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November 2012
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Roche Diagnostics:
An Interview With Dr. James Creeden p. 28

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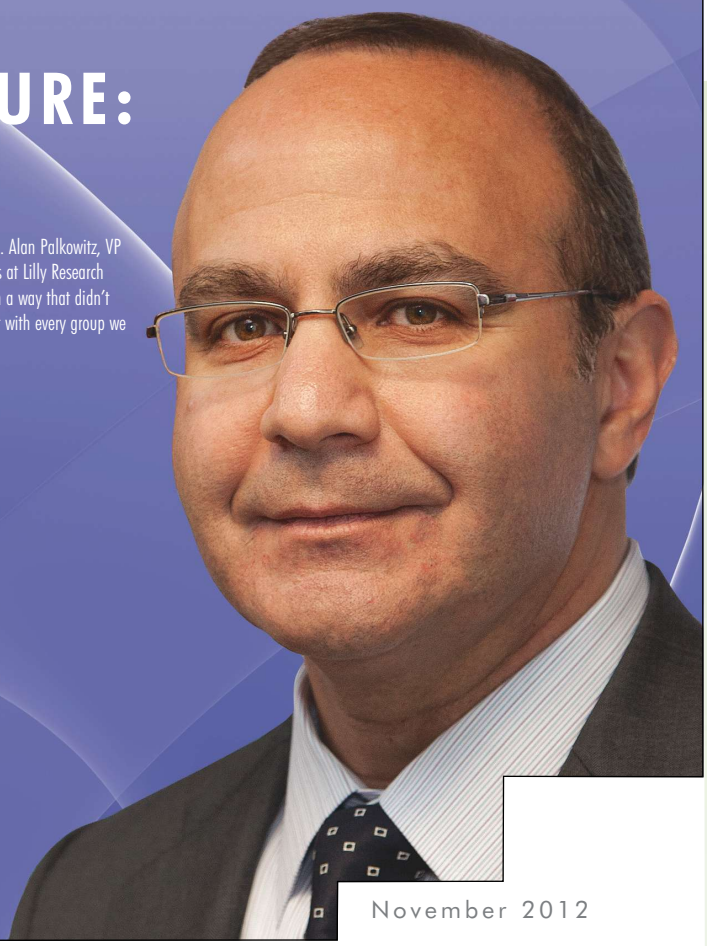
20 FEATURE: LILLY

When seeking external sources of innovation, Dr. Alan Palkowitz, VP of discovery chemistry research and technologies at Lilly Research Laboratories, explains, "We wanted to do this in a way that didn't require us to have a unique business agreement with every group we interacted with."



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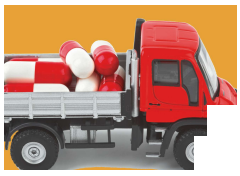

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EDITOR'S NOTE

Warning: Navigating Economic Uncertainty

Recent conversations around the 2012 United States Presidential election discuss how during uncertain times, when faced with choosing between two alternatives, one being a known commodity and the other an unknown, most people opt for the known. Why? Because it is more secure and provides for less risk. Uncertainty results in a cautious approach. Political unrest in the Middle East, the European debt crisis, and a variety of other factors have created global economic uncertainty, and its impact on the life sciences is evident. For instance, in our October issue Cindy Dubin painted a very bleak picture, noting how life sciences venture funding dropped to its lowest level since the third quarter of 2002 (see "Life Science Venture Funding Drops").

Traditionally, pharma stocks have been a safe haven for investors during an economic storm. Many analysts argue that this is no longer the case, citing pharma's dependence on sales from developed countries, governments seeking to cut costs, generic incursion, death of the blockbuster, and so on. In my opinion, however, the time is right to be looking at life sciences companies for investment. Consider that, at this writing, the Dow Jones Industrial Average (DJIA) is within 650 points of its all-time closing high of 14,164.53 (10/09/2007), and we remain in a recession. Three of the 30 companies which make up the DJIA are pharmas — J&J, Merck, and Pfizer, while many others have either strong ties to life sciences, or life sciences business units. With regard to these three, the last to have a stock split was J&J in 2001.

Another reason I feel good about the financial state of life sciences companies is based on demographic insight provided by Ken Gronbach, author of *The Age Curve*. In the book he points out that the two largest-ever U.S. generations will be spending heavily on healthcare. Baby Boomers, born between 1945 and 1964, will be buying lots of pharmaceutical products, hip and knee replacements — anything to stay young. The second-largest generation, Generation Y (people born between 1985 and 2010), has entered peak childbearing age (20-35), which will continue for 20+ years. Children require lots of healthcare. Global healthcare demands will continue to rise as well. For example, China already has more than 123 million people over the age of 65.

They say optimism breeds success. This is why we recently added the feature, "Companies to Watch" (page 10). Each month, contributing editor Wayne Koberstein takes a look into some lesser known life sciences companies, providing insight into how they were funded, what partnerships they've established, and what drugs they have in development. Though we continue to navigate in economic uncertainty, well-managed life sciences companies are poised to capitalize on opportunity. Are you poised to capitalize on life sciences?

Rob Wright
rob.wright@lifescienceconnect.com
@RFWrightLSL

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>
> - Glenn R. Siegele, President
> Omega Design Corporation

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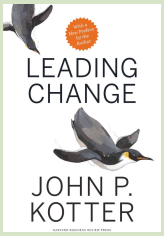

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ASK THE BOARD

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

Q: With recent advances in technology, why do a large percentage of compounds continue to fail in late-stage development?

There are many reasons. A recent examination by *Nature* writer Heidi Ledford, Ph.D., revealed that most product failures in Phase 2 and 3 trials are related to lack of efficacy or negative benefit-risk profile. Despite advances in technology, less costly and more predictable challenges remain. These include: shifting focus from "me-too" products to more innovative ones that carry greater risk as new targets, delays in translating the genomic revolution into novel targets, lack of good predictive safety and efficacy models, increasing trial complexity, greater scrutiny of safety profiles by all stakeholders, and continued high hurdles to satisfy regulatory needs. On the positive side, considerable progress is being made in many of these areas that should help industry realize the full potential of new tools and hasten the approval of new therapies.

John Orloff, M.D.
John Orloff, M.D., is the chief medical officer and SVP global development, Novartis Pharma AG. He also serves as chair, Pharma Portfolio Stewardship Board (PSB), overseeing safety and risk management plans for pharmaceutical products.

Q: Where do you see the next big breakthrough in companion diagnostics?

The world of diagnostics is moving away from population-based diagnostics toward precision diagnostics — high accuracy solutions that reduce over- and underdiagnosis. Precision diagnostics may be deployed on a stand-alone basis, but a strategically rich use is in pairing with a partner therapeutic, so-called "companion diagnostics." Although a misnomer in that the diagnostic and therapeutic are both companions, this paradigm employs highly accurate diagnostics to distinguish patients who truly have a given disorder and will benefit from a given therapeutic, from those who don't and won't. The classic example is the HER2 biomarker to separate breast cancer patients with a particular genetic signature from those without it in arriving at treatment decisions. Diagnostics are facilitating more precision-oriented, personalized healthcare in which error rates are reduced and therapeutic effectiveness is enhanced, enabling overall improvements in healthcare efficiency.

Mark Pykett, Ph.D.
Mark Pykett, Ph.D., has more than 15 years of pharma industry executive management experience. He has been a senior executive at multiple companies, including Neoprobe Corp., Talaris Advisors, Alseres Pharmaceuticals, CyGenics, Cytomatrix, and Oramax.

Q: What will be the next big technology breakthrough to revolutionize drug discovery and why?

There is great work happening in informatics, simulation, and modeling. One example is the notion of software-based laboratories in which we could run many thousands of in-silico experiments to understand biological pathways, compound properties, and patient populations. Scientists are developing entire organism simulations. Emerging analytics capabilities can assess a vast amount of "Big Data" of various types, discovering patterns and relative significance. Collaboration and orchestration technologies are already enabling profound transformation in the industry's approach to drug discovery, increasing our ability to leverage multiple expert entities in parallel drug discovery engagements. While perhaps not the next big breakthrough in drug discovery, it is worth mentioning the work with nanotechnology in treating disease. For example, Wyss Institute scientists have developed nanotechnology to assist in the delivery of drugs to cancer cells — this would impact the considerations as new medicines are developed.

Angela Yochem
Angela Yochem is the chief technology officer at AstraZeneca, where she forms strategic partnerships to drive innovation and business advantage through technology. Yochem has previously held senior roles at Dell, Bank of America, SunTrust, UPS, and IBM.

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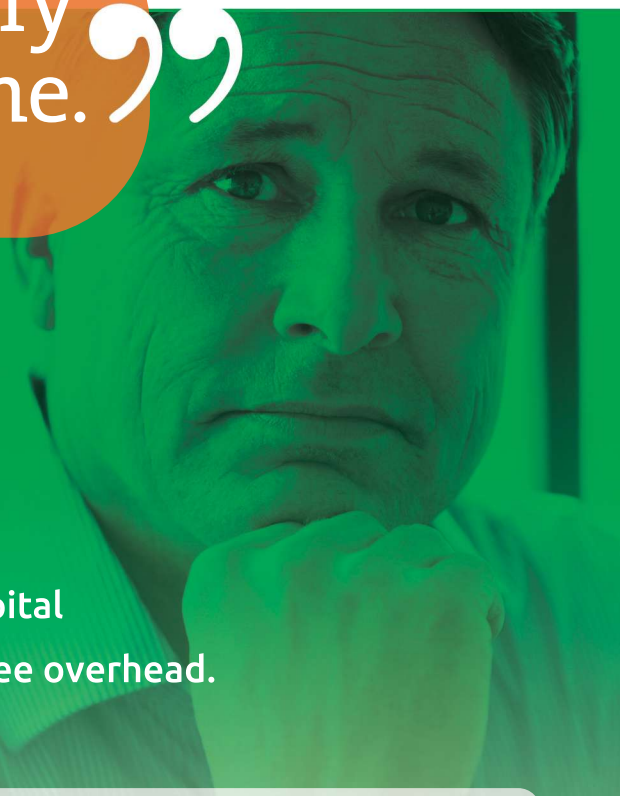

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By Wayne Koberstein

Aeras

Pandemic need produces a nonprofit player.

SNAPSHOT

Aeras (www.aeras.org) is a not-for-profit enterprise developing next-generation TB vaccines. It has a pipeline of vaccine candidates in preclinical, Phase 1, and Phase 2 development and partnerships with small and large companies, government and academic institutions, and nongovernmental organizations (NGOs). It aims to have a vaccine available worldwide in less than 10 years and ultimately protect people from infection, transmission, onset, and recurrence of the most severe forms of the disease.

WHAT'S AT STAKE

Although other companies and institutions are working on pieces of the TB challenge, and some have vaccine candidates in their pipeline, Aeras is the only player organized solely around the vaccine goal with integrated development and manufacturing functions all operating in a single organization. "We have the ability to take the innovative discoveries by academic scientists and other entities — drug candidates that might not otherwise move forward without our support — and facilitate their development and testing," says Aeras President & CEO Jim Connolly. "We're not looking ultimately for shareholder return or paying back investors in the classic sense; as a result, we are able to take more risks and form more flexible and nontraditional alliances than for-profit companies." Aside from its not-for-profit status, Aeras is a real company in every respect. It has six vaccine candidates in its clinical pipeline and is testing various vaccine platforms and TB antigens. It has built a $30 million production facility sufficient to supply its clinical trials and then some. And it is tackling the scientific challenge of developing the first vaccine effective in adults and against pulmonary TB. The clinical trials will determine which vaccine candidate or candidates survive.

LATEST UPDATES

- Aeras recently signed an agreement with GSK Vaccines, S.A. to jointly advance the clinical development of an investigational TB vaccine containing GSK's proprietary M72 antigen and AS01E adjuvant. A Phase 2b trial is scheduled to begin next year pending approvals from authorities.
- In August 2012, Aeras and IDRI started the first Phase 1 clinical trial of vaccine candidate ID93 + GLA-SE.

Part of the challenge is the lack of preclinical models and predictive assays to test any vaccine for this disease. "To test a TB vaccine to determine whether it is protective requires relatively large Phase 2b trials that can cost up to $30 to $40 million apiece," says Connolly. "We are fortunate to receive funding from donors and partners like the Gates Foundation, Wellcome Trust, and the U.S., United Kingdom, and Dutch governments, among others to help support our activities, but more will be needed as we progress into later-stage trials."

None of this is cheap or easy, and it will take other companies, governments, and NGOs working as partners with Aeras to pull it off. Inevitably, the vaccine will bridge the nonprofit and commercial realms. In fact, Aeras is already in partnership with several pharma/biopharma companies. However, Aeras will insist on wide access and "affordability" for any vaccine in distribution through partners. That limits but does not take away the financial incentives for such companies, according to Connolly. "TB affects the developing world, but it is also present in emerging markets like China and India, where higher price levels could be supported, as well as North America, Europe, and other commercial markets," says Connolly. The Aeras vaccine manufacturing facility and capabilities are able to support its work to develop TB vaccines as well as the efforts of others developing vaccines for neglected diseases. "We have been using the facility for our development work but it is still underutilized, so we are now looking to partner with more organizations, both not-for-profit and for-profit, particularly on process development and clinical lot manufacturing," he says. Even given the potential rewards, it is doubtful that any for-profit company could be as dedicated, integrated, and efficient as Aeras in reaching for the goal. Its special status allows it to rally a unique array of forces against a worldwide scourge that gets less attention from the industry's business side than many rare diseases.

VITAL STATISTICS

- Employees: 146
- Headquarters: Rockville, MD; Cape Town, South Africa
- Finances/Funding: Grant of up to $220 million over five years from the Bill & Melinda Gates Foundation
  - Government grants of about $10 million
  - Significant cofunding and cost offsets for TB vaccine development from research funders, pharmaceutical partners, and other partners.
- Research partnerships: Numerous partnerships with for-profit pharma companies and biotechs, academic and research organizations, other nonprofits, foundations, and governments.

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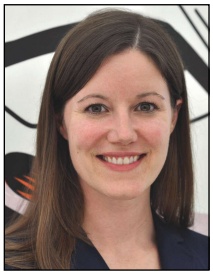

OUTSOURCING INSIGHTS

Essential Qualities Vary By Buyer Category And Business Size When It Comes To Outsourcing Relationships

By Kate Hammeke, director of marketing intelligence, Nice Insight

For buyers of outsourced services, identifying exactly which qualities make the greatest contribution toward a positive relationship with an outsourcing partner is an ongoing and ever-changing process. Depending on which adjectives are discussed as a list of CRO/CMO attributes, the ones that rise to the top will vary. Priorities also fluctuate relative to the individual prioritizing the attributes and the type of business for which they work. Also, it seems that as soon as one prioritization of qualities is identified, new information or technologies become available, and the precise mix of attributes changes.

The fluid nature of the drug development industry — one that is constantly adapting to new health challenges, therapeutic technologies, and regulatory legislature — is part of what makes it so difficult to define the priorities in partner attributes so the relationship functions like a strategic partnership to the benefit of both sponsor and CRO/CMO. The persistent state of flux reiterates the importance of keeping an open mind and learning from the experiences of one's peers. That way, the pressure to find exactly the right business for an individual project diminishes and is replaced by confidence in finding a company with the right mix of attributes that will make for a successful strategic relationship.

As soon as one prioritization of qualities is identified, new information or technologies become available, and the precise mix of attributes changes.

THE ESSENTIAL QUALITIES OF AN OUTSOURCING RELATIONSHIP

Recently, Nice Insight surveyed outsourcing buyers to ask them to separate the essential qualities of an outsourcing relationship from the nonessential and then to rank their essentials into a hierarchy that reflects their importance. The respondent group comprised four different categories of buyers of outsourced services — Big Pharma and Big Biotech as well as Midsize Pharma and Midsize Biotech. We wanted to focus on established businesses with a history of outsourcing, rather than including emerging or virtual companies for this particular study. We anticipated there would be differences with respect to the "essentials" and how they are prioritized across the different buyer categories.

Interestingly, Big Pharma and Big Biotech had more in common with respect to the way they prioritize outsourcing attributes than pharmaceutical companies or biotechnology companies of different sizes had with one another. For both Big Pharma and Big Biotech, "improved quality" and the "ability to use internal staff more efficiently" ranked third and fourth, following "reduced cost" and "operational expertise," which held opposite first and second place ranking between these two groups.

Greater differences emerged when reviewing how these two categories of buyer rank "general process improvement" — fifth in importance to Big Pharma respondents, yet eighth (last place) for Big Biotech. Conversely, Big Biotech ranked "gaining a competitive advantage" fifth, while Big Pharma ranked it seventh. One final key difference between the two is how they feel about access to "ad hoc support," which ranked last among Big Pharma respondents, but was a higher priority for Big Biotech than the potential to "increase shareholder value" or to gain "general process improvement."

KEY DIFFERENCES BETWEEN BIG PHARMA AND MIDSIZE PHARMA

Big Pharma and Midsize Pharma companies demonstrated differences in their ranking of essential qualities, especially with respect to use of internal staff. Midsize Pharma identified this as the number one priority when outsourcing, while Big Pharma ranked "ability to use internal staff more efficiently" fourth, after "reduced cost," "operational expertise," and "improved quality." The one area where Big and Midsize Pharma aligned was "access to ad hoc support," which both sponsor groups ranked eighth, reiterating it is least important for a CMO or CRO partnering with Big or Midsize Pharma companies.

Unlike pharma companies, respondents from Big and

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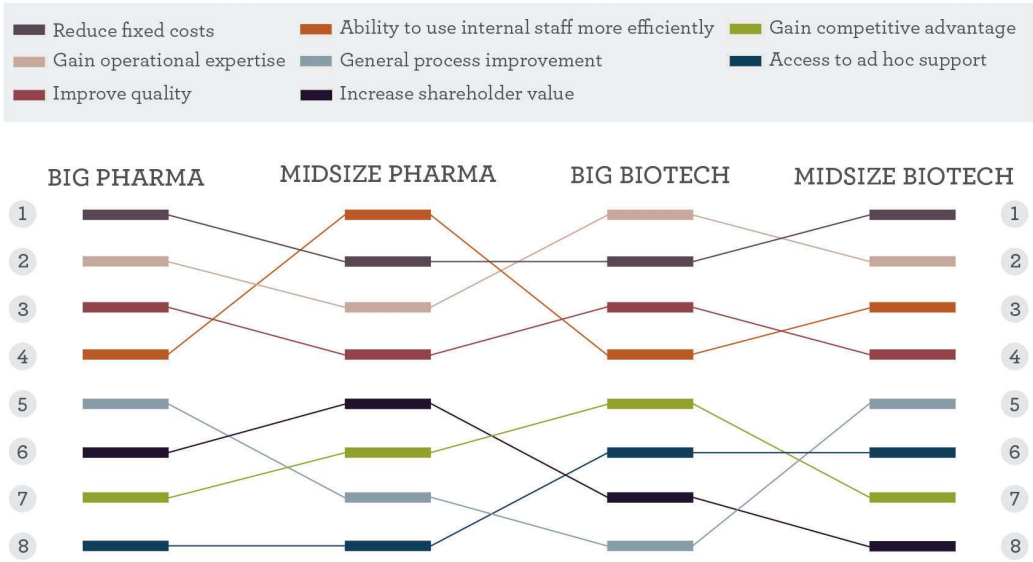
Midsize Biotechnology businesses gave higher prioritization to gaining access to ad hoc support by engaging outsourcing partners. However, this was where the similarities among biotechnology companies ended. The greatest differences in ranking were with respect to how Big and Midsize Biotechs view "gaining a competitive advantage," which was ranked fifth by Big Biotech and seventh by Midsize Biotech. Additionally, these buyers viewed "general process improvement" differently. This element ranked fifth among respondents from Midsize Biotechs and eighth — or the lowest priority — among Big Biotechs.

Understanding how buyers prioritize their essentials in gauging contract service providers can offer advantages to peers in terms of decision making in outsourcing. It equally helps the service providers to position themselves more strategically.

Among sponsors, knowledge sharing has enabled newcomers to learn from more established peers and adopt techniques that contributed to their success. Likewise, well-established companies with long-standing practices can potentially catapult their business to a new level of success by learning from the perspective of newer businesses in the industry.

NI Outsourcing Essentials Ranked by Buyer Category



Survey Methodology: The Nice Insight Strategic Partnering Survey is deployed on behalf of Nice Insight clients to a targeted group of outsourcing decision makers. The survey comprises ~40 questions geared towards understanding current outsourcing practices, present and future expectations from outsourcing partners, and which traits contribute to successful partnerships in addition to sources of dissatisfaction. [n=150]


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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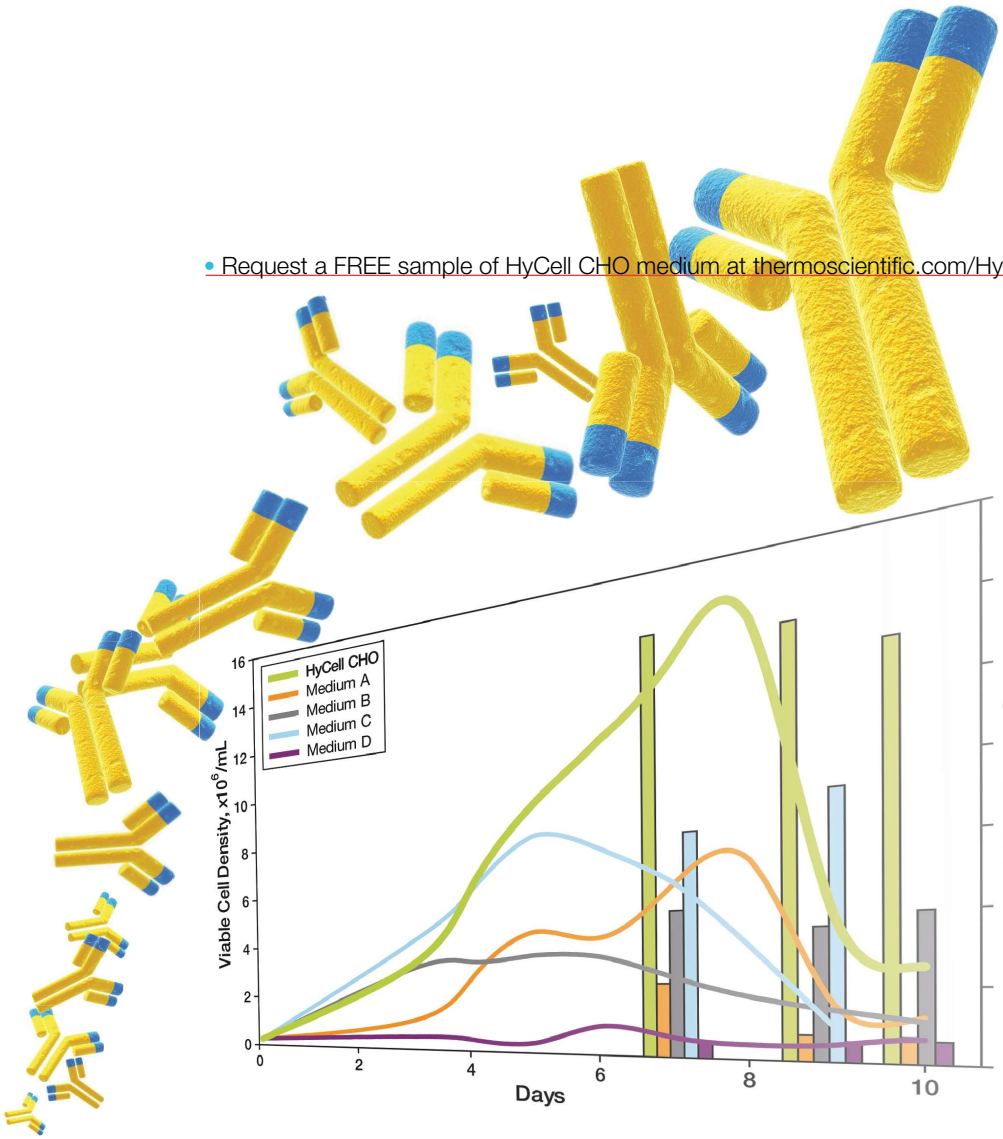

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BIO DATA POINTS

Single-Use Recycling Mismatch: BioPharmaceutical Manufacturers Missing An Opportunity

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

The biopharm industry is expressing increased concern over disposal issues associated with single-use devices. Although cost and economic issues continue to be a priority today, there is a growing gap between how manufacturers believe their plastic single-use system (SUS) devices should be disposed of and what is actually being done, according to results from our 9th Annual Report and Survey of Biopharmaceutical Manufacturers.

In our study, we asked 302 biotherapeutic developers and CMOs to tell us how their facilities dispose of SUS devices and compared the responses to opinions on what should be done (see www.bioplanassociates.com). The results were striking.

Almost 2/3 of respondents indicate that recycling is currently done by autoclave and landfill disposal. But, just one in five believes that this is what should be done. Burying bags in landfills has a major environmental impact because bag films are derived from polyethlylene, polypropylene, ethylene vinyl acetate, and nylon. These materials don't easily decompose.

Instead, the industry shows a strong preference for recycling, whether that be by sending devices, post-use, to a third party for recycling (62.4%) or back to the manufacturer for recycling (44.1%). Here, again, we find a deep gap between desire and reality. Just one in four is actually sending their devices post-use to a third party for recycling, and virtually none (1.1%) are sending them back to the manufacturer for recycling.

While these three methods constitute the preferred and most widespread manners for disposing of single-use devices, there are other discrepancies in the methods we identified:

- "Reuse in non-GMP applications" is only being currently performed by 9.7%, but recommended by about twice as many.
- "Incinerate as medical waste" is currently done by about 10% of respondents, but is considered to be a best-practice by about half that many (5%).
- "Reuse in GMP applications, with documentation and control" is another process performed by far less than recommend it.
- "Send back to manufacturer" is done by fewer than 5%, but recognized as something that should be done by over 15%.

Some comments we have received in the past regarding the issue include: "This is going to be a serious issue," "If single-use components could be manufactured from sustainable materials, that would greatly improve the image of the technology," and "The use of disposables must have a positive impact on cost as well as their environmental impact to justify their widespread use."

Industry expert Dr. Steven Chamow, president of Chamow Associates, says, "The move to single-use technologies will bring a very substantial waste stream from biologics production facilities. Because much of this waste stream is classified as biowaste, cost of disposal will be significant. Recycling can reduce the solid waste stream and potentially the cost of raw materials. This is an area that will grow in importance as use of disposables becomes more widespread, as it certainly will."

THE VENDOR'S RESPONSIBILITY

We also evaluated the importance of 13 attributes associated with single-use devices and compared that with the level of satisfaction (or dissatisfaction) with vendors to this industry segment. We found that the gaps between the service and products offered, and the importance of each attribute, can be used to prioritize specific areas that are both most important and most in need of improvement.

A number of respondents voiced that SUS sellers should assist in proper waste disposal. Yet it appears that this is not yet an important selection factor when considering single-use device vendors. We found that 31.5% of respondents consider vendor recycling programs to be either "very important" or "important" when selecting a vendor. Yet only 8% of the industry is satisfied with their vendor's current recycling programs.

This suggests that recycling programs are becoming a critical attribute for vendors and reflects overall attributes toward waste disposal — that is, concerns about waste disposal are becoming important, but are not actually inhibiting industry growth. (In our 2010 study, we found fewer than one in five respondents saying that waste disposal issues significantly reduce the respondents' usage of disposables.) Even so, vendors looking to differentiate themselves from their competition would be wise to consider this factor. This year, satisfaction with single-use vendors on recycling programs had the lowest level of satisfaction of the 13 areas we measured.

RECYCLING EFFORTS WILL GROW

Although today cost and economic issues are more important than concerns over environmental and disposal issues, recycling programs are becoming an increasingly burdensome problem, and vendors are increasingly being rated as unsatisfactory in dealing with recycling. As SUSs become more common — particularly in commercial manufacture — the focus will be on more recycling efforts that bring cost-effective, environmentally friendly alternatives to landfill solutions.

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Figure 1: Single-Use Recycling
What respondent thinks SHOULD be done vs. what facility is currently doing (multiple responses permitted)

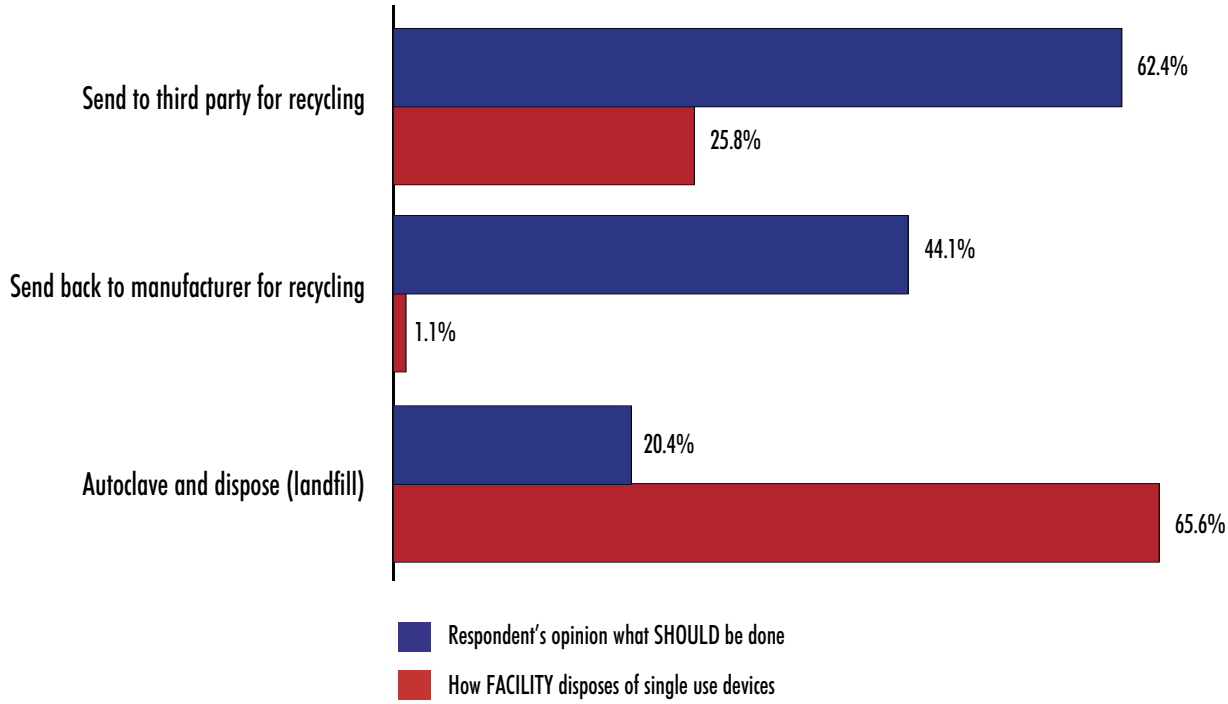
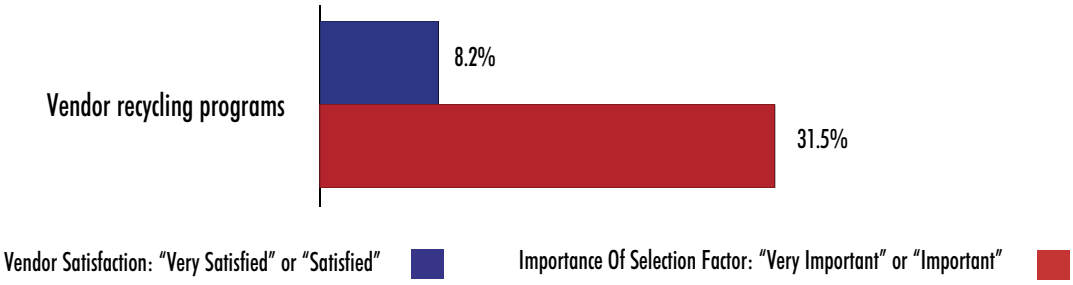


Figure 2: Single-Use Device
Comparing Vendor Satisfaction vs. Selection Attribute



Survey Methodology: The 2012 Ninth Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production in the series of annual evaluations by BioPlan Associates, Inc., yields a composite view and trend analysis from 302 responsible individuals at biopharmaceutical manufacturers and CMOs in 29 countries. The methodology also included 185 direct suppliers of materials, services, and equipment to this industry. This year's survey covers such issues as new product needs, facility budget changes, current capacity, future capacity constraints, expansions, use of disposables, trends and budgets in disposables, trends in downstream purification, quality management and control, hiring issues, and employment. The quantitative trend analysis provides details and comparisons of production by biotherapeutic developers and CMOs. It also evaluates trends over time and assesses differences in the world's major markets in the U.S. and Europe.

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Eli Lilly and Company — Open For Innovation

By Rob Wright

This year, the pharmaceutical industry is facing a loss of more than $33 billion due to patents expiring. Big pharma companies realize that to remain in the business of drug discovery, let alone in business at all, they need to become more innovative and long-term focused. Eli Lilly and Company is no exception, and it began implementing a number of long-range initiatives to spur innovation. One of these is the Open Innovation Drug Discovery (OIDD) platform, headed up by Alan Palkowitz, Ph.D.

But Palkowitz, a VP of discovery chemistry research and technologies at Lilly Research Laboratories, had a problem. How could Lilly attract people outside its own four walls to want to share their research? "We don't have infinite sources of money to pay for every idea before we know if there is any value," he expresses. He recalled mulling the problem over while at home during a holiday break and suddenly waking in the middle of the night with a solution. The idea, which he emailed to his colleagues the next day, was to use biological data as a form of currency to attract external parties to want to share experimental molecules, in a blinded fashion, and potentially collaborate. This proved to be the final key to the successful launch of Lilly's OIDD platform.

Alan Palkowitz, Ph.D.,
VP of discovery chemistry research and technologies,
Lilly Research Laboratories

GAINING ACCESS TO MOLECULAR DIVERSITY

According to Palkowitz, Lilly had spent a great deal of time and effort building its compound collection geared toward its targeted therapeutic areas of interests. Continued evolution of this compound collection was viewed as critical for future innovation. "One of the things we realized is that we had gotten to a point where further diversification of our collection was increasingly difficult when employing past methods, either through internal projects or through access to molecules through commercial vendors," he confides. Commercial vendor sources were becoming redundant and indistinct from what Lilly already had. Palkowitz wanted to gain "unbiased access" to compounds and scientific talent from other sources he knew existed, but had not been traditionally available to Lilly, such as academic settings, universities, and laboratories where synthetic chemistry is a key part of research programs and activities. But not many of these molecules have found their way into a drug development program. Other sources of innovation include small and emerging biotechs that are looking at new chemistry technologies and taking different approaches to spur new areas of discovery. "We thought, how do we uniquely access that dimension of capability, not only the molecules themselves, but maybe even the science and the thought processes behind them, as represented by the investigators, the originators of that work?" he wondered. The solution Palkowitz dreamed up was uncovering what these groups would value most — other than money. "Instead of paying for molecules up front before we were really able to understand their value, we thought of different types of currency that would be of value to academics and even small biotechs." The answer was to use biological data as a form of currency. The transactional value of data became the catalyst to gaining access to external sources of innovation, because, according to Palkowitz, biological data is what drives much of the understanding of hypotheses. "When someone has a molecule, and they have a hypothesis around how it might prove useful, being able to provide data on that is actually very valuable," he affirmed. "Data helps spur additional ideas of independent research and can also be the basis for the foundation for new research grants." Palkowitz realized however, that it wasn't just data, but data delivered timely, in a way that was not only meaningful but understandable to collaborators. But before he could

"Instead of paying for molecules up front before we were really able to understand their value, we thought of different types of currency that would be of value to academics and even small biotechs."

Alan Palkowitz, Ph.D., VP of discovery chemistry research and technologies, Lilly Research Laboratories

fully create the framework for delivering data, he needed to first solve another challenge —- how best to manage these external collaborations.

SOMETIMES INNOVATION REQUIRES STANDARDIZATION

Working with external partners is challenging because nearly everyone has their own ideas for how something should be done. Though Palkowitz was trying to gain access to external sources of innovation, he didn't want to do it in a way that created more headaches or costs for his company. He wanted to build the process using some of the traditional methods by which Lilly approached partnerships and collaborations. "We wanted to do this in a way that didn't require us to have a unique business agreement with every group we interacted with," he states. The solution was the development of a universal material transfer agreement (MTA) that would be acceptable to any university or small biotech and which did not have to be amended constantly or on a one-off basis. An MTA serves as a contract that governs the transfer of tangible research materials between two organizations, defining the rights of the provider and recipient, with respect to the materials and any derivatives. For help in developing the MTA, Palkowitz reached out to the Association of University Technology Managers (AUTM).

AUTM is a global network of members from more than 350 universities, research institutions, teaching hospitals, and government agencies, as well as hundreds of companies involved with managing and licensing innovations derived from academic and non-

GETTING THE WORD OUT

Ralph Waldo Emerson once said, "Build a better mousetrap and the world will beat a path to your door." Alan Palkowitz, Ph.D., VP of discovery chemistry research and technologies at Lilly Research Laboratories, was not willing to subscribe to Emerson's wisdom when he created Lilly's Open Innovation Drug Discovery (OIDD) platform. The whole idea is to interact with the community, which is not a one-way communication. To spread the word that Lilly was interested in partnering with a variety of external sources to find innovation, Palkowitz involved his corporate communications group for key press releases regarding the program. He suggests that when doing something as different as the creation of the OIDD platform, don't keep it secret. Articles about your program in a variety of journals and magazines serve as another form of advertising. In addition, Palkowitz believes the website (the company advertised the program on its website, as well as in a number of scientific journals) and positive customer experiences added to a strong word-of-mouth buzz. That interest was further enhanced through the use of open-innovation ambassadors — Lilly employees who would conduct scientific outreach programs and present at various conferences. Lastly, Palkowitz stresses to not forget the importance of providing the personal touch of making a phone call or sending personal letters to university department chairs to inform them of the program. Don't rely on the outdated wisdom of Emerson. If you are going to build a better mousetrap, build a comprehensive communications strategy to go along with it, so the world will know not only why they should beat a path to your door, but how to do so.

profit research. The organization provides numerous resources, including expertise in all areas of IP management. Palkowitz knew that in addition to the value academics and biotechs place on data, they are also highly concerned with protecting their IP. "There's always the sense of trust," he says. "Collaborators want to know how we are going to protect their structures, their IP. Will there be an opportunity to publish?" According to Palkowitz, AUTM was instrumental in providing input and advice on constructing the MTA, helping Lilly to proactively address these questions which often become pitfalls to successful collaboration. He also credits AUTM for helping in the broader design of the OIDD program. The creation of the MTA proved to be a real breakthrough for Lilly. "It allowed things to go smoothly once we launched the program, and we had a very high acceptance rate of the MTA," he states, "And without any need for modification." Elaborating, Palkowitz says, "We made it very clear with our material transfer agreement that it was a one-size-fits-all, and we weren't going to negotiate this every time with different universities," he explains. According to Palkowitz, one of the first instincts any tech transfer office will have when they get an MTA is to look it over, red line it with their own specific knowledge, and send it back. When this happened initially, he remained firm on the one-size-fits-all MTA policy. Presently, Lilly has 279 universities and small biotechs with which it collaborates in 31 countries around the globe. "We have about 650 individual investigators who have accounts and are routinely submitting compounds and receiving data," he explains. "We've had more than 100,000 compounds uploaded into the Web-based system for initial computer screening and have accepted about 60% of those to be screened in the program's biological assays." When you consider these numbers, you can imagine the amount of work Palkowitz would be creating for the Lilly legal group if he allowed each MTA to be individualized.

Palkowitz admits that, initially, Lilly did receive some pushback from some partners regarding the MTA. Involving AUTM proved beneficial in overcoming initial pushback, as the organization is external to Lilly and provided credibility for the

SPEND MONEY TO MAKE MONEY

How do you define customer service? Better yet, how do you define customer? For Alan Palkowitz, Ph.D., VP of discovery chemistry research and technologies at Lilly Research Laboratories and champion behind Lilly's Open Innovation Drug Discovery (OIDD) platform, it is every person who is interested in submitting a potential compound for investigation. These are all potential customers, potential future collaborators, and in essence, the foundation for potential future revenue streams for his company. In creating the OIDD platform, Palkowitz asked himself the following questions in relation to providing better customer service: "How do we eliminate a lot of the barriers, burdens, and hidden costs for our potential partners? How can we actually communicate in an efficient way and make information available?" The answer: Create bar-coded vials and utilize prepaid shipping. "All they have to do is enter their compound into a vial that's already bar-coded and send it back," he states. "This then seamlessly becomes integrated into our sample handling system while the structures are still blinded to Lilly." By removing some of the burden from the customer, both the company and customer benefit. Lilly benefits as well. Instead of receiving samples from different carriers in a variety of formats, with the possibility of missing or limited documentation, and creating more work for Lilly employees, the process is standardized. Palkowitz explains the bar coding and prepaid shipping as, "Trying to make the program a continuous part of our internal research activity." The process also facilitates the ease with which the company can track and trace information. The customer benefits by not having the out-of-pocket cost of having to pay for shipping.

When considering the cost of doing business, sometimes you need to look beyond initial dollars and cents. Lilly has already accepted around 60,000 compounds for physical screening, which is a lot of prepaid shipping. To give you an idea of the cost, let's say, hypothetically, that Lilly was using the U.S. Postal Service's flat rate prepaid shipping boxes which you see advertised on TV. These range in price from $5 to $45 dollars, depending upon the size of box and shipping zone. For 60,000 samples, this would translate into minimal spend of $300,000 to more than $2.7 million. This cost may not be a bad investment, especially if Palkowitz and his team find the next Zyprexa — a former Lilly blockbuster responsible for generating $2.5 billion in annual sales revenue. Sometimes you need to spend money to make money.

MTA. "We actually had AUTM endorse the program and the MTA, which we advertised in press releases as well as on the website," he states. "Once people saw this, they knew that we had really put a lot of thought into the creation of the program and the MTA."

In addition to reducing legal headaches, having a universal MTA streamlined and standardized the communication process between Lilly and external partners. It also provided time lines for when external parties that submitted a compound for screening could expect to receive data in return. Within three months, the submitter will receive a data report generated by Lilly for the submitted compound. The MTA also provided, that in exchange for the currency of the provided biological data, Lilly would have first right of negotiated access to the compound or collaboration. "If we see something interesting, Lilly would be able to collaborate, or maybe even access through a direct license, the compounds from the investigator, to use for our own internal purposes," he states. "If we go through the process and they're not interested, then it's certainly their prerogative to go off and use the data in any way they see fit." Lilly hopes that, by presenting itself as a credible and viable partner, researchers will want to continue to work with the company to enhance and uncover the potential of their science. Throughout the process, Palkowitz had to overcome both internal and external roadblocks to creating the OIDD business model.

OVERCOMING INTERNAL CHALLENGES

For Palkowitz, the initial roadblocks to internal adoption of the program were typical with this type of outside-the-box idea. He heard things such as "Academics will never go for it," "It's too complicated," and "You'll never find anything." His approach to overcoming these comments was simple. First, keep the team small. Addressing challenges is easier to overcome when the team is small and focused, allowing for streamlined communications. If his

team lacked specific expertise, Palkowitz would bring in different people to augment what he needed, when he needed it, and only for a limited time period, so as to maintain the team's size. In addition, keeping the team small helped to facilitate and maintain focus.

The second key to overcoming internal roadblocks was having a highly focused vision. "There are a lot of ideas of where to go, what to do next, and how to broaden different dimensions of the program," he states. "I've had to say, let's keep focused on the key job and collaborators, making sure we're delivering value for them, as well as for us."

The third key to overcoming internal roadblocks is team member selection. Palkowitz suggests finding members who really click with the vision. "I think it's important in any situation, when you talk to people about an opportunity, you can either select somebody because you think they have a certain skillset, or look beyond to assess somebody's passion, interest, and desire — even if they don't have the skillset," says Palkowitz. "Sometimes that takes you further, and I think a learning point is don't always go to the same sources when you have a new idea." Palkowitz describes being amazed by what people can achieve when they are truly inspired.

According to Alan Palkowitz, Ph.D., Lilly has 279 universities and small biotechs with which it collaborates, in 31 countries around the globe.

Inspiration, however, can be contagious, which ironically created another challenge to keeping Lilly's new team small. For as the program gained momentum, a lot of people wanted to join, and Palkowitz found himself having to turn people away. In addition to wanting to maintain the team's focus — something which he foresaw as being difficult with a large team — Palkowitz did not want the program to become a massive resource burn, especially since it was still growing and being defined. Presently, the number of full-time employees is just under five, with three being fully dedicated, while others provide fractional time commitments.

DON'T FORGET THE PILOT

The MTA and its endorsement by AUTM proved beneficial in overcoming external resistance to adoption. But don't forget to pilot to gain firsthand customer input. Palkowitz selected a few potential customers to test the program. His approach was to go to the biggest doubters and potential critics right from the start. Palkowitz admits that he and his team didn't have a lot of internal experience in developing this business-within-a-business, and this is why the pilot proved so valuable. "We got a lot of valuable input, because they saw the potential value and benefit to them personally and were eager to help us anticipate issues," he states. For example, through the pilot they learned that some of the details within the MTA, which he and his team may not have deemed as being very important, were very important to the customer (e.g. the ability and timing of being able to publish articles from the data). They shared sample reports of the data to find out what was instructive and what was confusing. How would they prefer to receive the data and in what format? What should be changed? All of this was taken into account in fine-tuning the program.

The team also gained insight from AUTM and the pilot as to how the website should look and feel. According to Palkowitz, the website turned out to be THE key part of the whole biological data transactional process. "This is the place where we advertise the business process, the MTA, the actual biological assays that we screen the compounds against," he explains. The website explains how the data is generated, from where, and what will be provided back to the investigator. The website (openinnovation.lilly.com/dd/) would also serve as the key to managing the logistical flow of information for every individual who develops an account, submits compounds, and receives data. Thus it had to be extremely user-friendly and approachable. For this, the team drew upon much of their daily personal experiences with conducting transactions on the Internet. "We really tried to model it after a common experience that everybody shares with e-commerce," he explains. The other benefit of creating the website was that it automated much of the process. This allowed the team to spend time on more important things, such as providing more of a personal touch to their external collaborators, viewing them as customers, not merely an idea machine.

TREAT YOUR EXTERNAL COLLABORATORS AS CUSTOMERS

Palkowitz refers to his external collaborators as customers and strives to treat them as such. He explains, "There are some things where we spent a lot of time, maybe some of the documentation, some of the systems we thought were really cool and important, but in the end, people want a phone call." This personal touch, considering the small size of the OIDD team, would not be possible without the standardization of the MTA and the automation of the submission process. To provide a more personal experience, Lilly actually created a help line for the site. If people want to see a face, Lilly offers webinars so customers will be able to ask questions interactively and not just have to read information on a website. Palkowitz claims this all came about only by doing a lot of homework up front to fully understand the needs of its customers, and it is why Lilly is open for innovation.


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"We're taking that first step, a leap of faith, to make the large investments in clinical trials that other companies are not making," says Dr. James Creeden, chief medical officer of Roche Professional Diagnostics.

The Rx for Dx Leadership at Roche

Dr. James Creeden, chief medical officer of Roche Professional Diagnostics, shares his views from inside the world's top-rated diagnostics business and a leader in drug-diagnostic combinations.

By Wayne Koberstein, contributing editor

What is a perfect drug but one that fits a perfect diagnosis? And in reverse, what is a perfect diagnosis but one that fits the drug — or any other treatment — to the condition? That being said, of course, nothing is perfect. But the standard steadily rises toward perfection, thanks to current scientific, engineering, and business initiatives in the diagnostics space. And arguably, at the head of companies in that space is Roche Diagnostics (RD), which claims 20% of the world's in vitro diagnostics (IVD) market outright, almost twice the share of its nearest competitor, Abbott. RD also topped the list of innovators in a 2011 report by the United Kingdom consultancy Diaceutics on companies pioneering personalized medicine with drug-diagnostic combinations.

Dr. James Creeden is the chief medical officer (CMO) of Roche Professional Diagnostics (RPD), the largest business unit within the Roche Diagnostics division, accounting for about half of the division's 10 billion Swiss Francs in annual revenue. Creeden offers valuable insights into the diagnostics industry, especially the development of drug-diagnostic combinations.

"My role as CMO of Roche Professional Diagnostics is twofold," he says. "I sit at the head of the department that's responsible for medical strategy and clinical development. We guide the decisions to develop and target certain disease areas which are the biomarkers in early development, and we also oversee the clinical development strategy and all clinical trials that are run later in development for all of the diagnostic tests that come through our business."

The bridge between diagnosis and treatment is medicine, in its largest sense — the understanding of healthy and diseased states, interpreted into models of disease mechanisms. In the business world, medicine also bridges the precommercial and commercial stages of the product life cycle. A Roche business-unit CMO like Creeden is charged with maintaining the medical bridge, keeping product development on the path to market acceptance by anticipating how the product will be used in actual medical practice.

Thus, Creeden shares not only the strategizing and decision making inside RPD, but also how the unit looks at the outside world, from professional and patient needs to payer concerns, regulatory challenges, and the competitive landscape. RPD's bread and butter is still in standard lab tests, but increasingly it leads in the intro-

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duction of drug-diagnostic combinations. It therefore offers some rich lessons and benchmarks for any company or team developing products in the same or a related space.

"Diagnostics are only about 2% of overall healthcare spend, but they determine about 70% of all clinical decision making," says Creeden. "If you look at the improvement in the number of tests in recent decades, innovation has brought a number of new biomarkers and vast quantities of useful data, both of which are not yet being recognized by reimbursement and regulatory systems. They are still treating most diagnostic testing as a routine cost when a test right now can be lifesaving and indicate which drug is going to work for a patient."

Commodification, the tendency for customers to regard and value diagnostics as low-margin commodities, is common, especially with RPD's predominant serum-testing products. Nevertheless, Roche Diagnostics continues to adhere to its strategy of "increasing testing efficiency and improving medical value," according to Creeden.

"The reimbursement environment doesn't always recognize products that deliver more value. Payers don't consistently reward value creation for the healthcare system, for example from screening methods that reduce disease later in life. They essentially treat diagnostic technologies as cost-based commodities, and that is a real challenge to us as we try to develop innovative products and justify the significant clinical research investments behind the new products."

DX IS CORE, NOT COROLLARY

Yet diagnostics are no longer just a side business to Roche's historically dominant pharmaceutical division. CEO Severin Schwan has made it clear that personalized medicine is on the way to becoming a core strategy for the company, with plans to match more than 60% of the drugs in its pipeline with companion diagnostics. The movement has gained momentum with the impending loss of patent on the drug that helped initiate it: Herceptin (trastuzumab). It is Herceptin's success with its companion diagnostic for HER2 that Roche aims to duplicate with most of its drugs.

In June 2012, the company announced a $300 million investment in new facilities at its diagnostics site in Indianapolis. It has also entered into a long-range collaboration with Merck to apply Roche's array and immunohistochemical (IHC/ISH), along with its investigational AmpliChip p53 technologies, in Merck's clinical development in cancer.

If diagnostics is an area of great expectations, however, it is also one of exceptional risk — today's acquisition target may become tomorrow's old news. In January 2012, Roche tendered a $6.7 billion bid for Illumina, only to drop the bid four months later. Although successful acquisitions in the Dx space are also common, such pullbacks are telling; the huge uncertainties about advanced diagnostic technologies add volatility to the acquisition strategy.

Creeden and his peers in the diagnostics division stand at the epicenter of expertise inside Roche, charged with guiding the evaluation and selection of emerging technologies. As novel biomarkers, assays, platforms, and products continuously bubble up from the cauldron of science and engineering, they must find a rational path to informed decisions at every level of the global business.

MATRIX MANIFESTS TEAMWORK

You might guess that the sheer pace of change inside Roche, brought on by the expansion of diagnostics, could cause some headaches. And you'd be right — though it might not be natural for an insider like Creeden to put it in those terms.

"Our biggest challenge internally is also one of our greatest assets as a large international company," he explains. "We're a well-organized matrix, so when we identify an opportunity to collaborate across the diagnostics units or between diagnostics and biotech or

pharma, we can quickly set up subteams to begin discussions and see whether there's any 'meat to the bone' there. We give them a lot of latitude to make decisions according to the goals and the priorities of the overall organization."

Translation: It's great being global, but it's a big deal to manage. The trick, implies Creeden, is to decentralize decision making but employ corporate resources as needed — something that requires a more formal system.

"We've recently introduced the concept of life cycle management for diagnostics that helps add a bit more structure to this matrix process and helps drive the individual strategies for our products and solutions," says Creeden.

FUTURE BLEND

Roche Professional Diagnostics (RPD), like its industry peers, focuses most of its products on large disease areas such as cancer, diabetes, and infection. How may the disease-area focus of RPDs change over time? Its Chief Medical Officer James Creeden answers:

"The interesting thing about diagnostics — particularly the central laboratories and point-of-care testing sectors that Roche Professional Diagnostics serve — is that we can never retire products. We need to provide all of the tests that physicians grew up using 10 or 20 years ago, as well as everything that's new. So our primary goal is to provide as broad a menu as possible. Regarding new products, it is definitely the responsibility of my group and the medical and scientific affairs organizations in our other business units to identify the disease areas where new diagnostics can actually add value. We've looked at a number of different areas and stratified them according to where new diagnostic tests are really needed, and we are actively steering our R&D efforts toward those. Although the industry as a whole has had a lot of success with oncology and inflammatory disease, we see continued success and growth in metabolic disease and cardiovascular disease. We also see a lot of work going on now in diseases that have been underserved in previous decades; here preeclampsia is a great example. It is relatively prevalent, a disease of otherwise healthy pregnant women, and there have been no advances in this field in two decades or so, and now we're starting to see a lot more progress. We also see a lot of work coming in Alzheimer's disease and brain injury. We focus on where there is an unmet need that diagnostic technology can really fill."

Life cycle management incorporates the time lines, evolving market intelligence, customer feedback, and other pieces of post-market development — literally driving by force and direction the strategies for each product. The full range of development-team members, from the investigator to the corporate levels, participate in the strategy making, following the principle of decision making at the lowest possible level.

Thus, not all medical-strategy decisions must come across his desk, Creeden says. "My global medical leaders, together with their business partners in the life cycle teams, are empowered to make medical strategy decisions as appropriate." If researchers on the pharmaceutical side want to discuss a biomarker hypothesis early in development, he says, the diagnostics side will assign one of its R&D scientists to advise the pharma team on critical aspects of biomarker development as early as possible. "This really helps them shape their thinking around the biomarker hypothesis and can strongly influence the drug-development thinking at a very early stage."

As the drug project matures, Creeden says the relevant life cycle team will assign more diagnostics product managers or late-stage developers to the life cycle team on the pharma side. It may also set up a corresponding team on the diagnostics side to make sure that the commercialization goals for the diagnostic products are also met.

PUSH FOR FAIR VALUE

Looking out from the inside, Creeden sees even more daunting obstacles for IVDs and Rx/Dx combos, especially in the regulatory and reimbursement spheres. The FDA regulates diagnostics as devices, but in a two-tiered structure that he and others say creates advantages for small companies making laboratory-developed tests (LDTs), which are regulated under CLIA (clinical laboratory improvement amendments) and not by the FDA. Similar potential "loopholes" for LDTs exist in Europe and elsewhere.

"The challenge we have is that the regulatory framework for diagnostics that exists today is not a level playing field," Creeden says, echoing the words of several FDA presenters in recent times. "We have one classification applied to large manufacturers, where we are expected to adhere to very high-quality manufacturing standards, and another applied to smaller laboratories, which essentially don't have to meet the same quality standards as we do."

LDTs have some possible benefits, according to regulators: They are available for small populations, allow rapid test development and deployment, and may save money for healthcare systems. Objectively, however, they may do harm: patients and physicians relying on what may be useless tests, labs overestimating

their validation ability, and companies that run the full gamut of Dx development — from design to manufacturing — left with a much higher regulatory burden.

Without a structural solution at hand, the only recourse is communication, says Creeden. "We communicate a great deal with the regulators. We recently had some great discussions with the FDA as part of their Experiential Learning Program (ELP), where we had an opportunity to teach them about our newest platforms and gave them an opportunity to come in and kick the tires and see how things work. Such exchanges make a big difference in improving the transparency between our people and the regulators. We've made our position and our challenges known to the agency, and it has made great progress in clarifying its position and plans for clarifying the regulatory environment, particularly with regard to LDTs. Thankfully, the European authorities are also taking note of the LDT situation and starting to take action, too. Clarity is extremely important to ensure that we can continue to make investments here."

Diagnostics struggle against low-value perceptions by payers as well, says Creeden. Today, the reimbursement environment doesn't recognize products brought to the market with a higher level of diagnostic-utility or clinical-utility evidence. It's essentially an open market for anyone who wants to bring a new technology on board. Nevertheless, he says, "It's good news for us that payers increasingly want to reward value creation; they want to reward products that come more fully supported by good evidence packages around them, so we're having a lot of discussions with them about the best ways to measure that value."

Creeden says his company has a duty to challenge the traditional cost-based perceptions with evidence-based arguments for recognizing the greater value of new Dx technologies. "We have a certain responsibility as an industry leader to take the first step, so we're taking that first step, a leap of faith, to make the large investments in clinical trials that other companies are not making. We believe that if we demonstrate the clinical value of our tests, the reimbursement authorities will start to reward that, and the regulatory authorities will start to recognize there are two different classes of products here."

Clinical value includes cost-effectiveness, Creeden acknowledges. The trade-off for higher pricing and reimbursement is lower treatment costs. "The key word is effectiveness — that is exactly the challenge for the diagnostics industry. Tests by themselves are not an intervention. So, setting up clinical trials that actually can demonstrate the effectiveness of tests can be challenging, and often as complex, if not more complex, than a lot of drug trials. They can also be very large, which means a significant investment."

Biopharms Embrace Companion Diagnostics To Advance Personalized Medicine & Address Drug Cost Concerns

By Cathy Yarbrough, contributing editor

Today Herceptin, the first biotech drug against metastatic breast cancer, is commonly referred to as oncology's poster child for companion diagnostics (CDx). However, in 1998, when the FDA approved Herceptin, the agency and the biopharmaceutical industry referred to the HercepTest for the HER2 genetic mutation as an *in vitro diagnostic*, not a companion diagnostic.

The term companion diagnostics likely was coined about 10 years later, when the Human Genome Project began paying dividends in the form of new scientific knowledge about the genomic underpinnings of cancer. "The science is beginning to lead us, and we're beginning to reap the rewards of the science by identifying biomarkers and correlating them with outcomes," said Greg Zdechlik, COO of diagnostics at Eli Lilly and Company. "I believe we're now at the beginning of a large wave of companion diagnostics."

In the next decade, industry experts said that most, if not all, new oncology compounds submitted for FDA review will be linked to companion diagnostics that screen for already known genomic mutations or newly identified single nucleotide polymorphisms. Because they enable physicians to select the right drug for the right patient at the right time, CDx may prove to be the enabling technology for personalized medicine.

"Twenty years ago, the paradigm was that for every 100 cancer patients treated, 10 benefitted," said Gbola Amusa, who heads European pharmaceuticals research and is global pharmaceuticals coordinator at UBS banking and financial service group. "If you could, instead, treat only those 10 patients, you would get the same result without putting through the 90 who don't benefit — and society gains. Ten years from now, this will be the standard."

ONCOLOGY DOMINATES CDx

Oncology dominates the CDx market because so many of the advances in understanding the genomics of disease have occurred in cancer. However, biopharmaceutical companies have not ignored other disease areas. At Lilly, for example, each disease therapeutic group is responsible for determining whether a tailoring strategy is viable for each compound under development, said Zdechlik. Every molecule will not have a CDx, but at least a tailoring strategy would have been considered, he added.

Because of its potential to limit new drugs to only those patients who stand to benefit, CDx provides a way for biopharmaceutical companies to address payers' concerns about the costs of medical treatments. "Obviously, payers are driving for more efficiency in how healthcare dollars are spent," said Zdechlik. "Before paying for a new therapy, payers want to know whether the drug could work. This could be accomplished through a predictive biomarker, or it could be accomplished by having biomarker evidence that therapy is providing benefit," he added. CDx provides an objective measure of the drug's potential to benefit a specific patient.

In addition to appealing to payers, CDx may allow biopharmaceutical companies to redesign clinical trials so that they enroll only those patients who are the most likely to benefit from the experimental compound. However, in general, CDx do not lessen the challenges of drug development and commercialization, because developing and commercializing diagnostics also is challenging work. "As with any innovation, developing companion diagnostics requires charting a new path, and that brings new challenges," said Ron Ellis, CEO and president of the bio-

tech company Endocyte.

"Identifying the biomarkers for a companion diagnostic is incredibly complex and requires a great amount of hard work," said Zdechlik. "I often compare it to searching for a needle in a haystack, since scientists must sift through multiple data sets to identify and correlate the signal or biomarker that reflects the patient's responsiveness to a therapy."

"One of the reasons that choosing biomarkers can be difficult is sometimes you don't know what sort of differential drug response you will get until at least 100 patients have been treated, which means that the drug is typically in Phase 2 before this information is available," said Dr. Stephen Little, VP of personalized healthcare at Qiagen.

TIMING IS CRUCIAL

To develop CDx for their drugs, many biopharmaceutical companies turn to diagnostic companies such as Qiagen. "There is a discovery element to identifying the biomarker," Little added. "It's important to start as early as possible to identify biomarkers, but it's not always possible to start as early as you would like."

Ideally a new drug and its CDx not only are simultaneously submitted to and approved by the FDA and the European Medicines Agency, but also are commercially launched at the same time. Timing is crucial to achieving a concurrent approval and launch. If the FDA labeling for the drug requires that the diagnostic test be used before the drug is administered, and the CDx is not yet approved or in the hands of laboratory directors and pathologists, both products could sit on the shelf, depriving patients of a potential highly effective and safe therapy and reducing the revenues of both partners. Thus, the biopharmaceutical company has to dedicate substantial time and effort in communicating and coordinating with the diagnostic partner to ensure "that the diagnostic is being developed in a regulatory-compliant manner that is faster or equal to development of the drug," said Zdechlik.

Many biopharmaceutical companies are embracing the diagnostics industry. "As the drug industry warms to the idea of personalized care and companion diagnostics, it has invested heavily in understanding the world in which the diagnostic industry operates," Little said. To provide that insight, many biopharmaceutical companies have hired experts, many of whom are diagnostic company veterans such as Zdechlik, who worked in the industry for 25 years before joining Lilly. "A biopharmaceutical company must have staff with expertise in diagnostics even if it is outsourcing its companion diagnostics," said Ellis.

PERSONALIZED MEDICINE UNITES CDx AND PHARMA

Diagnostics and biopharmaceuticals have a lot to learn about each other because their core expertise, development process, regulatory frameworks, and commercialization differ, experts said. "Traditionally, the core of diagnostics used to be chemistry and engineering, whereas the core of pharmaceuticals was the information and utility of the clinical sciences," said Little. "Personalized healthcare brings these two things together."

"To be successful, you have to understand your partner's world," said Little. "Thinking about pharmaceuticals helps us in diagnostics to understand what the drug industry is looking for. The pharma industry also has to understand what the diagnostics industry is about and that diagnostics are regulated products with a time line for development."

The regulatory process is more complicated in the U.S. than in Europe, said Little. At the FDA, the review of CDx occurs in the Center for Devices and Radiological Health, not the Center for Drug Evaluation and Research. The split means that the diagnostics and pharmaceutical partners must devote time and energy to ensure that both FDA divisions are informed about the total picture, said Zdechlik.

Conversations with the FDA should occur before clinical studies are launched, Ellis said. "Particularly in the case of imaging diagnostics, we are breaking new ground, so we have worked closely with the FDA to ensure we are gathering the data they'll require for potential regulatory approval," he said. "We have communicated early and often with the FDA," added Ellis, whose company, Endocyte, has developed a new category of CDx: companion imaging diagnostics to identify the folate receptor, which is overexpressed in ovarian as well as several other cancers.

Conversations with the FDA should occur before clinical studies are launched, Ellis said. "There are things you didn't anticipate. And you don't want to do something and then have the FDA come back and say, 'You didn't do it right; you have to do it this way,'" he added.

STRINGENT REVIEW OF CDx OCCURS AT FDA

"The FDA is a very open organization," said Little. "Colleagues in the pharma industry are often surprised when I talk about the openness, frankness, and helpfulness of our conversations with the FDA's device industry regulators in diagnostics."

Many people in the biopharmaceutical industry also are surprised that a CDx "most likely will require a PMA (premarket approval) application, which requires a very stringent regulatory review process," said Zdechlik.

The FDA, which issued draft guidance on companion diagnostic devices in 2011, "has had a consistent message for many years that the risk profile of the test should match the risk profile of the drug," said Little. "The agency expects to see the highest standards in analytical studies to prove the test's clinical validity and clinical utility. They want to know that the test actually works and that the measurement is linked to a specific patient outcome."

In the typical partnership with a biopharmaceuticals company, the diagnostics company not only develops but also obtains regulatory review and approval of the CDx. The diagnostic company is also responsible for the commercialization of the product. Thus, in selecting a CDx partner, the biopharmaceutical company must evaluate each diagnostic company's "scientific capability, ability to execute, and project management," said Zdechlik. "The diagnostic company also

must have a global footprint as well as regulatory, manufacturing, supply, and commercialization experience and capacity."

The diagnostic company has to "own the relationship with the laboratories and the pathology community," said Zdechlik, just as the biopharmaceutical company is responsible for reaching the physician community.

CDx NOW INCLUDES IMAGING

In oncology, CDx is often used more to predict rather than to monitor a patient's response to a specific drug, whether it is a new compound or an already approved and marketed medication. Until recently, the CDx methods were primarily tissue and blood analysis. Endocyte has created a third category by using companion imaging agents.

Endocyte's CDx, developed in-house, consists of a small molecule targeting ligand, which binds to the folate receptor and is linked to an imaging agent that identifies tumors that overexpress this target. In addition to using the targeting ligand in the diagnostic, the company's scientists have linked it to vintafolide, a novel small molecule drug conjugate that the researchers developed as a potential treatment for patients with folate receptor-positive cancers, which include many platinum-resistant ovarian cancers. "Eighty percent to 90% of ovarian cancers have this receptor," said Ellis.

Vintafolide is being evaluated in folate receptor-positive ovarian cancer patients in a Phase 3 clinical trial as well as in a Phase 2b clinical trial in non-small cell lung cancer (NSCLC) patients. This year Merck obtained a worldwide license to commercialize vintafolide.

Because it uses an imaging approach to identify the folate receptor, Endocyte's CDx does not require a fresh or stored tissue sample of the patient's cancer. "Research has shown that cancer receptors change over time," said Ellis. As a result, the folate receptor results from tissue obtained during surgery or biopsy may not accurately reflect the state of the patient's ovarian cancer when she is being treated. Endocyte's CDx can determine in real time whether a patient's tumor contains the folate receptor and is "treatable" by vintafolide.

Using its CDx imaging analysis, Ellis said, "We can ensure that the right patient gets the right drug. If you provide benefit to patients, you'll achieve success commercially."

How To Mitigate Pharma Supply Chain Risks

By Gail Dutton, contributing editor

Collaboration is the single best way to mitigate supply chain risks, as well as to enable significant improvements in terms of speed, on-time pickup and delivery, damage reduction, and other parameters, according to speakers at the September IQPC Cold Chain & Temperature Management Global Forum in Chicago. What organizations must accept is that communications and information-sharing goes both ways. By monitoring shipments and by accumulating, mining, analyzing, and sharing resultant data, logistics organizations throughout the supply chain can improve their operations and prevent future problems.

Johnson & Johnson understands that. Although its 50-person team knows its temperature control requirements and is alerted to excursions, "We need a more proactive approach," says Alan Davis, supply chain temperature control leader, Johnson & Johnson. Therefore, the company is validating a solution to identify and understand the trends. "We need to use the data to recognize not just whether there were excursions, but how close shipments came to experiencing excursions." With that information, the company can work with service and packaging material providers to strengthen the supply chain to prevent future excursions.

GLOBAL MONITORING

AstraZeneca has monitored shipments on its 400 international lanes for the past decade. Now it is analyzing that data to uncover patterns it can use to craft a global temperature management program. Actual numbers are confidential, but excursions have declined dramatically, says Christine Foster, senior quality assurance supplier manager, AstraZeneca.

Initial findings revealed a high number of temperature excursions in controlled room temperature shipments. Deeper analysis pointed to a limited understanding of route performance related to mode, seasonality, forwarder, and service and also showed global inconsistencies. In response, Foster says, "We updated the temperature monitoring system, harmonized route performance criteria, and [based upon excursion severity] prioritized our focus around air transportation."

AstraZeneca also performed a route risk assessment, which identified additional risks and led to the development of a global standard. For temperature monitoring, the company held a kaizen event and deployed multitemperature sensors and alarms, which dramatically reduced excursions. "We looked at passive and active protection," Foster explains, "and engaged our forwarders to ensure they understood our business. With access to our raw data, they now can proactively see trends and mitigate risks."

Working with TSS AB, AstraZeneca deployed the Cargo 2000 information system to provide data on routes to help identify risk mitigation strategies specific to each route. Because the information is managed through a central application, data quality and consistency have improved, and automatic ad hoc analyses of all routes are quickly available.

Likewise, Cubist Pharmaceuticals worked with its freight forwarder to monitor APIs being shipped from Italy to the U.S. Surprisingly, "We found the cargo made multiple stops before entering the U.S.," notes Michele Johnson, supply chain consultant. "Some of the unexpected stops were caused by scheduling changes, but more related to re-icing and other materials-handling issues." Subsequently, Cubist streamlined its supply chain to reduce handoffs, thereby reducing risks and costs.

Innovations in packaging and changes in transportation make it worthwhile to consider alternative modes of transportation. As railroads improve delivery times and truckers work in teams to minimize stops, intermodal and ground transportation are becoming options. These options come with tradeoffs, though. "Be cognizant of inventory carrying cost, stock on hand, and the urgent needs of customers," Davis cautioned. "If you move from air to ground, for example, you may need more inventory on hand, or customers may need to order earlier. Manufacturers also must account for the risk of longer temperature excursions and have solutions available to remediate midshipment incidents. Solutions include placing temperature monitors and GPS trackers on the cargo so incidents are reported and can be addressed in near real time."

UNDERSTAND HANDOFFS

In addition to being aware of stops and handoffs, pharma companies also should understand the environmental aspects of each lane. That includes passive thermal protection options for each lane, their complexity and repeatability, the feasibility of recharging batteries or passive heating or cooling materials at each handoff location, solutions' potential for refurbishment and reuse, and any seasonal variations.

Logistics considerations for controlled room temperature (CRT) also should be identified. Johnson & Johnson is reevaluating its legacy products to develop the same level of stability and temperature information that it has for new products, thus minimizing excursions. And carriers are beginning to temperature-map their facilities to better accommodate temperature-sensitive cargo.

Understanding airline SOPs also helps minimize incidents. For example, if an airline color-codes sensitive shipments, shippers should ensure their coding system doesn't conflict. Davis also advises affixing special-handling labeling in multiple languages, recognizing that for many handlers English is a second language. Additionally, "Movements at airports should be well-defined in SOPs. Interim airports may be challenging, and shippers may not be aware of all the transitions their products experience," Davis says.

Ground handlers, whether for the last-mile delivery or for handoffs in transit, also need access to the SOPs for their pharma clients, Davis insists. The information should include emergency contacts, temperature-controlled safe havens, monitoring systems in use, and real-time temperature and GPS visibility. "Handlers also need recurrent training, a strong understanding of pharma needs, and access to temperature-controlled warehousing options with surge capacity," he adds.

Customs facilities pose additional challenges. "They aren't always safe havens for temperature control," Davis points out. To lessen the risks, ship a test package through customs so the documents are on file before commercial-sized shipments are transported. "There are no guarantees, but customs approval of an earlier shipment helps mitigate challenges. The contacts on the ground at destination countries are very important, so establish them up front."

PROVIDER SELECTION

Particularly as temperature control shipping becomes more important, differences among logistics providers are emerging. In evaluating potential logistics partners, "Bayer HealthCare looks for three things: operational visibility, flexibility to manage risks, and reliability," says Carlos Castro, transportation/cold chain project manager.

Supply Chain

When Bayer HealthCare looked at its logistics chain, it established a baseline with key performance indicators to facilitate objective analyses. "The goal is to balance costs and risks," Castro explains. For example, "A particular transportation mode may save money, but may increase risk by making multiple stops. Therefore, it may be better to pay more to ensure there are no stops."

Cubist Pharmaceuticals relies heavily on its 3PL (third party logistics provider). Johnson says a full-service, end-to-end logistics provider is vital to ensure that packages are never held hostage to handoffs. It also insists upon a quality assurance approach to managing services.

Johnson & Johnson goes deeper, looking not only at its freight forwarders, but at the core strengths of those forwarders' partners. "Understand them. They make the difference between good and great providers," Davis says.

FedEx takes a similar approach, working with approximately five other freight forwarders. "We know the SOPs we need. We travel to their facilities and review their SOPs with an eye to maximum visibility, complete transparency, contingency preparedness, and responses to challenges. If they have no records of those challenges, they're either inexperienced, or they document poorly," says Ken May, Temp-Assure Solutions analyst, FedEx. "I look for partners who know their own weaknesses."

Speakers at the IQPC event advise pharmaceutical companies to supplement their primary logistics provider with secondary and even tertiary providers to ensure their goals are met. Logistics providers have different financial objectives, cultures, and regulatory concerns than their pharmaceutical partners, they point out. Those differences aside, a multitiered approach helps ensure the shippers maintain the flexibility to respond to new and evolving global challenges.

PACKAGING AND THE SUSTAINABILITY MINDSET

Companies at the IQPC conference support the notion of sustainable packaging, but haven't agreed whether single-use or reusable packaging best advances their goals. Single-use advocates still must deal with degradation and disposal, while reusable proponents struggle to ensure containers are returned and that packaging retains its properties throughout multiple uses.

When LifeCell recently piloted its reusable shipping system, it educated customers beforehand to expect a new, returnable shipper. "Make it very obvious," says Chris Masick, senior packaging engineer. "We added a label that said, 'Do not discard. I'm a reusable shipper,' as well as prepaid return labels to make it easy for customers to return shippers to the proper location. Some still get it wrong." For the recalcitrant, LifeCell relies upon tracking software to aid recovery. "The sooner you act, the better the chance of recovery."

Return rates depend largely upon the sustainability mindset at receivers' locations and regulatory compulsion. For example, "Canada had 100% compliance, and California was more receptive than our other American pilot locations," Masick says.

When it comes to packaging and logistics, Masick also advocates collaboration within a pharmaceutical division. "Stop working in a silo," he says. Instead, involve the logistics and quality assurance departments early in packaging decisions. "They may need to work with leasing agreements or review documentation to justify use of a certain product or may have other concerns that, when addressed early, help advance projects more quickly and amicably."

Dana Dallas, vaccine/cold chain program manager, Defense Logistics Agency Troop Support, encourages box and device manufacturers to collaborate, too. "Ideally, packing material would be designed for the box and delivered as a one-concept solution." Likewise, temperature monitors should be tested with passive solutions and the research made available so shippers know how specific solutions behave and understand where best to position monitors.

The mounting need for temperature-controlled shipping is complicating an already complex supply chain. The solution, speakers agreed, is close, consistent collaboration with trusted logistics providers. By sharing data, partners have the opportunity not only to address individual shipping issues, but to enact improvements that actually reduce excursions and improve service.

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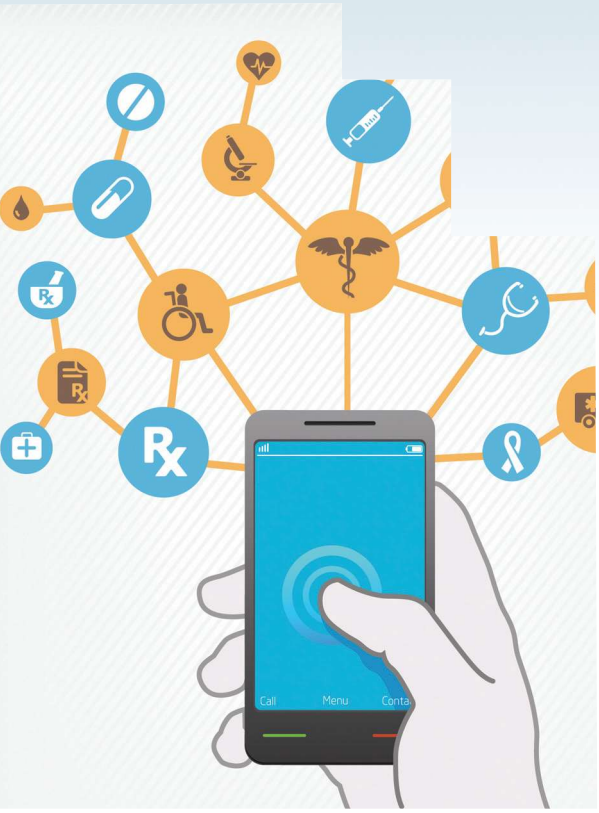

mHealth Could Cut Clinical Trial Time And Money In Half

By Cindy Dubin, contributing editor

Like it or not, the wheels of the Patient Protection Affordable Care Act 2010 (commonly referred to as "ObamaCare") are well in motion. One of the key requirements is that by 2014, there will be nationwide use of electronic health records (EHRs) — a systematic collection and digital record of electronic health information about individual patients or populations. EHRs are a critical component of the "digital healthcare ecosystem" that captures patient data, shares that data with healthcare providers, and improves access to that data. Other emerging technologies that create opportunity for engagement around health and wellness include mobile health (mHealth) and social media exchanges.

"It's important to understand that emerging technologies such as mobile health, remote monitoring, data analytics, and others are enabling healthcare reform this time around," says Paulo Machado, founder and CEO of Health Innovation Partners LLC, a strategic consultancy that works with a range of healthcare stakeholders to use technology in developing next-generation business models and solutions. "The digitization of healthcare is fueling a Healthcare Renaissance that will lead us to the triple aim of better care, better health, and lower cost."

OPPORTUNITIES IN CLINICAL TRIALS

One healthcare area that is being driven forward by technology is clinical trials. While clinical trials determine whether new drugs are effective on different groups of people, it can be complex to look at a variety of subsets of people. The ubiquity of smartphones — and the incredible amounts of data they collect — might change all that.

"There are incremental and radical opportunities that present themselves with digital technology," says Craig Lipset, head of clinical innovation at Pfizer. "It can change how we perform studies, engage patients around recruitment, capture data, and monitor data. Each of these steps can be reinvented with digital platforms and make clinical research a more transparent and integrated part of healthcare."

Once the healthcare information is seamlessly integrated across healthcare stakeholders, patients can be recruited faster and more efficiently. Researchers would be able to increase the likelihood of finding "better" candidates for their trials. "Theoretically, one could enter search criteria that would find how many patients exist that meet the criteria. The patients could be screened digitally to determine who is eligible for the trial-based specific criteria, then the investigators/physicians could be brought into the process," says Machado.

Since patients are already familiar with how their smartphones operate, once they are recruited into a clinical trial, real-time data capture becomes possible. This is a paradigm shift from conventional electronic diaries that often require providing patients with an unfamiliar handheld device exclusively for use in the study and which often provide one-way data input. Now, rather than visiting a clinical trial site, patients input the data to their mobile phones. This enables trials to occur wherever the patient is located. "Using mobile platforms to support capture of electronic diary data (e.g. ePRO [electronic patient reported outcomes]) in clinical studies is a real opportunity to leverage a technology that people are already familiar with — their smartphones," says Machado. Both ePRO and mHealth applications capture data, but most mHealth apps also confer some benefit and value to the patient, which in turn improves compliance in using the app to provide the data.

Sharing the collected data among

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all the trial stakeholders is an opportunity as well. "Typically, data capture and analysis of clinical trial data has been performed in buckets or silos, but emerging data management and analytics approaches would allow all interested parties access to the data for improved collaboration and faster turnaround times," says Machado. And, once a trial closes, analyzing the data becomes a more efficient process because the data has been captured and reviewed throughout the study, he adds.

COLLABORATING IN THE DIGITAL ECOSYSTEM

From the patient to the provider to the recruiter, digitizing healthcare will recast the roles within a clinical trial and realign business models as the stakeholders will share data and collaborate in new ways. For example, rather than just collecting patient data and walking away armed with the information, researchers will engage with patients at the commencement of the study to understand their needs and share information at the end of the study that could address those needs. Or, pharmaceutical companies can share the information with insurance companies to help the payers understand what medications work best for certain patients so that proper reimbursement occurs.

mHealth also will facilitate collaboration between atypical partners. "The landscape of clinical trials will be very different in the next decade in terms of how they are done and who the players are," says Lipset. "For a pharmaceutical company, this means being willing to collaborate with organizations that typically would be competitors, like other pharma companies. Pharma can come together to make the process more efficient because it ultimately benefits everyone."

As proof that this movement is afoot, 10 of the biggest names in drug development are joining forces to speed up new drug creation, and the resulting nonprofit aims to work with CROs to tackle some of the most vexing troubles in pharmaceutical R&D. TransCelerate BioPharma is the moniker for the collaboration, which joins Abbott Laboratories, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Pfizer, Roche's Genentech unit, and Sanofi.

In a release, the conglomerate established five targets for action: developing a shared user interface for investigator site portals, mutual recognition of study site qualification and training, developing risk-based site-monitoring approaches and standards, developing clinical data standards, and establishing a comparator drug supply model. "Most of these targets are what I would consider 'technology-enabled,'" says Lipset. "Those targets with the strongest technology alignment are around clinical data standards as well as a shared investigator site portal.

"TransCelerate BioPharma marks an important demonstration of collaboration to drive innovation," Lipset continues. "There is an appreciation that there are problems we simply can't address alone anymore, and there is no reason to do so because they are shared challenges. We are competitors in the eyes of Wall Street, but we can work together to address challenging areas."

TransCelerate is not centered on mHealth or digital, but instead on collaboration across industry R&D organizations to improve the drug development process. Of the five "workstreams" live at launch, several are strongly technology-enabled, such as the investigator portal. The work around improved data standards is very consistent with other data efforts in healthcare — standards for data help make data "liquid" (i.e. easily shared and transferred across systems) between research and healthcare and ensures that users can readily share and exchange data. "When data and health information is liquid, we can enable a future state of enhancing trial recruitment and study efficiency. Because then we can readily enable identification of very specific patients for individual studies (i.e. based on detailed health information, genetic information, etc.) and enable patients to opt-in to share their data for research," says Lipset.

TIME, MONEY, AND THE FDA

And while Machado wouldn't put a number to the time and cost savings possibly achievable using emerging digital technologies, he is optimistic that both could be cut in half — at least. "Maybe more, depending how aggressively the technology is adopted

PFIZER FORGES ON WITH mHEALTH

Last June, Pfizer set out to incorporate mobile technology in a virtual clinical study of its overactive bladder drug Detrol LA (tolterodine tartrate), with the aim of attracting 600 patients from 10 states across the U.S. The remote trial of Pfizer's was the first randomized clinical trial that patients could participate in entirely from home by using mobile phones and Web-based technology. The trial screened patients online, provided multimedia content regarding informed consent online, and enabled extensive data capture from patients online (including efficacy and safety).

The hope was this approach would save time, produce better data, and increase patient compliance, but the trial was halted after Pfizer failed to persuade sufficient numbers of patients to take part. The project does not represent a failure for, or withdrawal from, the use of the Internet or social media for patient recruitment, says Lipset. "We routinely use the Internet as a channel for recruitment in our studies and will continue to do so wherever it is appropriate," he wrote on the company's blog.

One reason the trial wasn't a complete success was because Pfizer was trying to do too much too fast. "We were testing a number of digital tools at once: online recruitment, screening, and consent; at-home study drug delivery; mobile- and Web-based tools for all data reporting; online identity verification; and a centralized investigator site," Lipset says.

But, all hope is not lost. Pfizer plans to relaunch the trial in 2013.

by life sciences companies and the regulatory bodies," he says. "We're talking about optimizing the clinical trial process, not changing trial durations. Recruitment and analytics — the flexible components — will change, but the amount of time the patient needs to take the medicine won't change."

Change could, however, be coming from the FDA with regard to mHealth. At the end of 2010, the FDA issued a draft guidance on electronic source, or e-source, in clinical trials. This means that the original record of a data element is captured electronically and must be followed with a detailed audit trail. The FDA promotes eSource in clinical studies because it will help to eliminate unnecessary duplication of data, reduce the opportunity for transcription errors, promote the real-time entry of electronic source data during subject visits, and ensure the accuracy and completeness of data (e.g., through the use of electronic prompts for missing or inconsistent data).

The industry is awaiting a final draft of guidelines for mobile medical apps, but it appears that the FDA is focused on mobile medical apps that assist in the development of clinical decisions for health issues. "The FDA is being forward-thinking as it puts out guidance about using electronic tools as source documents in clinical trials," says Lipset. "The industry needs an FDA that evolves and is creative, and so far, the agency has shown progress toward meeting that goal."

90% OF CLINICAL TRIALS TO BE DIGITIZED

Just as the FDA evolves in working with mHealth, so too must life sciences companies. Both Lipset and Machado agree there is a learning curve but that use of digital technology in healthcare is only at the starting line. "Patients are used to using devices such as smartphones, which are the types of tools that bring value to the clinical trial process," says Lipset. "We can collect data at unprecedented levels, develop better medicines, and better target medicines to particular patient groups."

The U.S. will not have a completely digital ecosystem this decade, points out Machado. He does believe that 80% to 90% of what needs to be digitized will be completed by 2030. "Until then, we will continue to see clinical trials that are part digital and part manual," he says. "We are not making the move to digital just for clinical trials. We are doing this to improve the quality of life. Better care, better quality, better value. Those three things will have a profound positive effect on clinical trials."

Smart Sourcing At The Outset

The Strategic Use of Cutting-Edge Suppliers in Early Drug Characterization and Development

By Wayne Koberstein, Contributing Editor

Years ago, the subhead for this piece would have made little or no sense to me. For one, I would not have thought the words "strategic, characterization, and development" belonged together. And how suppliers entered the picture, especially on the "cutting edge," would not have been obvious. Then, there's the title. Smart Sourcing? The Outset of What? Today it all seems almost too obvious, even though companies still struggle with applying the concept: Corporate strategy and product strategy must begin with the very definition of a product as a molecule worthy of scale-up and production, continuing through process development and beyond. When companies don't have the in-house resources to characterize and refine truly novel compounds, they must rely on suppliers who do.

More recently, I have had an education, thanks to my assignments for *Life Science Leader*. In particular, two conferences I covered for the magazine — the USP Biologics Standards Seminar and the AAPS National Biotechnology Conference — impressed me with the strategic importance of purity and potency in novel molecules. Those qualities affect safety and efficacy, of course.

But there are so many other characteristics of strategic importance that constitute or surpass them: pharmacokinetics, immunogenicity, bioavailability, delivery, stability, aggregation, fill-finish, and more. Such factors can have enormous effects on the strategic viability of the product in preclinical and clinical trials, manufacturing at all scales, reimbursement, regulation, and potentially medical practice.

Again, once stated, the proposition sounds perfectly self-evident, but I have the feeling many companies and executives still find it difficult to assimilate such thinking into their strategic plans.

This is not a pitch for outsourcing, however. It is reinforcement for anyone who has yet to embrace the idea of early, painstaking characterization — using the most well-equipped and innovative suppliers as needed to put your product and company on sound strategic footing. That means, before all else, recruiting the right talent and expertise into the company to separate the supplier wheat from the chaff. The COO and CSO should work together to guide internal managers through selection, setup, and ongoing relations with the external party. That expertise should include advanced knowledge of new technologies, standards, assays, processes, and other components of drug characterization and early development.

Getting those experts is an investment, admittedly, and investors seldom place much value on the early stages of compound development, especially related to manufacturing. It follows that the investment must be carefully justified at the conception of the company and development project and fortified as much as possible with an IP strategy. One model that covers both of those bases is a codevelopment partnership of company and supplier. As the two parties work together to develop assays, processes, and compositions unique to the product, the company may retain the resulting IP as an asset in its valuation. Meanwhile, the supplier may improve its capabilities, and thus its business generally.

INSIGHT FROM RECENT CONFERENCES

So far, I am only using logic to support my thesis, so I have not yet transgressed my outsider status in the outsourcing field. My reasoning is also grounded, however, in some of the examples I encountered at the aforementioned events. Given the general themes, most concerned biologic molecules, but with the oft-heard refrain that the lessons apply to many new small molecules as well.

USP's event centered on standards, yet it was clear the real driver of change in early development is technology. In simple terms, we can test new compounds in ever more sophisticated and accurate ways and increase our understanding of how purity vectors and potency attributes interact. The hunt for biosimilars has fostered recognition of "attributes and combinatorics" such as deamidation, methionine oxidation, glycation, high mannose fucosylation, sialylation, and so on. "Each term represents almost endless permutations adding to the complex challenge of characterizing large biomolecules and comparing one to another," I said in my report on the event.

The AAPS conference included testimonials from companies and suppliers on the relationships between parameters such as concentration, charge interaction, viscosity, and aggregation — and their influence on everything from patient immune response

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Bernard Helk of Novartis reported on the company's use of spatial aggregation propensity (SAP) technology, molecular simulations that predict formulation characteristics that can aid the screening and stabilization of biological therapeutic candidates. Other speakers, from a full range of company types and sizes, described using various new tools to analyze new molecules for potential toxicity, immunity effects, stability, comparability, fill-finish issues, and many other key attributes that can guide optimization.

This is an experience I believe all pharma/biopharma company executives should have. Go to a USP or AAPS event or any other one that you think might be technically over your head or if not that, too technical to suit your lofty strategic concerns. Now, I'm sure I'm talking to a very small crowd here and that most of our readers are much too sophisticated to need so didactic an exercise. Still, you might consider doing it anyway, no matter how hip you think you are. There is a value to walking on the street as compared to just imagining it. Everything moves much faster, and changes come with every step. You may well leave with a deeper understanding of why early development is critically important, and thus better prepared to justify investing in it.

THE IMPORTANCE OF SUPPLIER CHOICE

Back to suppliers. The ones you are looking for have applied original, scientifically validated insights to solving the problems you will face as you optimize your compound before sending it off into the real world of development and manufacturing. Again, sounds obvious, right? Well, this is where it gets difficult, because now you must do your homework, putting your company's time, expertise, and money on the line. And I can't help you there. I can just say this as you begin the journey: Make it a strategic exercise with the same priority as the design of a Phase 3 trial — which, of course, is a whole other subject.

Although some CMOs are certainly on the cutting edge of early development technology, not all such suppliers think of themselves as CMOs — or even as suppliers. Many regard themselves as biotech companies developing platforms or helping others develop products with those platforms. Others are academics, if particularly active ones. The SAP system used by Novartis came out of MIT. And the Novartis example also shows how the need for cutting-edge suppliers in this space is not confined to small start-ups. Large companies, at best playing catch-up in the manufacturing game, also have strategic reasons to find, select, and use them for maximum advantage.

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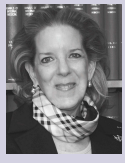

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The 5 Steps Of Contingency Planning

By David Walsh

Success sometimes reflects of the number of calculated risks we're willing to take both personally and professionally. That's why contingency planning is so important — it allows active risk management and proactive preparation rather than reactive decisions when faced with an emergency, which can result in failure. The following are the five basic steps of contingency planning for epidemic, pandemic, or other emergency situations.

1. PROGRAM MANAGEMENT

Most organizations start by recruiting a contingency planning team that includes at least one representative from each department and every level of management down to the most entry-level positions. The team members identify the objectives of the contingency plan for each department, and then the team conducts realistic risk assessments that lead to creating the outline for responding to every potential threat.

Depending on the nature of the threat, you may need to recruit specific teams to deal with particular issues during an emergency, such as off-site storage, information technology, procurement, customers, vendors, and supplies.

2. PLANNING

Have the planning team conduct a thorough, realistic risk assessment and business impact analysis. The risk assessment will be the basis for the business impact analysis, followed by hazard prevention and risk mitigation policies.

3. IMPLEMENTATION

The contingency plan will spell out clearly who (both internally and externally) gets notified and in what order. The first-tier people are most affected by the event and need information that will enable them to take immediate action.

The communications team is alerted to begin the second phase of both internal and external notification plans. Developing an emergency reporting form will help everyone have accurate facts from the beginning of the incident and throughout its eventual resolution. It also will aid the communications team in reporting facts and not speculation from other employees or emergency personnel.

The next notifications go to the second-tier audience — important but not on an immediate level — and may include customers, suppliers, vendors, utilities, and outside agencies. Notifications to third-tier audiences can wait for 20 to 30 minutes or up to an hour or more after the incident.

Eventually the contingency plan will guide the organization through each of the natural phases of the event and its goals: response, resumption, recovery, and restoration.

4. TESTING & EXERCISE

If your company has completed a contingency plan, you will have fewer worries depending on the exact situation.

Key learning: There must be basic supply infrastructure to provide key materials and resources prior to an emergency outbreak if that outbreak is to be controllable. The costs of such contingency planning are miniscule in comparison to a potential delay or inability to react in time.

5. PROGRAM IMPROVEMENT

Just because the immediate threat has passed does not mean there isn't work to do following any disaster or disease outbreak — human or animal. Although most major companies have been involved in short-term emergency situations, it makes good business sense to have long-term support plans in case you're dealing with an emergency, epidemic, or pandemic for days, weeks, months, or even years.

In an effort to become more proactive than reactive, government agencies are now doing periodic testing for a variety of contagious conditions and diseases. After the initial outbreak and containment of a pathogen, eradication can only succeed in situations where constant monitoring of the health of the infected population occurs until no more people or animals exhibit symptoms of the disease. The true measure of success comes when no other patients report symptoms over an extended period of time. Further questions need to be answered, such as, is the eradication program working, or is the disease dying off by itself?

Vigilance and frequency are the ongoing missions that governments are tasked with

and to be held accountable for to ensure the health and well-being of both humans and animals around the world. It is a mission we also share responsibility for those under our charge. The lessons continue as it is a case of not if, but when.

WHAT IF . . .

On a more personal level, what if the outbreak is within your company? What will your company do if movement within a geographic area is restricted for a day, week, or month?

What if a significant number of employees are too sick to work? For those employees who have not come down with the illness, how will they get to work if mass transportation is restricted or is prohibited from operating? Will your employees within the containment area have access to electricity, the Internet, and/or cell phone or land lines? What if we're stuck in our building for 24 hours or more?

How will the company keep its temperature-sensitive IMP or tissue samples stored at the appropriate temperature in the event of a power loss associated with some disaster? How long do we need to keep them at the appropriate temperature before they're ruined or, worse, dangerous? How many backup generators are required to keep our investment safe? What if we're ordered to evacuate? Do we need a refrigerated truck standing by? Will the authorities allow it in the area? Where will there be fuel available to refill it? Where will we send it to wait out the situation?

Many companies keep temperature-controlled packaging on hand in case their refrigerators or freezers do lose power. Many passive systems can maintain temperature control for 24 hours up to five days. Companies that provide temperature-controlled packaging often keep an extra amount of dry ice on hand for their customers in an emergency. Then we have to ask ourselves, will the dry ice supplier be able to get here?

Developing a system of pre-alerts can help life sciences companies prepare at least a week or two before products or services are needed. Generally speaking, we recommended having a minimum reservoir of products on hand to last one month at least. Outbreaks can last two to three months or longer, so managing stock components is crucial.

In the life sciences industry we need to ask ourselves, do we have an off-the-shelf solution in house or will we need to adapt components to fit the current situation? Do we need to start from scratch? During a crisis your company may need to design a new protocol that enables you to accelerate the prototype, testing, and validation processes.

Think Geographically

Will our suppliers be able to get to us? Or will we have to go to them? Having at least one major component supplier within a day's drive of your office or manufacturing facility will allow maximum flexibility in the worst-case scenario. We recommend you have a backup supplier for that one in every state (or region) surrounding your base of operations or manufacturing facility in case of geographic restrictions.

Exercise

No matter how detailed and well thought out any contingency plan is, it is worthless without practice. Your company should practice a disaster plan at least once a year and preferably twice. The opportunities to learn from each practice will help refine and streamline the contingency plans for better employee safety and an enhanced company reputation.

About the Author

David Walsh founded DGP Life Science in 1998 after developing a unique packaging solution designed for the transportation of samples suspected of containing the BSE (Bovine Spongiform Encephalitis or "Mad Cow Disease") prion. Mr. Walsh is widely regarded as an expert in environmentally sustainable business practices and is often called upon to give presentations on the subject.

Industry Leader

Accelerating Drug Development By Harnessing Technology

Thomas Grundstrom

Thomas (Tom) Grundstrom is VP, integrated processes and technologies at Quintiles, and the global head of Quintiles Infosario, a solution that integrates data, systems, processes, and therapeutic expertise.

The biopharma industry has always taken well-deserved pride in being rooted in the life sciences, using the fields of medicine and biology to develop a vast range of life-changing therapies. Today, however, in order to meet the challenges of rising product development costs, generics, and patent cliffs, the industry must reach out to another discipline — information technology — to accelerate clinical development and to bring drugs to market faster, better, and cheaper.

How can biopharma take advantage of the latest IT? A decade ago, the finance industry faced a similar situation in which banks had to decide whether to continue doing things "business as usual" or embrace technology to deliver the best product to their customers. Now, we cannot imagine a world without online banking — and we have those early adopters to thank.

The biopharma sector is at a similar point in its evolution and has the opportunity to tackle its challenges through technology-based solutions and/or collaborations with CROs to plan, design, and execute clinical development. This approach can help companies get the most out of their core strengths in the life sciences.

ACCESS TO DATA IS ESSENTIAL

A large and growing number of trials are being run by CROs, so how does a biopharma company reap the benefits of the latest information technology? Biopharma executives considering a CRO to partner with in the technology space should recognize that it involves a change in approach from the typical relationship between biopharma companies and CROs. Traditionally, the CRO has been viewed primarily from a client-vendor perspective and as a source of cost-effective headcount. However, partnerships with a technology focus demand that both parties move beyond that limited position to a relationship where trust is built through transparency and shared access to data that allow biopharma and its CRO partners to work side-by-side to make proactive decisions to identify signals and trends. Biopharma companies that fully grasp the trust-through-transparency partnership model realize it is access to data that is essential, rather than physical custody of data. As a result, these companies are reaping the greatest rewards from new technology — to aggregate data from multiple sources into a manageable format, enabling views across studies, programs, and portfolios leading to a greater probability of success.

ADDRESS ALL PHASES OF CLINICAL TRIALS

Today, information technology that simply automates clinical trial processes that drive incremental change is not enough. Visionary companies need technology solutions that drive more effective processes — triggers, alerts, and calls to action — to improve efficiency during each of the four major cycles within clinical trials. In the first cycle of identifying suitable sites, biopharma would benefit from historic information about which geographies or sites are appropriate for a specific study or therapeutic. In the second cycle, patient recruitment, instant access to data across sites, studies, regions or therapeutics on the recruitment rate, screen failures, or the impact of specific inclusion/exclusion criteria, could better inform users how to modify the trial protocol at the earliest stage for optimum patient recruitment. In the third cycle, maintenance, data on protocol deviations, queries, subject safety issues, and drop-out rates could be used to minimize delays. Finally, at database lock, early information on data readiness would save time and point to where efforts should be focused to clean the data.

Systems as a Service, or system hosting, is another approach where technology can help to drive efficiency in clinical trials and produce potential cost savings. In this case, technology is leveraged across multiple companies, while retaining access to best-in-class systems, thereby converting fixed costs to variable costs.

The pressure is on for biopharma to radically improve the drug development model, and forward-looking companies realize that harnessing data creates an advantage in driving their promising molecules to market.

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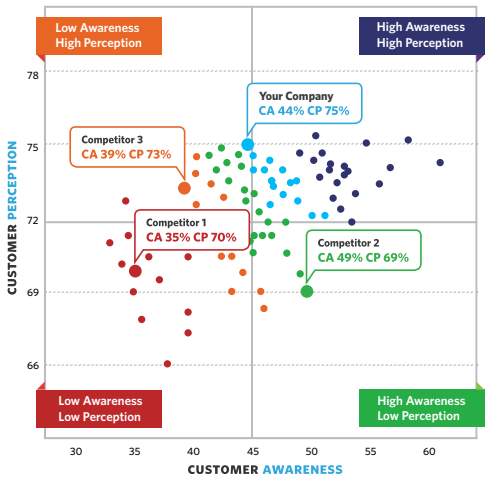

7 therapeutic categories

25 outsourced service categories tracked

6 phases of drug development

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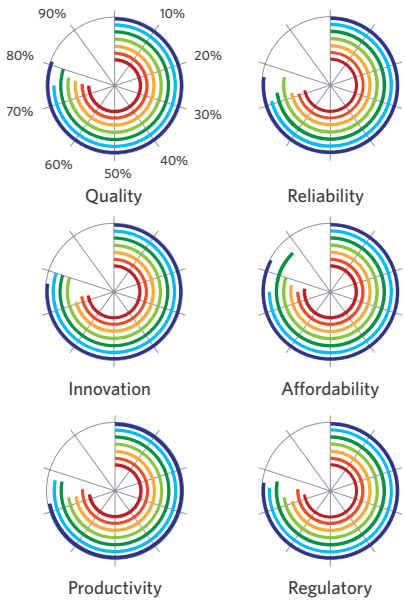

CUSTOMER AWARENESS BREAKDOWN

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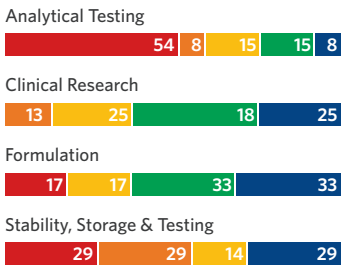

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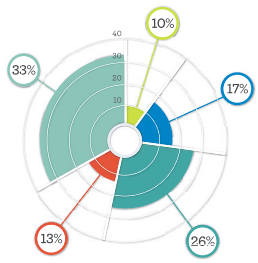
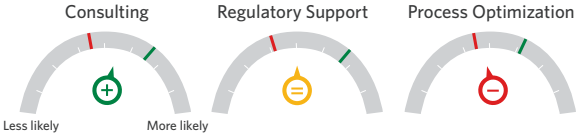


6 key departments are represented

LIKELIHOOD OF WINNING A PROJECT BY SERVICE



⊕ indicates the profiled company has a greater likelihood of winning a project over other providers of the same service. ⊜ indicates the company scored at parity with the median. ⊖ indicates the company is less likely to be selected for the project than competing businesses offering the service.

Quantifying The Potential Value Of Orphan Drugs

Rare or "orphan" diseases typically affect fewer than 200,000 patients in the U.S. — about 1 in 1,500 people. While this is not a large patient pool, it is still seen as an attractive market for pharma companies to pursue in R&D. In the last decade, government incentives, longer exclusivity rights, and advantageous pricing structures have launched an explosive growth in the development of orphan drugs.

Thomson Reuters sought to quantify that growth and the extensive potential of orphan drugs. Using predictive modeling, the team compared the total value of orphan drugs from 1990 to 2030 and published its findings in *Drug Discovery Today* ("Orphan Drug Development: An Economically Viable Strategy for BioPharma R&D") and in a Thomson Reuters report, *The Economic Viability of Orphan Drugs*.

In the past, orphan drug development was considered risky due to low expected return on investment in an expensive R&D program with a limited patient population. Collectively, however, the number of people affected by rare diseases continues to grow. The National Institutes of Health and the European Organization for Rare Diseases estimate there are 7,000 rare diseases worldwide, and the list increases by about 250 each year.

The tide for orphan drugs changed in 1983 when the U.S. government passed the Orphan Drug Act. Designed to encourage the development of drug therapies for rare diseases, the Act provided unique incentives, including seven-year market exclusivity, tax credits covering up to half of R&D costs, R&D grants, and waivers of FDA fees. During the next 17 years, other countries followed suit with similar acts, offering a new level of security to companies undertaking the orphan drug cause.

From 2001 to 2010, the CAGR of sales of orphan drugs was 25.8% compared to 20.1% for a matched control group of non-orphan drugs. The orphan drug sample set also revealed notable characteristics: 40% of the orphan drugs in the sample set were oncology-related (compared to 10% in the non-orphan sample), and there was a larger share of biological orphan drugs than small molecule orphan drugs. Additionally, 25 of the 86 orphan drugs studied were blockbusters — that is, 29% had annual sales greater than $1 billion, a percentage that stayed consistent from 2000 through 2010.

Our analysis suggests the CAGR of orphan drugs will outperform non-orphan control drugs over the next 20 years due to several factors:

- The high representation of biological orphan drugs. Biological orphan drugs are expected to retain their economic value past patent expiration since most biological drugs are currently less susceptible to generic, or biosimilar, erosion.
- The impact of the smaller patient populations will be offset by higher pricing supported by unmet medical needs and fewer competitors. For example, Soliris, designed to treat paroxysymal nocturnal hemoglobinurla, a life-threatening blood disease, brought in $541 million in total sales in 2010, even though it was the industry's most expensive drug that year (costing over $409,000 annually) with an estimated U.S. patient population between 4,000 to 6,000 people.
- The ability to reposition an existing orphan drug to treat additional rare diseases increases profit opportunities. Of the top 10 orphan drugs studied, six had more than one rare disease indication with a peak value of $34.3 billion in overall revenue potential versus $8.1 billion for drugs with a single orphan indication. Out of the entire sample set, 15% had subsequent rare disease indications.
- Extended market exclusivities will insulate orphan drugs from generic competition longer. In the U.S., orphan drugs are granted seven years of exclusivity (versus five years for non-orphan drugs), further protecting them from generic erosion.

Two of the largest challenges facing orphan drug developers are the ability to locate and recruit patients and the logistical issues surrounding trial organization. However, trials for orphan drugs are significantly shorter and have greater regulatory success, potentially offsetting increased R&D costs. Along with other significant benefits, including tax credits, favorable reimbursement, fewer approval hurdles, longer exclusivity, lower marketing costs, faster uptake, and premium pricing, orphan drugs may be an unexpected effective strategy to future profitability.

Dr. Kiran Meekings

Dr. Kiran Meekings is a consultant within the Thomson Reuters Professional Services group. With more than seven years of experience in the life sciences sector, she has a broad background encompassing clinical and scientific research, pharmaceutical equity research, pharmaceutical market analysis, and consulting.

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Urgency: Leadership's Strategy Accelerator

By Randy Ottinger

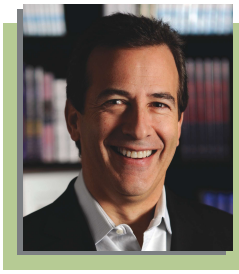
Once a company has identified an opportunity in a marketplace, the real challenge is then to successfully implement that strategy, meaning that the mindset of the organization must change from an old way of doing things to the new way. While there is no magic bullet, a key to the successful implementation of strategy is to create a broad sense of urgency throughout the organization about the opportunity the company is pursuing and to engage as many employees as possible in it. Here are some insights about how to create broad-based urgency and why it is important.

Bring The Outside In — During the development of a strategy, it is critical to bring in multiple points of view from a variety of sources. Customers, partners, investors, and employees all have valuable insights to share. Strategies are not developed well in a vacuum, but are best built when multiple perspectives are considered that provide clarity about the window of opportunity that exists for the company. Sometimes the opportunity relates to innovation and growth, but just as importantly, it can relate to efficiencies. Often it's the lowest rung of employees that identify those opportunities to streamline. Bringing in other stakeholders early on can help create urgency and credibility around the new strategy.

Align Senior Leaders Around A Clear Opportunity — In a previous column, my colleague Dennis Goin talked about aligning senior leaders. I'll underscore his point: It is critical that senior leaders are aligned about the opportunity they are pursuing in the marketplace, as well as the strategies that are critical to achieving success. When senior leaders are united, excited, and urgent about an opportunity, that feeling often spreads throughout the organization. It's almost impossible to galvanize employees to change when their superiors are inconsistent about the way forward. Senior leaders must model the way.

Engage Employee Volunteers — Most life sciences companies are run in a top-down model, with the "answers" coming from relatively few senior leaders. One way of accelerating strategy implementation is to engage many people throughout the company to find innovative, new ways to achieve the strategies that have been developed by senior leaders. While engaging employee volunteers is partly about communicating in creative ways that touches both the heads and hearts of employees, it is also about creating a "want to" attitude where employees are encouraged to volunteer to support the key strategies of the company. That "want to" attitude can evolve into a "get to" culture, where employees believe they have the permission and encouragement to find better ways of doing things within their sphere of influence.

I've seen life sciences companies realize success when thousands of urgent employees have raised their hands to help the company achieve its strategies, leading to rapid product introductions and significant cost savings. For those companies, urgency and strategy go hand in glove. Done right, urgency is an accelerator that helps organizations seize market opportunities more quickly.



Randy Ottinger is an executive vice president at Kotter International, a firm that helps leaders accelerate strategy implementation in their organizations. He can be reached at randy@kotterinternational.com.

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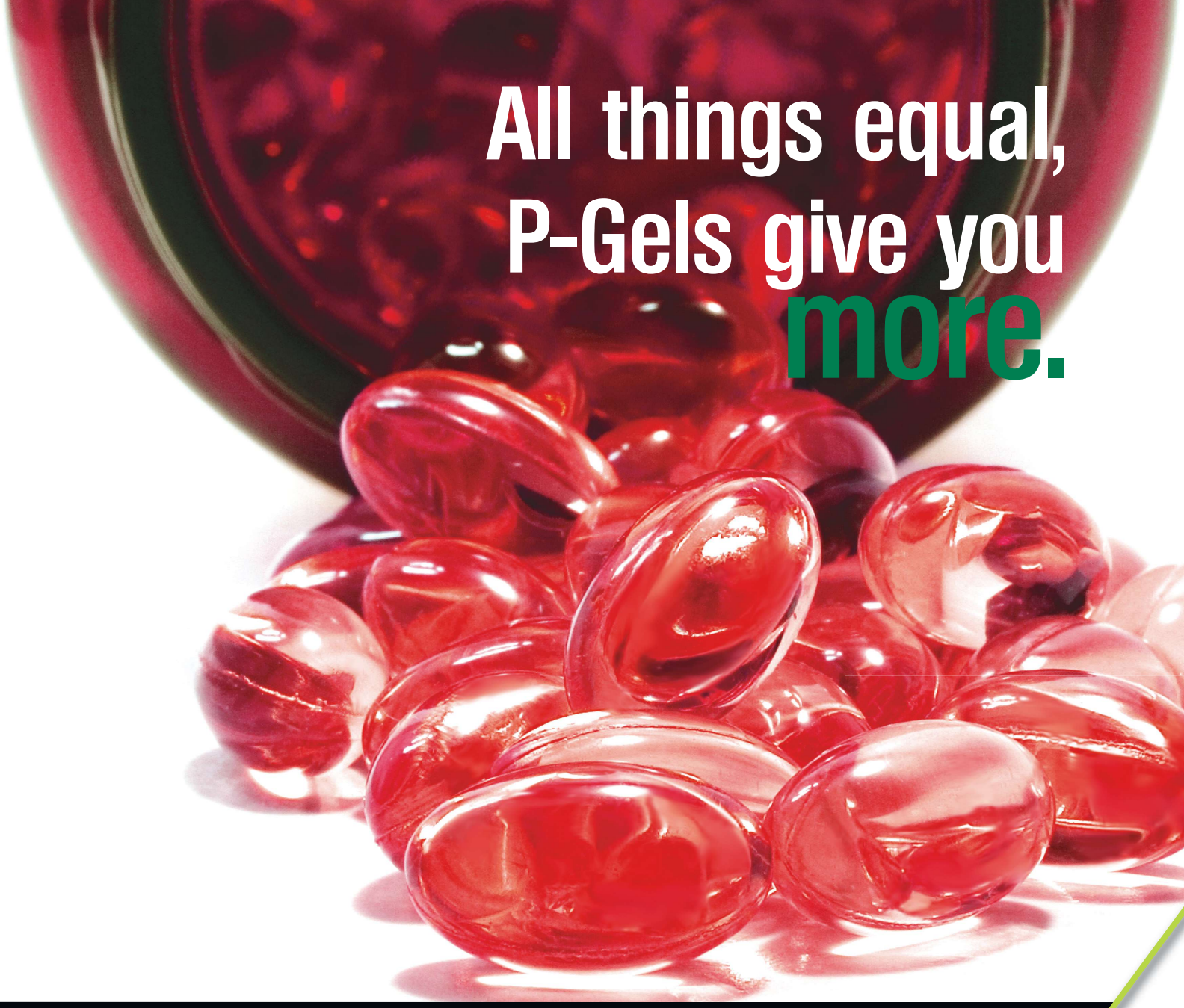

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