareness and education of the dangers of counterfeits and associated risk-mitigating practices. Includes internal and external educational programs, consumer alerts, internal knowledge portal, and on-line awareness training for both new and experienced employees.
4. Influencing Public Policy. Collaborations with legislators, regulators, and other government agencies on anti-counterfeiting laws and policies. Includes collaborating with national and member state governing bodies, industry associations, trade groups, customs and border protection, law enforcement agencies, and nongovernment organizations (NGOs).
5. Operations Best Practices. Enhance the security of supply chains through increased visibility and control of product flows and by influencing the practices of suppliers, trading partners, external manufacturers, and customers. Includes distributor management, information systems, in-transit security, channel strategies, packaging safeguards, and track-and-trace systems.
6. Technology Adoption. Provide assessments and use cases for authentication and track-and-trace technologies to the product/package to either deter counterfeiters or assist in identifying fake goods in the supply chain. A layered approach to technology adoption is recommended to reduce the risk of being compromised by counterfeiters.
7. Global Deployment. Locate brand protection experts on the ground in high-risk zones of counterfeit trade. Provide enterprise support for incidents and best practices implementation. Serve as liaison with internal and external stakeholders, and work with local governments and customs authorities.

Together, these elements provide a useful road map for establishing a brand protection organization within your company or remodeling the brand integrity programs already present. They also provide the basis for setting goals and objectives for the enterprise and for informing regional and local anticounterfeiting teams.

In summary, by establishing an enterprisewide culture of no tolerance for counterfeits, pharmaceutical and biotech companies are taking a resolute stand against those who are violating their brands and placing their patients in jeopardy. A well-designed and well-resourced brand protection organization, preferably positioned at the enterprise level, provides the proper organizational platform to sustain anticounterfeiting programs and work proactively across all functions to create new sources of business value.

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Trials & Innovations

By Wayne Koberstein, executive editor

Why do new drugs fail to reach the market? Oh boy, what a question — one sure to cause a stir anywhere you go. Regulators get much of the blame from industry and, to an increasing degree, vice versa.

Among us commoners, though, the general impression when a drug fails is it wasn't a good drug. Those mysterious chemists and formulators must have gotten it wrong way back in the lab. They should have known the drug would not only fall short of helping patients, but even harm them. Well, perhaps they did, and perhaps they should, but the plain truth of it is this: innovations don't just happen on the bench, they also happen, however miraculously, in clinical trials.

Drug sponsors and suppliers have an enormous stake in new drug approvals, an elite cadre of innovations we collectively call "innovation." Even if a drug fails later in the process, after a given supplier helps it along, the failure's repercussions reach all the way back to the beginning. Just ask the people whose jobs disappeared in the latest R&D restructuring by their company's Big Pharma client. Clinical sourcing rises and falls on the fate of individual drugs in development. Conversely, even the earliest actions performed with a drug in development affect its chances of success.

A clinical trial is not an experiment but a test of the evidence, like an engineering analysis, leading to a yes or no conclusion as to legal use. To a structural engineer, human drug trials are like measuring all the stresses before opening the bridge to traffic. Nevertheless, trials do yield experimental data, and to the extent the data adds to or changes scientific understanding, the trial may unfortunately never catch up to its own findings. Unless you can change the endpoints in response to the feedback of new science and treatment, the trial may become obsolete long before it ends.

Because trials are not set up as experiments, however, the data they produce is rarely reproducible. In fact, a general lack of reproducibility plagues most biomedical research, even at the experimental stages, according to Ulo Palm of Forest Labs. At the R&D Leadership Forum last February, Palm argued that the ubiquity of poor practices in bio/pharma R&D makes most published drug data "misleading or flat-out wrong." Like a weak radio transmission, the noise of error overwhelms the signal of "statistically significant" findings of safety and efficacy.

This point is so important, yet much too complicated to cover adequately here, that I am inserting the following sources, even though I also placed them in one of my previous blogs: "Handbook: Quality Practices In Basic Biomedical Research (QPBR)," WHO, 2006; and "Best Quality Practices For Biomedical Research In Drug Development," American Society For Quality (ASQ), 2012. As I said then, the documents "offer direction toward common data standards that could ameliorate the problem."

Another speaker at the Forum, Ken Getz of Tufts CSDD, blamed many clinical trials failures on the so-called reforms that were supposed to make trials more, not less, effective. Expanding eTrials, moving trials to emerging markets, greatly boosting the number but reducing the size of sites, and outsourcing site management were all intended to lower cost, spread risk globally, speed trials, and improve patient and investigator retention. But Getz said the complications the reforms added actually had a negative effect on those areas. He called for a "reboot" that emphasizes investigator and site quality.

In a surprising number of cases, trial design and execution sideline otherwise promising candidates. Poor selection of endpoints, mishandled recruitment, bad data management, and disordered site management are often at fault.

An example of critical trial design was recently noted by legal expert Allan Green, comparing two competitive Phase 2 trials for the orphan condition Fabry's Disease. (http://www.fdaregs.com/index_files/Page560.htm) The first product failed to gain FDA approval because the sponsor picked a dose not studied in Phase 1, chose a subjective primary endpoint (pain reduction) for one study, added too many secondary endpoints that produced contradictory results, and conducted faulty data auditing and analysis. The second product ultimately won approval largely because the sponsor determined the Phase 2 dose with a previous dose-ranging study, worked with the FDA to define a surrogate endpoint for accelerated assessment of its primary endpoint (renal function), and produced clean, straightforward data.

Fabry's is such a rare disease that the FDA required only Phase 2 studies for the two products described, but Phase 2 failure also afflicts many nonorphan drugs. According to the U.K.'s Centre for Medicines Research, the Phase 2 failure rate is running at about 80 percent, compared to about a 50 percent

failure rate in Phase 3. You would expect and even prefer Phase 2 rates to outweigh the Phase 3s, but it remains a challenge — and, yes, an opportunity — that both rates have been rising.

Regulators offer more than rhetorical support for clinical trial effectiveness — partly in improving consultation of the type just described but also where it counts most for industry, helping more trials succeed. The most outstanding current example in my mind is in oncology. Richard Pazdur, director of the FDA's Office of Oncology and Hematology Products, has cited poor endpoint selection and insufficient patient populations as common problems with trials for drugs his office has famously rejected. He credits better practices in part for the new crop of cancer drugs the FDA has been rapidly approving. Lesson: Interact with regulators early and often, specifically with your clinical trial and generally with guidances, workshops, and consortia dedicated to GCP (good clinical practice).

A LEAP OF VISION

You may notice I've said nothing so far about personalized medicine (PM). To be honest, I accept that PM and Dx/Tx combinations may help patients with true rare diseases in ideal settings, but I fear the PM approach is becoming a closed and tightening circle that may condemn the industry to marketing mostly tiny-niche products with infinitely bloated price tags. I see no mere coincidence in the three out of four top areas (besides cancer) where clinical trial failures prevail: metabolic/diabetes, neurology, and cardiovascular. All of those are historical territories for primary care medicines. You, the industry, say medical need is always the guiding light for R&D? Or have expensive clinical implosions and "niche mania" caused you to look away from the largest needs of all?

Consider this. What if improved models, operations, and basic practices could put a dent in the late-stage failure rate for primary care drugs? The same question might apply to broadly applicable oncology drugs such as immunotherapies. Would that make the medical need there more visible?

Failure is inevitable, and maybe even necessary overall. The fact is, science depends on failures to advance in knowledge and understanding. But to fail in an experiment is one thing; in a clinical trial, quite another. One teaches, the other also teaches, but in a costly and often destructive way. No matter how reformed or unreformed your system, what matters most in producing real innovations is the quality of planning and decision making at every stage leading up to and extending through clinical trials.

Strategic Approaches To Risk-Based Monitoring In Clinical Trials

By John Whitaker, Ph.D., and Amy Kissam

With drug development costs reaching between $800 million and $1.2 billion for each successful product, biopharmaceutical companies are trapped between mounting pressure to reduce development costs and the need to ensure better outcomes from clinical trials. Generics, lower approval rates, and global testing requirements are driving increases in development costs, yet outcomes remain uncertain in terms of both regulatory approval and market acceptance. In addition, large payers such as Medicare continue to exert downward pressure on prices. These shifting dynamics mean biopharms and CROs must employ a more strategic, end-to-end approach to clinical trials — one that begins at the design and planning stage, is data-driven, and features workflows that direct the right resources to the right tasks, without compromising overall quality.

For real change to occur, biopharms and their clinical research partners must make better use of data to plan and manage the delivery of their clinical trials. This is particularly important in the area of clinical trial monitoring, where the industry has begun to embrace a more strategic approach. The practice of risk-based monitoring is strategic in that it allocates resources across a study based on data criticality, patient safety, data integrity, protocol compliance, and impact to operational delivery. This approach starts with a risk assessment, which includes identification of core critical data that supports endpoints, patient safety, and the overall clinical development plan. This risk assessment then becomes the foundation for operational strategy and the initial monitoring plan. Throughout the conduct of the trial, monitoring effort is escalated and de-escalated based on key risk indicators (KRIs) and data trends.

The industry, while mindful of its mission to develop better delivery models that improve quality and reduce cost, remains conservative in its adoption of new technologies and innovation in clinical trials. Sponsors still tend to tread cautiously due to the perception that new technology or process change may introduce additional risk to the regulatory or approval process. Even as regulators have more formally endorsed risk-based monitoring in recent years, industry adoption of these alternative monitoring approaches has been slow, and challenges remain in translating these concepts into effective clinical practice.

THE CHANGING PERSPECTIVE

The historical regulatory concern may be waning for some companies based on recent publications from regulatory authorities. In 2011, the FDA and the European Medicines Agency (EMA) issued their respective positions advocating for risk-based monitoring of clinical trials, and have opened the door to a new industry paradigm. The FDA and EMA both acknowledge that traditional 100 percent source document verification (SDV)-based monitoring approaches are not always the most effective in ensuring adequate protection of patients and data integrity.

The FDA notes that no single approach to monitoring is appropriate or necessary for every clinical trial and recommends that each sponsor design a plan that is tailored to the specific patient protection and data integrity risks of the study. In most cases, such a risk-based plan would include a mix of centralized and on-site monitoring. In its guidance, delivered in a reflection paper, the EMA says better solutions are needed to ensure that limited trial resources are best targeted to address the most important issues and priorities, especially those associated with predictable or identifiable risks to patient safety and data quality. The agency also encourages the incorporation of quality tolerance limits for the clinical trial procedures involved. These measures can direct the oversight and monitoring of patient safety, data

integrity, and protocol compliance, resulting in more need-focused monitoring strategies.

While adoption may be slow, there is a large amount of interest and growing momentum in the industry. Helping drive those efforts is the Clinical Trials Transformation Initiative (CTTI), a public-private partnership launched in 2008. A major part of CTTI's mission is to identify monitoring practices that, through broad adoption, will increase the quality and efficiency of clinical trials. Several related collaborations are affiliated with CTTI. One example is TransCelerate BioPharma Inc., a nonprofit founded by 10 Big Pharma companies in September 2012. The alliance, which has since grown to 17 members, has launched five precompetitive initiatives, including a program focused on establishing a standard framework for risk-based monitoring. This includes common tools and triggers to identify risk and categorization criteria for low-, medium-, and high-risk trials. The initiative will also test a validated approach through pilot trials and be vetted by regulators.

A KEY PIECE OF THE PUZZLE IS DATA

In a more strategic data-monitoring approach, clinical researchers design a fit-for-purpose data verification model. Instead of reviewing trial data using the traditional 100 percent on-site SDV approach, researchers may opt for centralized data review where possible and implement a sampling plan for the on-site review of data. This sampling plan is designed prospectively based on the initial risk assessment and may be consistently applied across all sites in the study or varied based on identified risks at the region, country, and even site level. Additionally, the strategy may be designed to adjust as site risk changes throughout the progression of the trial and incorporate the escalation or deescalation of review effort based on KRIs. This approach can result in more efficient data gathering and analysis, with the potential to significantly lower development costs for new drugs. Further, a holistic, well-designed monitoring approach, leveraging near real-time flow of data, can offer these savings while maintaining, or even improving,

oversight of patient safety and data quality.

The building blocks of a strategic data-monitoring plan are targeted and triggered monitoring strategies. Targeted monitoring may involve various techniques, such as continuous, fixed, and random sampling methodology. This strategy includes a reduced SDV approach that is aligned to critical data, patient visits or selected patients, depending on the risk-benefit profile of the trial. Triggered monitoring supports an added level of risk management by predefining triggers for planned or additional on-site and off-site attention. These triggers are event-based around data volume and data quality and determined by thresholds of accumulative work and/or quality.

To maximize the potential of targeted and triggered monitoring, the role of centralized monitoring should be leveraged. Centralized monitoring is ideally positioned to coordinate targeted and triggered strategies. Many organizations limit the functionality of centralized monitoring to an administrative role that coordinates on-site activities. However, the potential contribution for this group goes far beyond this administrative role. There is evidence that centralized monitoring can be more effective than on-site monitoring in detecting data anomalies, such as fraud and other nonrandom data distributions. In addition, electronic data capture (EDC) systems are making it possible to implement centralized monitoring methods that enable decreased reliance on on-site monitoring. The availability of data in aggregate form provides central monitors visibility to potential risks or trends, which may warrant additional scrutiny off-site or on-site. To realize these potential benefits, it is important that centralized monitoring teams are multidisciplinary. The ideal team will have clinical monitoring experience coupled with data analysis skills. These teams should also possess strong medical and safety surveillance perspectives.

Coming on the horizon is the promise of using statistical methods to augment existing monitoring strategies. The concept here is to use the reported data to guide the review and verification process. By applying statistical methods to identify inconsistent data points or patterns of data at a site, these signals can then be used to focus additional data review and investigations. These methods can also look for many other signals, including analyzing the data for trending, whether in the values themselves or attributes of that data such as the time of data collection. Data can be analyzed to determine if there is a directional bias or inconsistent variability (too much or too little) at a site, within a patient, or across an entire trial. The benefit of this approach is to further reduce the amount of data clinical researchers need to look at. They can plan to review less data initially, knowing that the statistical methods will provide a safety net to trigger additional guided data investigations as needed.

EARLY PLANNING IS PIVOTAL

Before deciding on the optimal monitoring approach for a trial, establishing a strong operational strategy is essential. Beginning the process early in development will allow for a more holistic approach to streamlining the protocol and risk identification. Building the operational strategy starts with the biopharm and CRO aligning their therapeutic expertise and leveraging that knowledge with historical data to clearly define potential risks and identify critical core data. Clinical teams should appropriately identify risks that are related to patient safety, potential barriers to regulatory approval, and risks to the delivery of quality data on time or within budget. These risks must be identified and fully vetted by a cross-functional team, with particular attention paid to three main categories: scientific and medical risks, regulatory risks, and operational risks.

Once trial risks have been identified, the goal is to eliminate, reduce, or mitigate them as much as possible. If a risk cannot be completely eliminated, biopharms and CROs must ensure that they clearly document the risk mitigation strategy, including which data, tools, or systems will be used to signal when that risk is about to occur and what type of remediation will be necessary. It also is important to isolate those trial procedures or activities that are considered essential to supporting the evidence needed for product approval. This will enable more informed discussions about potential areas where there may be excessive procedures in place that could expose patients to risk.

CLINICAL TRIAL EXECUTION AND CONTROL

After a trial's operational strategy has been established, the focus shifts to the delivery of the strategic data monitoring plan. Monitoring activities should focus on the critical measurements identified in the protocol and on preventing important and likely sources of error in their collection and reporting. Biopharms and CROs must put systems in place that provide the data transparency needed to support a strategic data monitoring plan — one that may combine a centralized approach with targeted or triggered strategies.

The ability to use tools that aggregate large datasets is critical and enables a more risk-adaptive monitoring approach to be adopted across a trial. Potential metrics could include differential data between sites around patient recruitment, serious adverse events reported, and reports of noncompliance. Simply collecting large amounts of data, however, does not mean statisticians will be able to identify unfavorable trends, potential risks, or safety issues. With the many data repositories that already exist, the challenge is integrating data streams into reliable intelligence that allows biopharms and CROs to make better and more timely decisions. It comes down to how well disparate data can be leveraged to make the right data available at the right time to support planning and operational delivery of clinical trials.

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Adaptive Clinical Design Addresses The Uncertainties

By Cathy Yarbrough, contributing editor

When a traditional, randomized, controlled clinical trial fails, it's not unusual for the study manager to comment, "If I knew before the trial began what I know now, the trial would have been planned differently." To avoid this post-trial scenario, many biopharmaceutical companies are adopting adaptive clinical-trial designs, which allow the number of dosages and other trial-design elements to be modified at predetermined time points and under specific conditions outlined in the trial protocol.

The adaptive trial design allows managers who are planning a new trial to predict what they likely will regret at the end of the study. "If you're anticipating that you'll regret that the trial didn't test a larger dosage, the trial can be designed to also evaluate that dosage should the results dictate it," said Scott Berry, Ph.D., a senior statistical scientist and president of Berry Consultants. Unlike a traditional trial, an adaptive clinical trial "sequentially updates what is known about the drug or device under study," he added.

Adaptive clinical design also addresses the uncertainties that often exist before a study begins regarding the ideal sample size, dosages, treatment durations, and analytic method to use for evaluating the end point. Even the choice of end point is sometimes not clear.

In a traditional randomized clinical trial, the study's leaders deal with these uncertainties by using the best information available before the study begins. Despite the uncertainties, the sample size and the other design elements must be locked in before patient recruitment begins and are immutable for the entire length of the trial. "An adaptive design allows you to take advantage of the new information generated during a trial about, for example, the best therapeutic doses so that the randomization process can be modified to hone in on these treatment arms by assigning more patients to them," said Dr. Berry.

An adaptive clinical trial can be blinded or unblinded, according to the FDA's draft guidance for industry, "Adaptive Design Clinical Trials for Drugs and Biologics," published in 2010. However, the draft guidance states, "the risk of bias is greatly reduced or entirely absent when adaptations rely only on blinded analyses and the blinding is strictly maintained."

THE FDA SUPPORTS ADAPTIVE CLINICAL DESIGNS

The FDA has indicated its support of adaptive clinical trials. In 2006, CDER Director Janet Woodcock, M.D., said, "Improved utilization of adaptive and Bayesian methods could help resolve the low success rate and the expense of Phase 3 clinical trials."

Bayesian refers to the probability and statistical methods based on the concepts of Thomas Bayes. Classical statistical approaches also can be used to design an adaptive clinical trial. However, the Bayesian approach often is more appropriate for complicated clinical trials that ask many questions, said Dr. Berry.

Over 40 Bayesian adaptive clinical trials are listed as ongoing, terminated, or completed on www.clinicaltrials.gov. Among the ongoing trials is Eisai Inc.'s Phase 2 study of the investigational compound BAN2401 for the treatment of early Alzheimer's disease. BAN2401 is an mAb antibody directed at the protofibrils that are believed to be the toxic form of amyloid leading to the pathological changes in the brain that characterize Alzheimer's disease. Eisai selected the Bayesian adaptive design for the Phase 2 study because "it mitigated our uncertainties about the dosage, treatment duration, and end point that should be used in the trial to determine whether the drug has a clinical benefit and is disease-modifying," said Andrew Satlin, M.D., executive VP of the neuroscience general-medicine product-creation unit at the biopharmaceutical company.

Persuading Eisai's leadership was not that difficult, he said, because "everyone recognized that we needed to do the trial differently" because of the high-profile failures of three previous conventional Phase 3 studies of experimental Alzheimer's drugs. Those trials were not sponsored by Eisai but other major biopharmaceutical companies.

A traditional Phase 2 study of BAN2401 would have been very large and costly, Dr. Satlin added, and would not provide Eisai with the opportunity to learn the most effective — and least effective — dosages and other design elements that should be

incorporated in the design for a future large Phase 3 study. "The Bayesian adaptive trial design will teach us what to do in Phase 3," said Dr. Satlin. Because the current Phase 2 study is blinded, Dr. Satlin and his team members at Eisai and the investigators at the trial sites are unaware of the trial data, including any modifications to the trial design that result from the interim analyses of the data.

ONLY THE COMPUTER "KNOWS"

In the Eisai study, only the computer system running the trial has access to the unblinded patient data, and it uses sophisticated computation algorithms to direct the analysis of the data and modify the trial if specific contingencies occur, Dr. Satlin said. The algorithms are based on the extensive pretrial simulations and scenario planning by Dr. Satlin and his staff. "We thought through the possible outcomes that could occur if we evaluated five dosages," he said.

The biostatistics experts on Dr. Satlin's team calculated probability distributions for the effects of the different dosages. The algorithms use these probability distributions during the multiple planned interim analyses. Also during the analyses, the trial's longitudinal model adjusts the probability distributions based on all of the patient outcome data up to that point in the trial. If an interim analysis reveals that the highest dosage is the most effective, and the lowest dosage is the least effective, the randomization process adapts by assigning fewer patients to the least-effective dosage arm.

"Another possible outcome is that none of the dosages will work," he said. If futility is determined, the trial's computer system is programmed to alert Dr. Satlin's team so that the trial can be terminated.

The trial's computer system also informs Dr. Satlin and his staff if an interim analysis indicates an obvious clinical benefit of the drug. If this occurs before the completion of the trial (cutoff point for the estimated meaningful difference in change from baseline on primary end point for BAN2401 compared to placebo is 25 percent), Eisai will be able to trim development time and cost by initiating a Phase 3 trial while the Phase 2 trial is ongoing, he said. If a Phase 3 trial occurs, its design will be conventional, he said.

"Once we learn from the Phase 2 study everything we need to do to design a Phase 3 trial so it will be successful, there is no longer the need for a Bayesian adaptive design, and we avoid the complexities and added work associated with a Bayesian adaptive design," said Dr. Satlin. "Also, regulators are more comfortable with a traditional design for Phase 3 because there is no possibility that trial modifications have been done, and therefore the results are easier to interpret."

The BAN2401 study is the first, but will not be the only, Bayesian adaptive trial sponsored by Eisai. A new insomnia drug and another Alzheimer's disease drug soon will be evaluated in Bayesian design trials.

Global Business Update

Pharmaceutical Market Access In Brazil

By Davide Zaganelli

With expectations to reach 30 percent of the nearly $1.2 trillion U.S. global spend and 50 to 70 percent of the $70 billion annual U.S. growth forecasted in the pharmaceutical sector by 2016, it is clear why emerging markets are considered the new frontier. They are the new hope for a pharmaceutical industry that is seeking new strategies and partnerships to balance the stagnation in more mature markets.

Today's emerging markets — quickly growing, increasingly competitive, and culturally, socially, and economically diverse — defy a uniform approach and instead call for local business planning based on a comprehensive and global perspective. For this reason, international pharmaceutical companies must be willing to implement market-specific strategies and local thinking within their global business strategy. Nevertheless, evolving political stances, increasing international competition, and rising local manufacturers are toughening market-access environments and creating new, and sometimes unexpected, risks for drug makers.

Brazil is one of many examples showing how quickly business conditions for drug makers are changing and how important it is to identify, evaluate, and foresee such changes as early as possible to improve and consolidate market positioning. This article provides an overview of the latest trends regarding pharmaceutical taxation, strategic partnerships, and generics promotion.

LATEST REFORMS AND NEW CHALLENGES

With over $220 billion of healthcare expenditure, a strong economic growth, and drug prices adjusted annually (2.7 to 6.31 percent increase estimated in 2013), Brazil is destined to become the third-largest pharmaceutical market by 2020 after the U.S. and China.

Despite its strong economic growth, Brazil faces increasing pressure to control healthcare expenditures and, at the same time, promote innovation and improve access to healthcare. Pursuing this difficult task, decision makers are discussing several initiatives, some of them already converted into law, which will reshape the pharmaceutical market in the following years. In a context of increasing competition and stricter regulatory hurdles, Brazil will become a much more challenging business environment.

DECREASING TAXATIONS ON PHARMACEUTICALS

Even though international companies operating in the Brazilian healthcare market are approximately 20 percent of the total healthcare manufacturers based in Brazil, they represent 75 percent of market share.

Decreasing taxation on medicines for human use is seen as an effective way to promote and incentivise over 550 laboratories that represent the internal pharmaceutical sector. Two different measures adopted in the last six months confirm this strategy:

On Nov. 28, 2012, the Brazilian Committee on Constitution, Justice, and Citizenship approved a replacement bill proposing a constitutional amendment that would prohibit the collection of taxes on medicines for human use. Import taxes, however, will remain in place as it was recognized that "the import tax serves as an instrument of government economic policy, which should continue providing the flexibility to maneuver its rates and the need to protect the domestic market from indiscriminate entry of foreign products."

More recently, on March 13, 2013, a tax-deferral measure was officially published to suspend goods-circulation taxes in the state of São Paulo for domestic products and imported pharmaceutical ingredients or intermediate drug products purchased by the Foundation of Popular Medicines (Fundação para o Remédio Popular). The Foundation is linked to the São Paulo department of health and is responsible for developing, producing, and distributing pharmaceutical products in Brazil. This rule is valid for imported generic or biosimilars not yet available in the country.

SEEKING NEW PARTNERSHIPS

Brazil recognized that the development of technology in healthcare is necessary

CHANGE

IS COMING

NORWICH IS CHANGING THE FACE OF OUTSOURCING
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to strengthen national industrial manufacturing, reduce dependency on product importations, and achieve better control over expenditure. To date, 34 technology transfer partnerships between public and private laboratories have been established for the production of 28 drugs (including Pramipexole, Tenofovir, Clozapine, Quetiapine, Olanzapine, Tacrolimus, Rivastigmine, and Donepezil), and 3 vaccines. According to the Ministry of Health, at least 20 new partnerships are expected over the next four years, including biological products and medical devices.

In the medium and long term, stakeholders are not only seeking internal development, but they are also hoping to increase competitiveness of Brazilian pharma companies abroad. A further step in this direction was made early this year when the Brazilian president, Dilma Rousseff, announced that the recently created Brazilian Enterprise for Research and Industrial Innovation (Embrapii) will be responsible for promoting partnerships between public innovative research institutions and private companies to create new products and processes.

Brazil Key Facts

States	27
Population	205 million
Total Expenditure on Health	220.2 (US$ billions)
Total Expenditure on Public Health	47% (of total expenditure)
Out of Pocket Expenditure on Health	57.8% (of private expenditure)
Total Pharmaceutical Market	34.8 (US$ billions)
National Public Healthcare System	SUS (Sistema Único de Saude)
Outpatient Clinics	65,000
Hospitals	6,000
Immunization Clinics	23,000
Private Healthcare System	Healthcare Insurance Based
Coverage	25.1% (of total population)
Aggregated Healthcare Insurance Revenue	41.8 (US$ billions)

INCREASING GENERICS MARKET SHARE

Generics were introduced in Brazil 30 years ago with distrust from both general consumers and prescribers. Nowadays, the generics market share in Brazil is still lower than in other markets (e.g. 26 percent in 2012 compared to 66 percent in Germany and 60 percent in the United Kingdom and U.S.), but it is expected to increase to 45 percent by 2020. According to the Pro-Generics Association, by the end of this year the market share of generic drugs should increase to 30 percent.

Trying to capitalize on this broad and increasing interest from decision makers, the generic drugs industry is proposing that new generic drugs, such as those whose patents have expired and do not have other generic competition in market, should be granted priority by ANVISA (National Health Surveillance Agency Brazil) in order to decrease regulatory time for authorization and increase access to healthcare. The prominent players in Brazil's generics market are Brazilian companies Medley, EMS Sigma Pharma, Eurofarma Laboratórios, and Aché Laboratórios Farmacêuticos and Indian multinational Ranbaxy Laboratories Ltd.

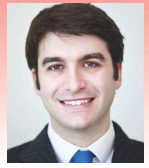
WHAT DOES THIS MEAN FOR YOUR COMPANY?

In the coming years, the favorable healthcare environment will allow local companies and generic drug makers to rapidly increase their market share and negatively impact on international manufacturers of branded products. Moreover, key decision makers are expected to adopt stricter regulatory, pricing, and reimbursement regulations to further develop internal pharmaceutical manufacturing.

As a direct consequence, market access in Brazil will become increasingly challenging for international pharmaceutical companies, making it necessary for global businesses to evaluate and adapt their business strategy to local realities. Strategic offerings, including technology transfer agreements, will be a key factor to secure continued market sales growth in the following years. International pharmaceutical companies should also consider financial/outcome-based pricing agreements and other alternative approaches to meet the increasing demand for access to healthcare without impacting excessively on budget.

Keeping track of legislative, pricing, and reimbursement changes; foreseeing how competitors' launches will impact your portfolio; and linking Brazil to global decisions and international referencing pricing are essential to identifying and bending gaps and trends shaping the pharmaceutical market in your favor.

About the Author



Davide Zaganelli is senior consultant and global market access manager at Alliance Life Sciences Consulting Group. With a keen interest in Latin America, he manages market access, pricing, and business strategy activities in both emerging and established markets, supporting pharma and biotech companies in maximizing effectiveness and product potential.

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Access To Big Data Accelerates Discovery And Cuts Drug Development Costs

Well before the term "Big Data" was coined, scientists grappled with how to manage the explosion of discoveries producing a plethora of information about newly discovered biological entities. This accelerated information growth about cellular activities and disease pathways could not have been imagined 60 years ago when James Watson and Francis Crick elucidated and published their seminal work on the double helical nature of DNA. This escalation in genomic, proteomic, and metabolomic information is reflected in the increasing records in scientific databases worldwide.

Today's medicinal chemists and molecular and cell biologists often rely on sophisticated computer-based resources to assess a therapeutic area and to more efficiently interpret and analyze large volumes of information, so they can get back to the laboratory more quickly.

THE VALUE OF PARTNERSHIPS, DATABASES

New molecular entities that are biopharmaceuticals, versus small organic molecule therapeutics, are estimated to comprise more than 30 percent of the 5,000 potential therapeutics currently in research and development. Like their pharmaceutical colleagues, biotech companies deciding to pursue the treatment of a disease commit huge sums of capital that will be invested over the lifetime of a project. Before making a financial commitment like this, it is vital to know as much as possible about the intended project. Is the disease pathway known? Are there any validated targets in that pathway? Is anyone else solving or working on the problem? What does the patent landscape look like? Can any existing therapies be improved? In the rarified atmosphere of the boardroom, the answers to these questions, which are almost never straightforward, must be determined before a company decides to invest between $1.5 and $4 billion, Burrill & Company's estimated cost to bring a new therapeutic entity to market. To help control the cost of this investment and to move as quickly as possible through all aspects of development and eventually clinical trials, biotechs have sought outside help with aspects of the project where they may have limited inhouse experience. Development partners with a targeted expertise can aid in controlling development costs and in moving a promising therapy to market more quickly.

In addition to establishing strategic partnerships, using large, scientific, electronic databases can provide background and insights into what has been accomplished and what hasn't worked yet regarding a particular drug. These databases also can help with ferreting out unpromising candidates early, intensifying efforts on candidates promising the greatest impact, and collaborating with external partners possessing specific expertise that could help the drug discovery process move faster and ultimately control costs.

REMEMBER TO INVESTIGATE PATENTS, TOO

As commercial organizations and academic institutions worldwide seek to monetize their research results, patents have become an increasingly important part of the world's published scientific information. According to the American Chemical Society, in 2012, more than 70 percent of newly recognized substances came from patents, compared to about 14 percent in the mid-1970s. Furthermore, the Asia-Pacific countries, led by China, are currently responsible for the huge patent growth worldwide.

At the inception of a project, discovery scientists using large scientific databases can find information about what has been patented and who else is investigating in the same area.

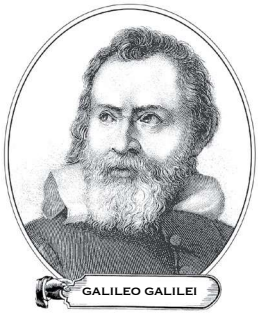
Advanced scientific search technology also enables a scientist to quickly view all other therapeutic indications and their literature references that a particular drug is correlated with (e.g. antiviral, antitumor and dermatological agents, analgesics, immunosuppressants). Additionally, the protein targets that the drug may inhibit that have been reported in the publicly disclosed literature are also easily available.

Considering Big Data includes the wealth of biological and chemical information available to the biotech industry today, the problem of easy access to that information has been mostly solved. The challenge in today's information-laden world is separating the reliable material from the simply available. At the beginning of a biopharmaceutical project, access to large, curated scientific databases using electronic search and discovery tools will provide a thorough picture of the research landscape and help scientists efficiently plan and synthesize new ideas and collaborations.

Roger Schenck

Roger Schenck is manager of the Chemical Abstracts Service (CAS) Content Planning Department where he works with customers to ensure that CAS is building the right databases for the future.

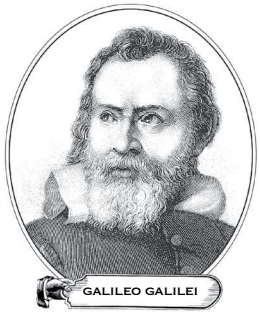
Compare impartial peer reviews to find the ideal CMO



Company No. 1

Facility newly acquired from Big Pharma

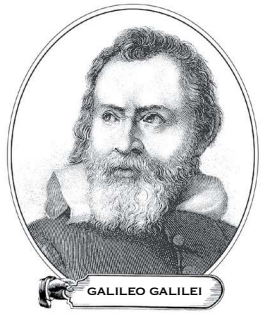
Problem with cultural integration



Company No. 2

Production capacity increase at facility

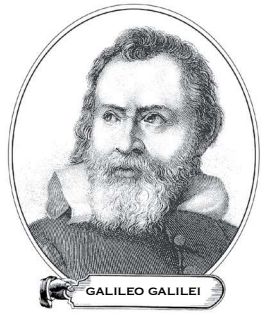
Lengthy regulatory validation required



Company No. 3

Mammalian and microbial cell line offering

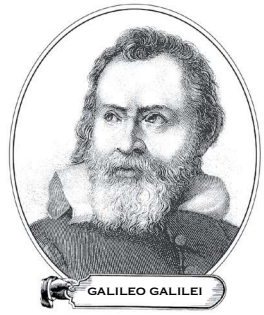
Potential for cross contamination



Company No. 4

Project involves large molecule tech transfer

Requires regulatory filing change



Company No. 5

Potent compound capability / experience

Risk of contamination due to facility layout

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How To Strengthen Biotech's Pipeline? Partner With Academia

The year 2013 has already been an impressive one for advancements in biotech. For example, at Cornell University, a team created artificial body tissue from gels found in animal collagen and cartilage. At Tufts University, biologists harnessed bioelectric cancer detection, which assumes tumor sites exhibit a distinct voltage or bioelectric signal compared to surrounding cells. And at the University of Washington, researchers used minute coloring material to pinpoint proteins in cancer cells, analyze cells unaffected by treatment, and attempt to predict which cells may become cancerous and why.

All of these advances came from academia, not biotech companies, which is why I strongly believe that integrating academic institutions with the research and development pipeline — and having access to their facilities and research potential — to be of major importance. Leaders of companies developing cutting-edge treatments ought to be especially attuned in the benefits that can accrue from such relationships.

At present, California represents America's largest arena for biotech investments, along with both research and production. A focal point for the success and growth there comes from strong, mutually profitable relationships between companies and leading academic institutions. Collectively these institutions represent a central partner for the biotech industry that allows for an ever-growing synergy of discovery and commercialization.

University collaboration has not only resulted in creating unique opportunities — such as the initiation of clinical trials for the current clinical indications in development pipelines — but also provided guidance for the direction of new technology and product development.

From a business standpoint, the relationships that allow academic institutions to provide a research outcome are only one of the components of importance. There is also the impact — i.e. how the new knowledge derived from a collaboration with a university can contribute to future efforts and, ultimately, a company's performance. When evaluating an academic collaboration, companies should consider if the following are possible due to the collaboration:

- new therapeutic product opportunities?
- new and more effective treatment processes?
- novel innovations and optimization of a delivery platform?
- intellectual property, clinical know-how, or processes that enhance competitive advantage?

At present, California represents America's largest arena for biotech investments.

In turn, a university that engages in this kind of partnership with a company adds to its prestige in several ways. It offers an opportunity for its faculty members to further demonstrate their value — and embellish their professional records — by engaging in research outside of the ivory tower; it allows university management to demonstrate to its trustees, benefactors, and alumni the importance and relevance of its research programs; and it offers a potential new stream of revenue depending on the nature of the agreement and the outcome of the research.

I believe biotech would be well-served by building a community that includes researchers and academics as well as industry professionals.

Working together, the biotech industry and academia can improve not only biotech's bottom line but the public's healthcare options as well.

Punit Dhillon

Punit Dhillon is president and CEO of OncoSec Medical Inc., a biotechnology company developing its advanced-stage ImmunoPulse DNA-based immunotherapy to treat solid tumor cancers.

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The Benefits Of Building A Cognitively Diverse Team

Ed Henkler

Creativity and innovation are the lifeblood of any research organization, yet the media is filled with tales of biopharmaceutical companies struggling to discover and develop novel compounds. Hiring efforts often focus on top graduates from top schools, a strategy that guarantees excellent product but not innovative behavior. If you follow this strategy, all members of your team will tend to have a similar way of approaching problems. A professor from an Ivy League school once told me that the primary difference between his students and those at a neighboring city school is that the latter did not realize they were as smart as the Ivy League students. Tap into this market, and expand your recruiting efforts to second-tier institutions. Their top graduates are very smart and may surprise you with their work ethic and insights. A Google search on "Fortune 500 CEOs and their colleges" will demonstrate how many colleges have produced successful graduates, and you will also find that 35 of these CEOs did not even graduate from college.

Disability And Innovation

In 2009, approximately 750 million people had some form of disability, and baby boomers are driving that total higher rapidly. Hiring individuals who are disabled may pose some issues to resolve, but it can increase the possibilities dramatically. Many companies have discovered that hiring individuals who are differently abled can strengthen their productivity while reducing turnover and injury rates and increasing retention. The most well-known example is Walgreens, which has two distribution centers, each employing more than 40 percent individuals with a disability. These two sites outperform most of the other centers and have demonstrably improved morale. The bottom line is that our world still provides inadequate accommodation for individuals with disabilities. Ingenuity and inventiveness are essential to handle tasks others take for granted. Hiring employees who are differently abled virtually guarantees a more creative and innovative team. It's also the right thing to do.

Engage The Worker Bees

D. Michael Abrashoff wrote a marvelous leadership tale, "It's Your Ship: Management Techniques from the Best Damn Ship in the Navy." Unfortunately, in spite of a capable crew, only a fraction of the highly advanced ship's technology was being employed. Abrashoff created a culture of "it's your ship," resulting in everyone feeling personal responsibility for increasing the effectiveness of their station and their ship. He consistently engaged his frontline employees in strategic decisions, recognizing that their system expertise was at least as valuable as the theoretical knowledge of his senior leaders.

Problems are best solved by the people who routinely manage the associated activities. This is not intended to disparage the "chosen," only to suggest that while they have a role, they aren't the only ones who can contribute. As you engage more and more of your employees, innovation can become the norm. A chain is only as good as the weakest link — strengthen all of them!

Ed Henkler works with companies, from start-up through large cap multinational, to bring their strategic plans and big ideas to life. Engaging the right people at all levels ensures that they remain committed well past the excitement phase. For more info, go to http://edhenkler.com/.

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

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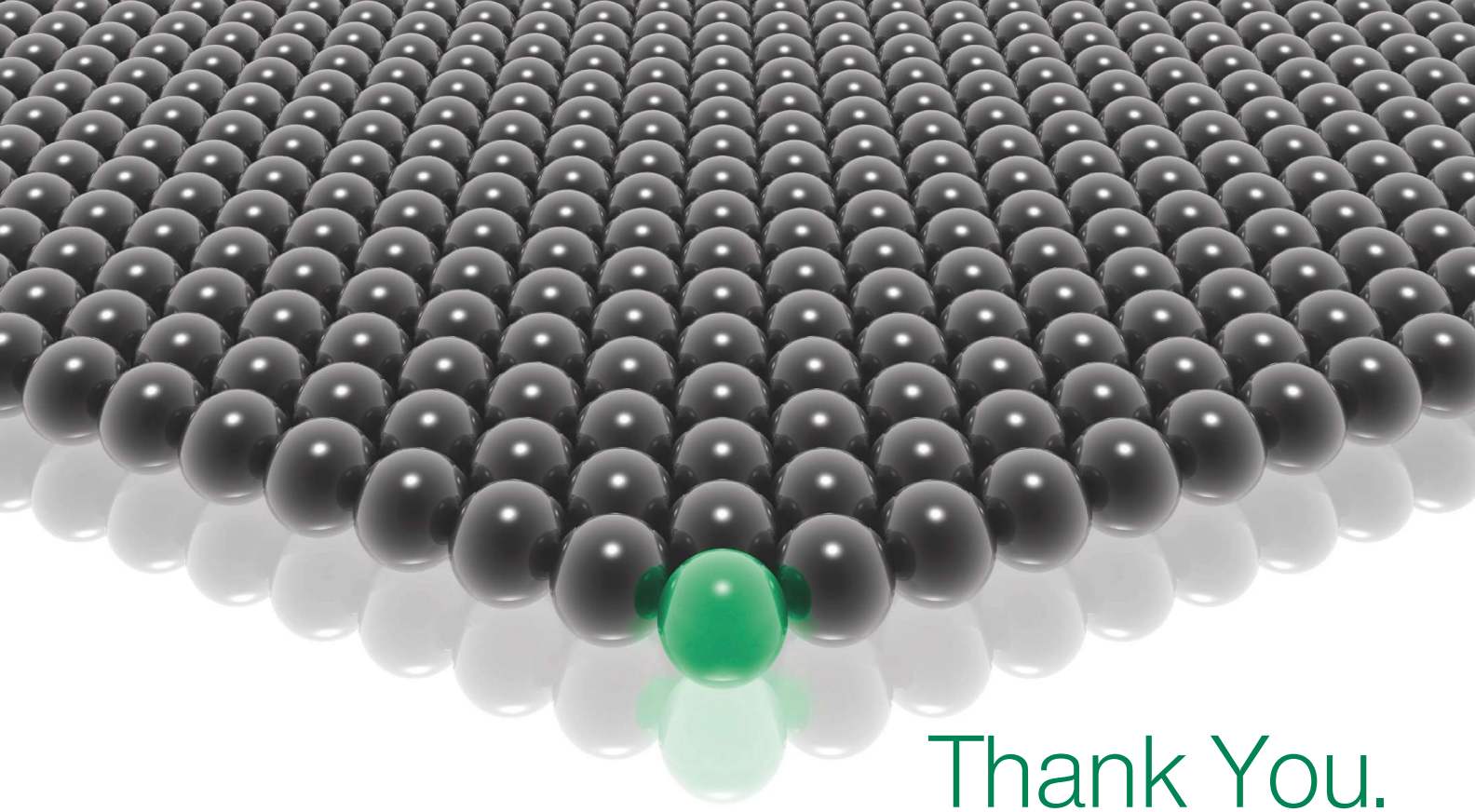

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