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A Forgotten Majority:
Diversity In Clinical

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Changing The Culture At Sandoz U.S.

"We weren't meeting [customer] needs and it was really negatively impacting our performance." p. 20

Don DeGolyer,
president, U.S. unit and head of commercial operations, North America,
Sandoz

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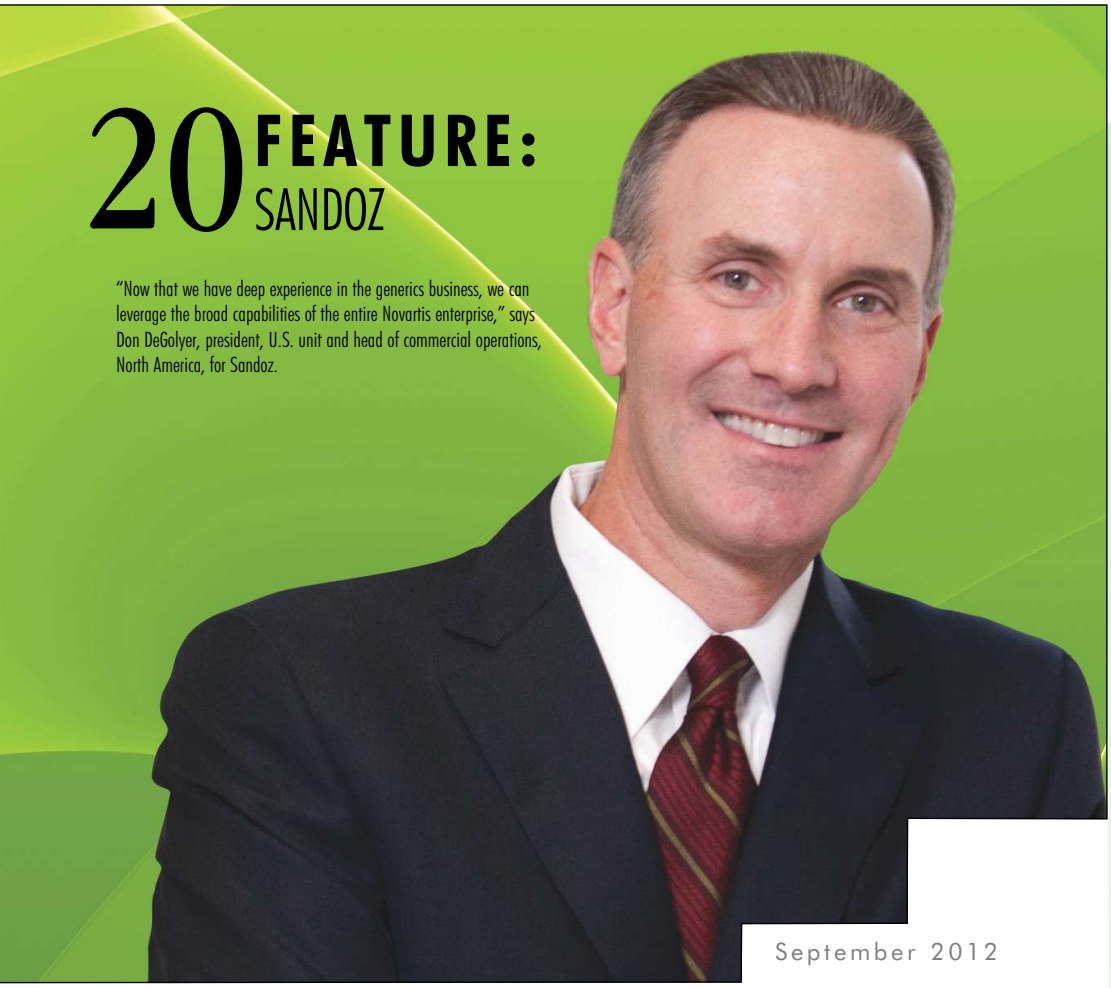

20 FEATURE: SANDOZ

"Now that we have deep experience in the generics business, we can leverage the broad capabilities of the entire Novartis enterprise," says Don DeGolyer, president, U.S. unit and head of commercial operations, North America, for Sandoz.

September 2012

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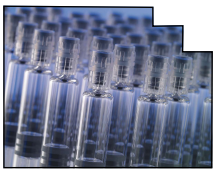

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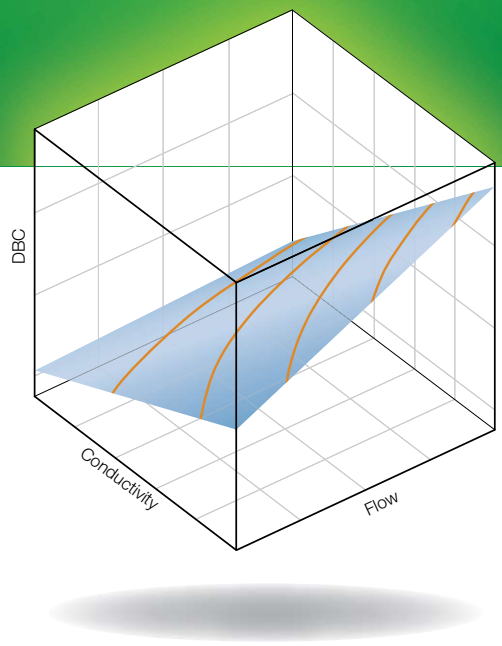

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EDITOR'S NOTE

A Pricey Path To Drug Discovery

This past July, GlaxoSmithKline (NYSE: GSK) agreed to buy Human Genome Sciences (NASDAQ: HGSI) for $3.6 billion. These two companies are no strangers to each other, having established a codevelopment agreement in 2006 for BENLYSTA, a prescription IV infusion treatment for systemic lupus erythematosus. Among much fanfare, the drug received FDA approval in March 2011 as the first approved treatment for SLE in more than 50 years. Obviously, GSK saw enough value in this product and the HGS' pipeline to buy the company. In a press release, GSK CEO Andrew Witty said, "The transaction meets GSK's strict financial criteria for acquisitions, and we expect we will deliver significant returns over the long term. This is a natural next step in our 20-year relationship with HGS." But I began to wonder what Witty was seeing that I didn't. Let me explain.

HGS was founded in 1992 and went public just one year later. By 2000, the company had raised more than $2 billion in investments. From 1998 to 2011, the company's annual reports indicate a net income loss for every year except 2009, and these total around $2.2 billion. So what is it that GSK found so compelling it was willing to pay a 99% premium over HGS' April 18, 2012 closing share price of $7.17/share? One approved drug, BENLYSTA, which I estimate as potentially helping a market of around 322,000 U.S. citizens suffering from SLE, or a little more than 0.1% of the U.S. population. I would also like you to consider the fact that BENLYSTA is an adjunct therapy, meaning it is added on to other commonly used lupus treatments. So patients with SLE can take the cost of whatever they are currently taking and add around $35,000 a year — the current price for BENLYSTA in the U.S. So if just half of the potential market buys this drug, we are looking at about $5.6 billion in annual sales. I guess the $3.6 billion dollar price tag for HGS wasn't so bad after all when you also add in some other assets — Raxibacumab, a new anthrax treatment already being purchased and stockpiled by the U.S. government, and Mapatumumab, a potential treatment for cancer. Raxibacumab and BENLYSTA are already producing revenue, though the billion dollar mark is a bit far off.

But HGS had other assets of value — people for example. Yet, I guess the HGS leadership team wasn't part of the asset valuation deal. Just 15 days after the announced acquisition, GSK replaced the CEO, CFO, and five other executive-level positions. This is not an uncommon practice. Acquiring companies often believe they can do better without the help of the acquired company's executives. Let's hope so in GSK's case. When you consider BENLYSTA was first identified in 1996, factor in initial investments, 10+ years of losses, severance packages, and the billions to acquire HGS, it has to be one of the longest, most expensive, and successful drug development projects on record.

Rob Wright
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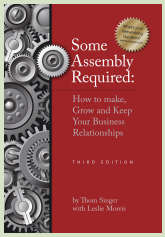

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ASK THE BOARD

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

Q: What is your opinion on innovation/creativity as a key characteristic for life science leaders?

Innovation and creativity are especially important traits of life science leaders. To advance scientific breakthroughs, it is critical to think not just "out of the box" but "out of the building," thereby tearing down mental boundaries and challenging what is known technically, scientifically, clinically, and strategically. Life science leaders must also think globally. The life sciences are advancing at an accelerated rate, yet the more we know, the more we realize what we don't know. Life science leaders must focus on practical translation of the science while being mindful of the convergence of multiple disciplines like ethics, information technology, and economics. This demands creativity and innovative thinking.

Leslie Williams
Williams is president, CEO, and founder of ImmusanT, Inc., an early-stage company focused on peptide treatments for autoimmune diseases. She has more than 20 years of industry experience.

Q: What are some key components which often get overlooked when developing a value-driven clinical program?

One is the development of a robust definition of "value" for the drug from internal and external stakeholders, including payors, leading to an evolving target product profile that has strategically taken into account the market and current/future competitors. From this foundation, study designs need to be developed with key opinion leaders that minimize/contain cost and risk and maximize/maintain value. Relationships with the payors need to be developed early on in your clinical development program so that organizations can get a better understanding about expectations in reimbursement upon drug approval. There needs to be regularly occurring, disciplined evaluations of the development cost, risk, and ROI of the clinical program due to changing variables such as the competitive landscape, other competing clinical programs, and new regulatory hurdles.

Dr. Mitchell Katz
Dr. Katz has 26 years' experience in the pharma and biotech industries, including preclinical research, pharmaceutical operations, and regulatory affairs. In his position at Purdue Pharma L.P., he is the executive director of medical research operations.

Q: What do you see as being the next big game-changing technology in cold chain shipping?

The new trend is to migrate from cold chain to temperature-controlled shipping to include frozen, refrigerated, and controlled room temperature (CRT) products. Temperature monitoring has been the main focus for a long time. However, regulators are asking about humidity monitoring and the effect of light. In addition, the need for all technology to demonstrate the supply chain integrity (SCI) should be utilized. Progress in the application of RFID, real-time monitoring, enhancing security measures in overt and covert solutions, and track and trace should help in avoiding the illicit activities of the counterfeiters. Allocating a stability budget for transportation should assure the quality, integrity, and efficacy of the temperature-controlled product when it reaches the patient.

Rafik Bishara, Ph.D.
Dr. Bishara is the chair of the Pharmaceutical Cold Chain Interest Group (PCCIG) within the Parenteral Drug Association (PDA). He had a distinguished 35-year career with Eli Lilly & Co. as director, quality knowledge management and technical support.

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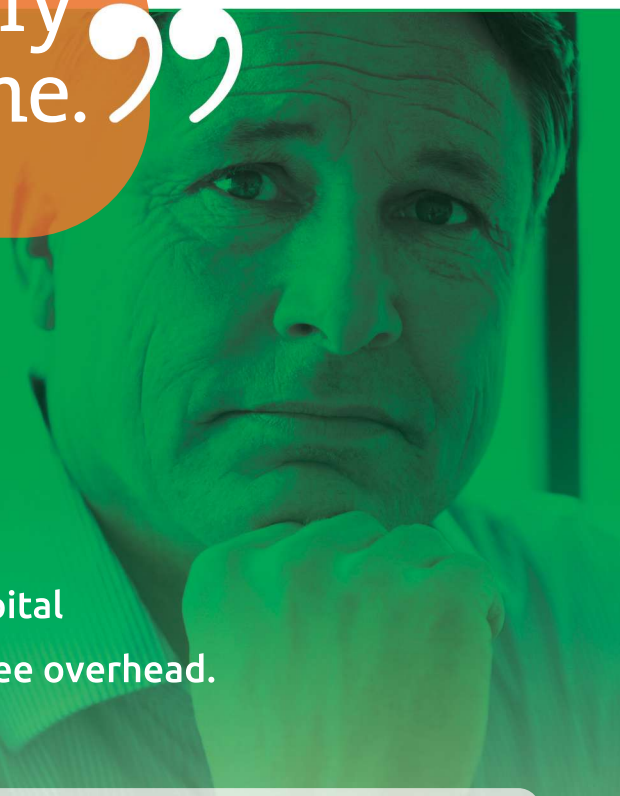

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By Wayne Koberstein

PsiOxus Therapeutics

Destroying cancer cells and beating a deadly wasting disease are on this company's brave agenda.

SNAPSHOT

PsiOxus is exploiting novel mechanisms to fight cancer directly along with its indirect but lethal effects. In mid-July, the company landed funding for Phase 1 and 2 trials of ColoAd1, a "systemically available oncolytic vaccine" that selectively enters cancer cells and proliferates inside like a virus, killing the cells — an interesting marriage of targeted and immunotherapeutic strategies. It also has the first product in development (Phase 2) for cachexia, the wasting syndrome that is the actual killer of a huge number of cancer patients, with a "conservative" market potential of $4 billion, and is developing the same molecule, MT-102, for similar wasting conditions such as sarcopenia, which affects many elderly people. PsiOxus also has two platforms in preclinical development for enhancing viral-based vaccines: PolySTAR (polymer-coated stealthed viral vectors) and PolyMAP (potent polymerised synthetic TLR adjuvants).

Dr. John Beadle, CEO

LATEST UPDATES

- July 2012: Funding from $34 million Series B for Phase 1 and 2 development of ColoAd1 for colorectal and other cancers.
- April 2012: Expansion of facilities at Oxfordshire, UK, to double lab workforce

WHAT'S AT STAKE

Why do people die of cancer? Like many of our worst diseases, death does not always come from the cancer itself, but from its secondary manifestations — the two most deadly being devastation of the immune system and destruction of the body itself, aka cachexia. PsiOxus has plunged bravely into both areas; the first is a vaccine that makes up for a patient's immunodeficiency by installing its own replicating attack force inside cancer cells to destroy them; the second is a molecule that blocks a recently identified pathway to cachexia. Destroying cancer cells sounds almost like a throwback to earlier times, before molecular-targeted drugs put the emphasis on impeding their growth. Instead of aiming for select cancers and patients, the PsiOxus vaccine brings back the concept of a more general treatment, theoretically for any cancer or any patient. The cachexia drug would be the first active therapy for the condition; nutritional approaches have never worked. What's more, the drug's MoA (mechanism of action) may apply to other wasting conditions with big potential markets. So many promising theories and approaches to treating cancer have fallen to the stubborn realities and clever defenses of the disease — what gives PsiOxus confidence that its approaches will succeed where most others have failed? "Developing cancer therapeutics is certainly a high-risk business, and it is important to de-risk the approaches as much as possible, as early as possible," says the company's CEO, Dr. John Beadle. "Our approaches to cancer are unique but also have a significant degree of specific de-risking in each case. ColoAd1 is particularly exciting given its unique mechanism of action, which does not rely upon apoptosis (which is the terminal pathway for virtually every existing cancer therapy). Resistant cancer cells are often resistant to apoptosis but are still susceptible to ColoAd1. This is an exciting new approach and hence carries the risk of failure, but in order to de-risk this program we have done our most significant preclinical work using fresh human tissues and cell lines, since animal models are so poor at predicting these potential effects in humans." Many thought leaders in cancer immunology believe that future patients will be treated with combinations of different immunotherapies rather than a single one. But if the PsiOxus vaccine proves safe and effective, they will undoubtedly welcome it, along with the cachexia drug, into the armamentarium.

VITAL STATISTICS

■ Employees: 19; Headquarters: London, UK.

■ Funding (Total $42.8 million):
- Series A, $8.8 million, with participation by Imperial Innovations Group, Invesco Perpetual (February 2010)
- Series B, $34 million, with participation by Imperial Innovations Group, Invesco Perpetual, SR One, and Lundbeckfond Ventures (July 2012)

■ Research partnership funding:
- $2.8 million translation award from Wellcome Trust Phase 1 and 2 trials of Oncolytic Vaccine (September 2011)

■ Partnership:
- With Ark Therapeutics Group, for production of ColoAd1 oncoloytic adenoviral product using Ark's proprietary suspension based single-use process (ATOSUS)

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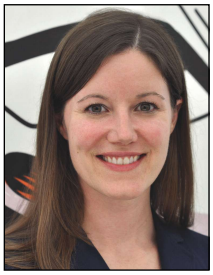

OUTSOURCING INSIGHTS

A Diversified Portfolio Of Contract Providers Might Improve Results

By Kate Hammeke, director of marketing intelligence, Nice Insight

Since its inception, the primary goal of Nice Insight's Pharmaceutical and Biotechnology Outsourcing Survey has been to optimize collaborations between CROs/CMOs and sponsor organizations. The benefits of improved collaborations play out in many forms and offer advantages every step of the way — from reduced costs, improved staff efficiencies, and increased shareholder value, all the way to much-needed therapies reaching the market more quickly and being more affordable for consumers. Outsourcing Insights has been a platform for Nice Insight to share simple strategies on how to get the best results from an outsourcing relationship, whether that relationship is tactical or with a preferred vendor or strategic partner. Each of these different types of outsourcing relationship has its merits.

If a CRO focuses exclusively on engaging in strategic partnerships, the company may be inadvertently missing out on the bulk of sponsors' financial outlay.

In the contract research market, most sponsor organizations engage CROs in relationships that fall into each category — only 5% of our survey respondents state that **all** of the CROs they work with are strategic partners. Results from a recent strategic partnering survey indicated that, in fact, approximately 1/3 of total outsourcing expenditure on early-stage development is spent with each type of alliance. This is both interesting and important for CROs to understand because for several years talk in the industry has focused strongly on a "strategic partnership model." So much so, that the investment firm Morningstar has reported that "this type of partnership model has been key to CRO success and growth" (referring to an 11.1% increase in CRO revenue in 2011).

However, if a CRO focuses exclusively on engaging in strategic partnerships, the company may be inadvertently missing out on the bulk of sponsors' financial outlay. Overall, sponsors indicated that they spend more than 2/3 of this expenditure with tactical providers (37%) and preferred vendors (34%). As a contract service provider, the key is to know when to position your business to attract each type of relationship and how to win business slated for each category.

Similar to building an investment portfolio that will maximize profits while limiting risks, diversity is essential. Diversity in outsourcing alliances — from both the sponsor side and the contract service side — protects each party from the old cliché of putting all one's eggs in a single basket and elicits benefits from each of the different types of relationships. For the same reason that a financial advisor should steer an investor away from putting all of their money into one type of stock, it's not a good idea to focus all business development efforts on one type of relationship structure. From the sponsor perspective, there will be times when the benefits of engaging a CRO on a tactical level outweigh the benefits of using a preferred provider or strategic partner for the same job.

Each time Nice Insight has asked sponsor audiences about their interest in forming strategic partnerships (defined as a long-term, win-win commitment that maximizes the effectiveness of both participants' resources), the collective response is that they're strongly in favor — fewer than 10% of respondents are neutral or uninterested. However, when these same respondents move on to a series of questions that help discern their true outsourcing rationale, the results frequently indicate tactical motivations.

This is a fundamental challenge to the strategic partnership philosophy because the reasoning used by these decision makers doesn't always correlate with the results they say they want. Affirming an interest in strategic partnerships, yet placing a heavy emphasis on "process" over "outcome" or "access to capacity" over "access to *best in class* performance" highlights a somewhat paradoxical situation.

The graph on the following page shows the characteristics selected by respondents that best coincide with their business's operating model for working with outsourcing partners. Understanding and applying this information will help CROs to refine their approach by interpreting and focusing on the underlying factors that prompted the sponsor to outsource the services. It may also help sponsors to better clarify their own true outsourcing motivations and identify opportunities to reap the benefits of outsourcing to a wider spectrum of CROs.

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Tactical vs Strategic Motivations for Outsourcing

Survey Methodology: The Nice Insight Pharmaceutical and Biotechnology Survey is deployed to outsourcing-facing pharmaceutical and biotechnology executives on a quarterly basis/four times per year [Q2 2012 sample size 2,402]. The survey is composed of 750+ questions and randomly presents ~30 questions to each respondent in order to collect baseline information with respect to customer awareness and customer perceptions on 300 companies that service the drug development cycle. More than 1,200 marketing communications, including branding, websites, print advertisements, corporate literature, and trade show booths are reviewed by our panel of respondents. Five levels of awareness from "I've never heard of them" to "I've worked with them" factor into the overall customer awareness score. The customer perception score is based on six drivers in outsourcing: Quality, Innovation, Regulatory Track Record, Affordability, Productivity, and Reliability, which are ranked by our respondents to determine the weighting applied to the overall score.


Walker

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

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BIO DATA POINTS

Adoption Of Most Single-Use Applications Continues To Increase

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

Disposable devices continue to make advances in manufacturing and are becoming increasingly common in most areas of biopharmaceutical manufacturing, especially at clinical scale production. In our Ninth Annual Report and Survey of Biopharmaceutical Manufacturers, we asked 302 biomanufacturers to review the applications most commonly employed for disposables at their facilities. We then examined the growth of these devices over the past seven years.

This year, not unexpectedly, we found that among the biomanufacturers and CMOs, almost all are using devices such as disposable filter cartridges (89.1%) and tubing for disposable applications (88.2%), while other common applications include depth filters (84%), buffer containers (81.5%), and connectors/clamps (79.5%). At the other end of the spectrum, membrane adsorbers show the lowest penetration (at the same time, these devices show the most rapid growth rate).

Biopharm manufacturers seem to finally be implementing disposable bioreactors.

Interestingly, despite nearing levels of saturation in some early-stage manufacturing, most devices continue to show increasing adoption rates. Indeed, of the 14 applications we identified, 11 are being used by a greater proportion of respondents this year than last, and aside from an outlier year in 2008, 9 of these are at their highest point of penetration in the seven years we have tracked them.

Some of the biggest areas of growth from last year included:

- buffer containers (81.5% this year vs. 76.5% in 2011)
- bioreactors (76.5% vs. 68.1%)
- mixing systems (68.1% vs. 54.8%).

DISPOSABLE BIOREACTORS GROWING

Looking back over the data starting from 2006, we find that three applications have shown by far the fastest growth in market penetration — that is, in the percentage of facilities that are now using these products, compared to 2006. For comparison, connectors and clamps grew at 9%.

1. Membrane adsorbers jumped 40.9 percentage points in market penetration from 12.9% in 2006 to 53.8% in 2012 (CAGR of 26.9%).
2. Bioreactor usage has grown from 21% penetration in 2006 to 76.5% in 2012, a 55 percentage point increase (CAGR of 24%).
3. Mixing systems usage has increased from 19.4% in 2006 to 68.1% this year (CAGR of 23.3%).

Separately, we asked our respondents to indicate the bioreactor types they would likely specify for a new clinical or commercial scale biologics facility two years from now. Two-thirds (66.7%) said they would implement batch-fed single-use bioreactors for clinical scale, compared to 53.5% that would opt for batch-fed stainless steel bioreactors for commercial manufacture. Other types of bioreactors, including perfusion, presented with lower adoption rates.

DISPOSABLE BIOREACTORS ARE HOT

We also asked respondents to indicate which disposable devices and systems had been introduced over the past 12 months at their facility. Of the 14 leading devices, the most common "newly introduced" systems included:

- bioreactors, production
- bioreactors, seed
- buffer prep systems
- mixing systems
- buffer storage systems.

The fact that this year disposable production bioreactors take the lead in terms of newly introduced systems suggests that biopharmaceutical manufacturers are taking the step from active consideration of these systems to actual implementation, and that the market for these systems is rapidly developing. When taken in combination with the data showing respondents' choice of disposable bioreactors for future commercial manufacture to be almost on par with stainless steel, we can see that the industry is moving to a place where single-use products — and in particular, bioreactors — are commonplace in commercial manufacturing.


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Figure 1: Selected Devices — Usage Of Disposables In Biopharmaceutical Manufacturing, Any Stage Of R&D Or Manufacture, 2006-2012

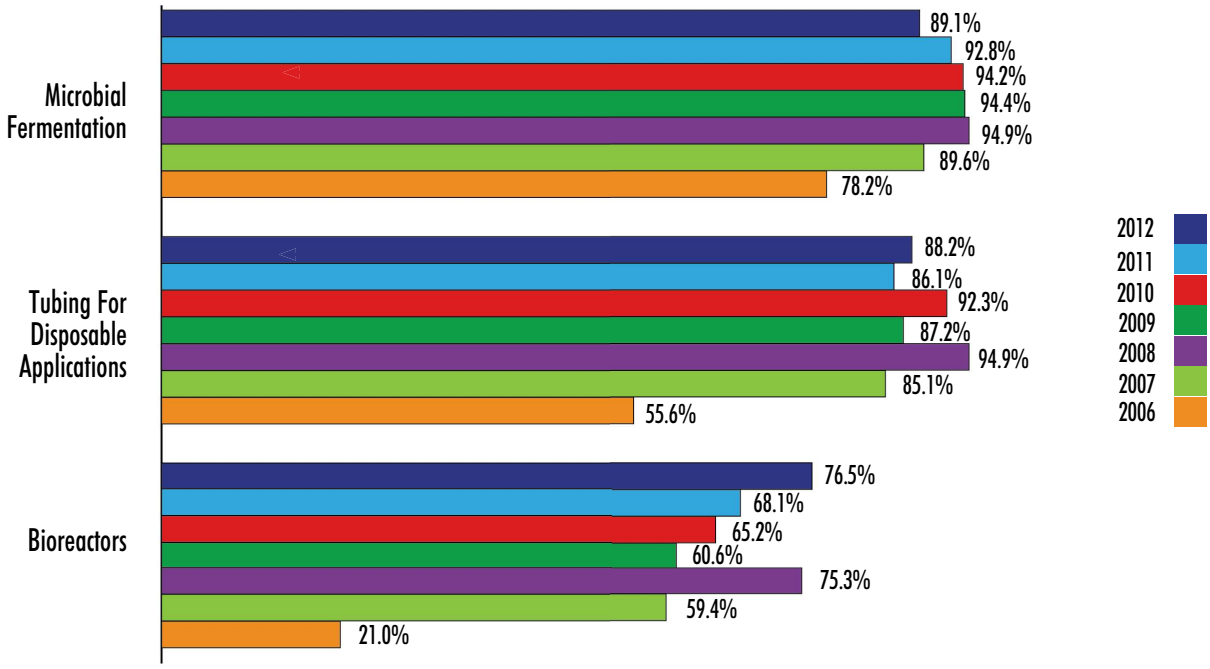

Figure 2: Selected Average Annual Growth Rate, Disposables, 2006-2012

(Note: Not growth in sales, this growth is in application first usage within a facility.)

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 contract manufacturing organizations (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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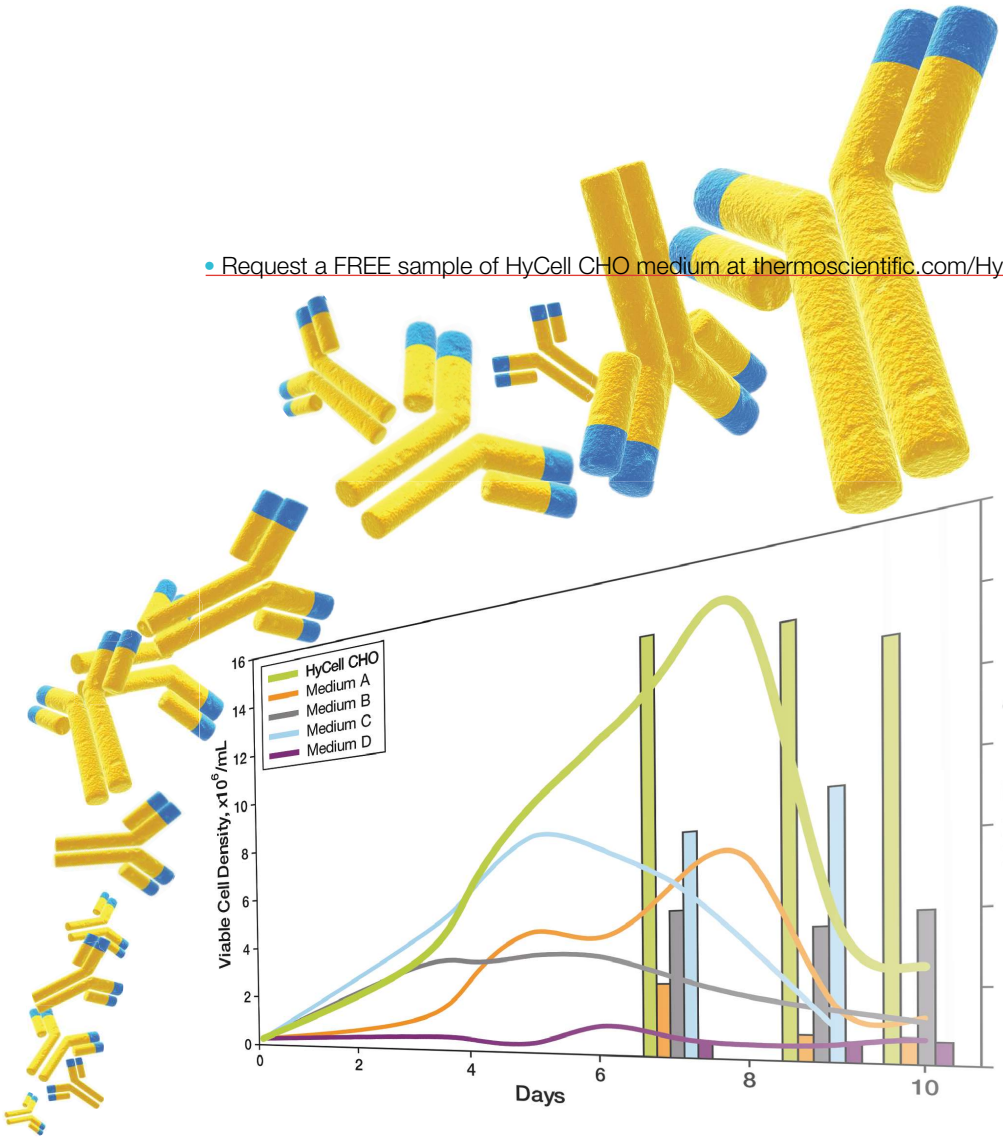

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Don DeGolyer, president, U.S. unit and head of commercial operations, North America, for Sandoz, says when he took his position in March 2010, the U.S. company had lost traction in its markets and in its operations.

Rediscovering Generics —

Sandoz Vows To Serve Patients First

By Wayne Koberstein, contributing editor

An old man on a bicycle in Basel once reminded me of the old Sandoz, one of the original maverick innovators in pharma. He looked just like one of the scientists at the Swiss giant on his way home from the discovery lab, both quixotic and professorial. By that time the old company had combined with Ciba to become Novartis, reducing Basel's mighty three to only two, including Roche. So when the name Sandoz was resurrected for the new Novartis generics division, it was unclear whether corporate was being ironic or downright cruel to the spirit of its innovative predecessor. But after several challenging years in the division's largest affiliate, Sandoz U.S., the initial ambiguity has faded, and a new picture is emerging. According to Don DeGolyer, president of the U.S. unit and head of commercial operations, North America, the Sandoz generics business he now leads has returned to old values — patient needs and access on the one hand, innovation on the other.

What DeGolyer describes is nothing less than a reformation of Sandoz U.S. that allowed it to put the difficult times behind. "Not only did we make the transition but we also restored Sandoz to its rightful place here in the United States," he says.

RETURN TO BASE

DeGolyer says that when he assumed the helm in March 2010, the U.S. company had lost traction in its markets and in its operations. "We had a negative CAGR from 2007 to 2009. Here we were — the largest country within Sandoz, which has a presence spanning 140 countries — but we weren't leveraging all of our assets. Our complex and differentiated portfolio focus was clearly in line with where the industry was headed. But we had a long way to go in building our product base and market share."

Omnitrope, the only Sandoz biosimilar marketed in the United States, had a mere 5% market share in 2009, he says. "We had a good commodity portfolio, but the market was evolving as we were getting our hands around the market dynamics — pricing, growing competition — and many of our key accounts were consolidating. There was not enough focus in the company on creating future value with our complex products portfolio."

"Complex products" is an industry term that applies to generics that are difficult to develop, manufacture, or commercialize. Straight generic versions of off-patent prescription drugs are still the bread and butter products for Sandoz and most of its competitors. But economics and technology are driving the once-stalwart generics fold into the complex camp. Many companies in the industry now combine new formulations, delivery systems, and support services for generic compounds into "complex" products that have the potential to generate sustained growth.

At least, that's the theory. Complex products present complex problems — in conception, in development, in production, in every way that taxes a company's management, operations, and resources. By that equation, DeGolyer believes Sandoz comes out ahead of the pack. It's not really a boast when he says, "Many companies talk about complex products, but the difference between Sandoz and some of our competitors is the fact that we're delivering on that promise." Sandoz does lead with a global portfolio of complex products that comprises well over 40% of its total portfolio by sales.

The difference between the company's current market leadership and previous performance is inarguably dramatic. As DeGolyer says, "The entire Sandoz team is proud that today our results speak for themselves."

The simplest and most meaningful measure is sales growth. 2010 reflected the pace of change with a 42% growth in sales. And despite the much higher baseline, 2011 still showed an impressive 25% — making Sandoz the fastest-growing company in the U.S. generics market, according to DeGolyer.

How Sandoz found a pathway back to relative prosperity and purpose is the main lesson of this article. DeGolyer — asked to describe the thought-and-action process the company traveled to its turnaround — gives a detailed and instructive account, potentially useful to any executive charged with a similar challenge.

GIVE A LISTEN

"The first thing I did was to go on 'a listening tour' of the company's employees and customers," he says. "I first asked them what they liked and wanted to preserve about the company, and then, what would your wish be to measurably improve the company? And then finally, how would you compare us to the competition? And what I heard from our employees is that we were a good company with quality products and people, but we were very internally focused."

Specifically, DeGolyer says, company functions were "siloed," keeping to themselves, resisting any collaboration with each other. The internal focus led to isolation of the company as a whole. Beyond sales and marketing, which he had previously headed, he saw a lack of focus on the external markets and customers. "As I was visiting people on the shop floor, I found some employees didn't know who our customers were, which I found very surprising."

WINNING TO PLAY

Don DeGolyer has been president of Sandoz U.S. and the head of commercial operations for North America since March 2010. He has a broad range of GM responsibility that includes three commercial operating units, plus the research and development sites at its East Hanover, NJ headquarters campus. He also oversees five manufacturing sites as well as business development and licensing among the 16 direct reports heading various functions. He joined Sandoz in October 2009 as senior vice president and head of U.S. commercial operations, which was his introduction to the generics business. He was responsible for the company's retail, institutional, and biopharmaceutical operating units and oversaw all of the new product selection for development activities. Prior to that, he was senior vice president of U.S. managed markets & established medicines at Novartis Pharmaceuticals Corp. and was also a member of the company's executive committee there. Before joining Novartis in 2002, he was president of global therapeutics for Oxford GlycoSciences, a U.K.-based company in proteomics and rare diseases. He began his pharma-industry career at Pfizer and J&J, progressing through various roles of increasing responsibility. Thus, his experience includes branded medicines, mature products, generics, and specialty medicines, and even a bit of healthcare IT. He is now the vice chair and executive committee member of the GPhA (Generic Pharmaceuticals Association). Married, with two children, he grew up in a family business, working in his brother's delicatessens on Long Island from the age of 14 and eventually running them on the weekends. "It taught me responsibility, leadership, and frankly, a customer focus, which really plays through how we approach the Sandoz business." DeGolyer also grew up playing competitive sports, including on his high school basketball team when it won the New York state championship in 1979 and as captain of the University of Rochester basketball team. "All of that teaches you preparation and determination, a will to win, and teamwork. Those qualities also come into play every day at this company and have been key to restoring the luster to Sandoz in the United States."


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Unlike the airline commercial where the boss hands everyone a ticket, DeGolyer couldn't send all his employees out to meet the customers in person. His solution was to bring key customers into the company so all associates could hear the bitter truth: "We weren't meeting their needs, and it was really negatively impacting our performance. We learned that our customer engagement and communications were not where they needed to be, we needed to expand our product portfolio with key accounts, and our strategy needed to focus on achieving leadership in the very attractive and rapidly evolving U.S. marketplace."

Big internal changes were forthcoming. Cultural norms, for example, discouraged operational functions, such as manufacturing, from looking outside to the world of customers, normally the exclusive realm of the commercial team.

"What I wanted to build was a mentality that centered on speed and simplicity for our customers," DeGolyer says. "But we had to put a much greater priority on systematically developing people who would be role models for strong leadership and accountability. One employee described the situation to me: 'We spend more time fighting ourselves than we do the competition.' If we were going to turn the business around, we needed to understand and prioritize our customers' agendas and work together across every function of the company toward a common purpose."

To encapsulate the new "market- and customer-based" strategy, DeGolyer defined the company's overall goal: "to be the most respected generics company in North America." Progress would be measured by five main parameters: product quality, company growth and performance, development of a complex-product pipeline, productivity, and employee culture and talent. "At the core of it all," says DeGolyer, "is the unifying aim of serving our customers and, ultimately, patients."

"We put a face on our vision and mission by talking about real patients like senior citizens, folks on a fixed income, or people who are out of work. We saw it as a noble mission to provide access to high-quality and more affordable medicines for those patients."

Those words, "access, high quality, and more affordable" hearken back to the beginnings of the generics industry in the United States, when a grand political compromise wedded an ensured period of exclusivity for branded medicines with a mechanism for multisourcing off-patent drugs. At that time, the first companies to produce generics were fueled with a mix of profit motive and populist idealism. Perhaps the industry had since drifted into a kind of low-margin commodities culture with insufficient focus on innovation. To ensure that Sandoz successfully bucked the trend inevitably required an overturn in personal attitudes and even personnel, as DeGolyer relates.

"In our company culture, there was not enough focus on performance. We made it very clear that mediocrity was not acceptable, and we believe in a fact-based, performance-oriented culture." People got the message that the new culture may not be for everyone. At the executive level, he says, the resulting turnover produced a diverse and deeply experienced leadership team. "Today, we have a very diverse leadership team with experience ranging from generics to brands, to various markets including Europe, India, and Latin America."

Higher cultural standards paralleled efforts to improve the quality of the company's products. From 2008 to 2010, the industry had experienced a four-fold increase in FDA warning letters, at a time of greater demands for product quality from regulators and customers alike. Compliance and quality are a top priority for Sandoz, DeGolyer says. "Being part of Novartis and having one global standard for quality across our enterprise is ultimately an advantage, and we're redoubling our resourcing in this area, to enhance technology, systems, and people. Our goal is to achieve competitive advantage through quality — and quality above and beyond mere compliance."

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THE POTENTIAL OF BIOSIMILARS

Broadening the product portfolio fulfilled another key strategic imperative, says DeGolyer. Sandoz U.S. now sells several hundred products and has increased its development pace as well as portfolio size and variety. As mentioned, its line now includes a much larger portion of complex products, particularly biosimilars, injectables, ophthalmology, respiratory, and dermatology products.

Biosimilars represent both potential and real growth for Sandoz at this point. Its human growth hormone, Omnitrope, has expanded in market share from 5% or number seven in its market in 2009 to 18% or number two currently, says DeGolyer, giving credit to some patient-friendly ancillaries. "We enhanced our patient support services, we made improvements to our device, we achieved formulary access with managed care organizations, and we built out our specialty field force." Worldwide, Sandoz is the global leader in biosimilars and is pushing forward aggressively with development of a large portfolio.

Injectables are famously challenging to produce, store, and deliver, but they are critical to treatment in so many therapeutic areas and applications, and no company like Sandoz could compete without them. And there is no use competing if you can't stay ahead of the pack. Sandoz has used acquisition and organic growth to expand its injectables production and supply chain and, together with other measures, become the market leader there as well. One "complex injectable" product (enoxaparin), launched in July 2010, has become the first generic to claim blockbuster status sales of more than $1 billion in 2011. A previous acquisition, of Ebewe (Parenta in the U.S.) in 2009, had added other complex (oncology) injectables to the portfolio.

Ophthalmology products have further lengthened the litany of "number ones" for Sandoz in the U.S. and global markets. It achieved leadership in that category with the 2011 integration of Falcon, the U.S.-based generics business of Alcon after Novartis acquired the global eye-care company.

Respiratory category growth is another longer-term opportunity. Sandoz did, however, acquire a "significant amount" of generic respiratory products and expertise for its pipeline with its purchase of Oriel Therapeutics in 2010, DeGolyer says.

Dermatology took Sandoz on a big leap forward with its July 2012 acquisition of Fougera. That purchase not only created a new U.S. and global number one in generic dermatology in the company, but also a small branded dermatology subsidiary of Fougera, PharmaDerm.

INTEGRATED THREAT

Despite the apparent success of the Sandoz turnaround in the United States, it may still seem a bit strange that the now-leader in generics exists inside Novartis, one of the world's largest innovator companies — albeit an unusually diversified one. But one conjecture about Sandoz the pundits can no longer make, says DeGolyer, is that it suffered because of that association. Instead, he says, the causes of its challenges proved to be among the most basic problems in business: lack of performance and customer focus.

Far from being a handicap, says DeGolyer, being in the Novartis family is a "significant advantage" as well as a complementary arrangement. "Now that we have deep experience in the generics business, we can leverage the broad capabilities of the entire Novartis enterprise. It is a virtuous cycle: We offer patients and payers a range of options, and at the same time, we are increasing access to affordable, high-quality medicines. So we view the branded and generics businesses as absolutely complementary."

For Sandoz, however, DeGolyer says the main competition is not other Big Pharma companies but the top-tier generic competitors — "the top four companies that make up almost 50% of the U.S. generic prescription volume." Still, he believes his company has the best of both worlds. "The value of being inside of Novartis is that it's more than just resources; it's the fact that we can see the branded business, generic business, and specialty business all converge and being a part of the whole global portfolio that allows us to leverage the range of capabilities in the corporation, whether that's clinical, manufacturing, regulatory, commercial, or, not the least among them, recruiting top talent."

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Sanofi:

Betting On North America

By Cliff Mintz, Ph.D.

French-owned Sanofi is one of the world's largest pharmaceutical companies. However, over the next year or so, the company is facing patent expiry of some of its biggest blockbuster products. Further, unlike many of its competitors, Sanofi was slow to respond to the increasing importance of biologics and biotechnology products to address unmet medical needs.

To remedy this, Chris Viehbacher, who became Sanofi's CEO in December 2008, decided to diversify the company's portfolio and pursue a strategic focus based on three key principles: increasing innovation in R&D, seizing external growth opportunities, and adapting the company's business model to meet future challenges. Moreover, Sanofi's acquisition of Genzyme in 2011 for $20.1 billion signaled the company's new focus on biotechnology and its entry into the orphan drug market.

Despite Big Pharma's growing focus on emerging markets, Sanofi believes the North American market (most notably the U.S.) will continue to drive the direction of the global

pharmaceutical and biopharmaceutical industries over the next few decades. To accomplish this, Sanofi recently appointed industry veteran Anne Whitaker as president of its North America pharmaceuticals business.

One of Big Pharma's few female executives, Whitaker leads Sanofi's pharmaceuticals business in North America and oversees all pharmaceuticals operations within the region including diabetes, oncology, cardiovascular and specialty care, biosurgery, renal, U.S. medical affairs, commercial strategy, planning and excellence, consumer healthcare (Chattem), and Canada pharmaceuticals.

Whitaker began her career at the Upjohn Company in 1991 as a metabolic disease specialist. She joined GlaxoSmithKline (GSK) in 1992 as a sales representative and held various leadership positions in the commercial organization. In 2007, she became GSK's VP of critical and supportive care before being appointed senior VP of leadership and organization development from 2008 to 2009.

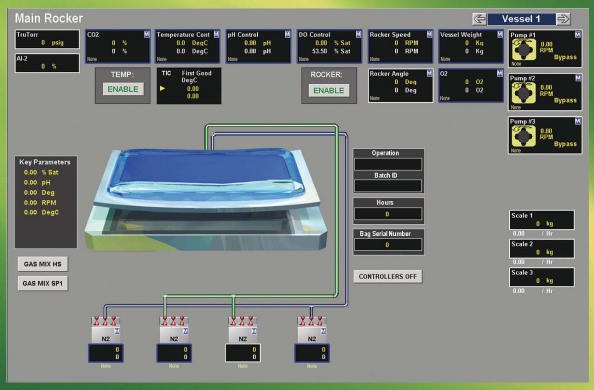
In 2009, Whitaker became senior VP and business unit head, cardiovascular, metabolic, and urology (CVMU) at GSK where she had full commercial responsibility for leading, developing, and managing strategic performance of the CVMU business. She was appointed to her present position at Sanofi in September 2011. Whitaker holds a bachelor's degree in chemistry with a minor in business administration from the University of North Alabama.

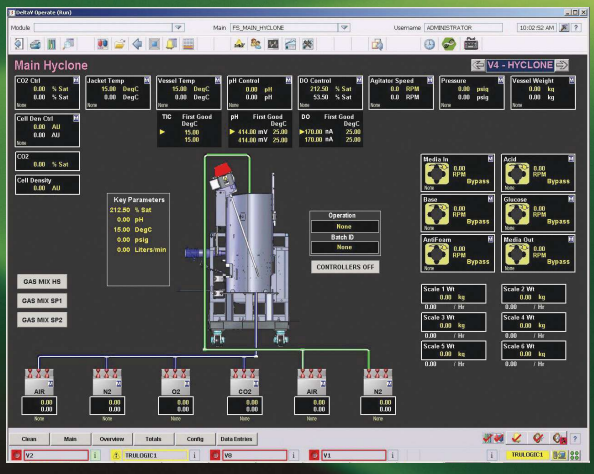
I had an opportunity to chat with her about Sanofi's new drug development and business strategies, the company's growing focus on biologics and biotechnology products, and the role of women in the pharmaceutical industry.

Question: Sanofi, like other major pharmaceutical companies, has lost or will lose patent protection of some of its blockbuster brands over the next few years. What are some of the strategies being implemented to compensate for these losses?

Whitaker: To combat loss of patent exclusivity for some of our larger brands, we developed new strategic plans that will enable Sanofi to become more efficient and better able to effectively meet the total healthcare needs of the patients who use our products.

Anne Whitaker,
President of Sanofi North America Pharmaceuticals





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To that end, we have implemented a global diversification strategy (being brought to life in North America) that includes, in addition to our pharmaceuticals business, Chattem, a consumer healthcare business that Sanofi acquired in 2010; Merial, our animal health business; Genzyme, for rare diseases and MS; and of course, our vaccines division.

Chris Viehbacher and I strongly believe that a diversified healthcare company is the way to build a sustainable business going forward in the future. Furthermore, we are also shifting the organization to be very patient-focused. By looking at patients' needs first, we are moving into new areas where we have not been active before, including medical devices, iPhone apps, and services for patients with chronic diseases like diabetes and some cancers. Because of this, we believe we are going well beyond simply developing new molecules and offering patients better health outcomes and solutions to help to improve their lives.

Another strategy that is being implemented to bolster new product development is expanding beyond our internal R&D capabilities via innovative partnership and alliances with external entities.

A good example is our investment in Warp Drive Bio, an innovative start-up company in Cambridge. In this case, we partnered with a venture firm to identify and invest in companies with novel ideas and technology platforms. More recently, we entered into collaboration with Harvard's Joslin Diabetes Center, which will bring together Joslin's expertise in diabetes research and Sanofi's strengths in discovering and developing patient-focused products for diabetes management.

Finally, we are also leveraging social media, digital capabilities, and crowdsourcing to help us to better understand patient needs and more successfully commercialize our products. Moreover, there is an internal corporate commitment to expand our digital platform and to learn how to better engage, interact, and respond to customer and patient needs and expectations. This is definitely a learning process for us, and we are refining and tweaking it as we move these initiatives forward.

Question: In the past, other pharmaceutical companies like Sanofi have pursued a diversification strategy with limited success. Why will Sanofi succeed where others have not?

Whitaker: In the past, some pharmaceutical companies may have pursued diversification strategies simply because they could, hoping that expanding corporate capabilities in multiple areas like consumer and animal health would ultimately pay off. In contrast, our diversification approach has been carefully orchestrated by Sanofi's executive team and is very strategic by design.

While we will continue to be a leader in bringing new medicines to market, our new and ongoing patient focus allows us

WOMEN IN PHARMA

There are seemingly very few women executives in the pharmaceutical industry. Why?

I often look around and wonder where all the women are! I think that we have a lot to learn in pharma about creating pathways for women so that they can develop and succeed as leaders and executives. I believe the pharmaceutical industry must recognize that women may need different kinds of support (as compared with men) to take on leadership roles. At Sanofi U.S. we are looking at ideas to better meet the needs of women that include part-time opportunities in leadership roles, more telecommuting, and increasing remote working opportunities. Certainly, there are many other things that we can and will evaluate to better help to promote leadership roles for women in our organization.

What are some of the factors that may have impeded upward mobility for female pharma executives?

When I look broadly at the industry, what has been missing for me is the flexibility required for female executives to succeed. That is, flexibility related to the pace of career advancement for some women and, in many cases, establishing the right work-life balance (depending upon life circumstances) to meet the daily demands of a particular job. Further, in my experience, it is sometimes a matter of encouraging women to step out of their current role, take a risk, and try something new. To that end, I believe mentoring is vitally important for many women. And at Sanofi, we are focusing on and developing a variety of mentoring programs to help women navigate their way into leadership roles. Also, we are encouraging women to openly and candidly talk with their bosses about the support that they will need if they put themselves forward for a leadership opportunity at our company.

Do you have any advice for women who are considering pursuing leadership roles at pharmaceutical or other life sciences companies?

The core elements of my own road map for success are persistency, passion, authenticity, resilience, and courage. I think to succeed in this industry persons (male or female) need to be extremely goal-oriented, competitive, focused, and possess outstanding communication skills. Being persistent, tenacious, and assuming responsibility for your own career trajectory certainly increases the likelihood of rising to a leadership role in pharma. To succeed in business (and invariably push through difficult times), you must be passionate about what you are doing and your industry. Finally, to be an effective leader, you must be able to energize others to innovate and effectively navigate a career path by building advocacy along the way.

to bring solutions to patients beyond just supplying prescription drugs. For example, we are developing a line of diabetes care products in our consumer healthcare division that will offer persons with diabetes better tools to manage their illness and lives. Also, we are pursuing a similar approach in oncology. These healthcare solutions are consistent with what I am hearing from the FDA where there is a growing emphasis on OTC products to provide greater access to treatments for patients who must manage chronic diseases such as diabetes, cardiovascular disease, and cancer.

Finally, there are some synergies between our assets in human and animal health that we are leveraging to develop new treatments in both divisions, as well as our ongoing commitment to develop new prophylactic vaccines including one for Type 1 diabetes.

Question: Sanofi has been involved in 101 acquisitions and partnerships between 2009 and 2011. Is M&A a vital component of Sanofi's new growth strategy?

Whitaker: Our CEO has made a commitment to Sanofi stakeholders to strengthen and grow the company, and M&A is part of that strategic plan. To that point, Genzyme, Sanofi's largest acquisition to date, was a great strategic move and represents a key growth platform for the company moving forward.

The 2011 Genzyme acquisition gives Sanofi greater breadth in the biologics space, a more diversified portfolio with small- and large-molecule assets (today as well as in our pipeline), and an infusion of fresh innovation.

We have learned a lot from Genzyme's patient-centric culture and hope to continue to draw on those characteristics as we move Sanofi forward. Also, the Genzyme purchase showed us the importance and benefit of looking externally, to complement our existing internal solutions.

Finally, Sanofi goes to great lengths to preserve what is good about its acquisition partners like

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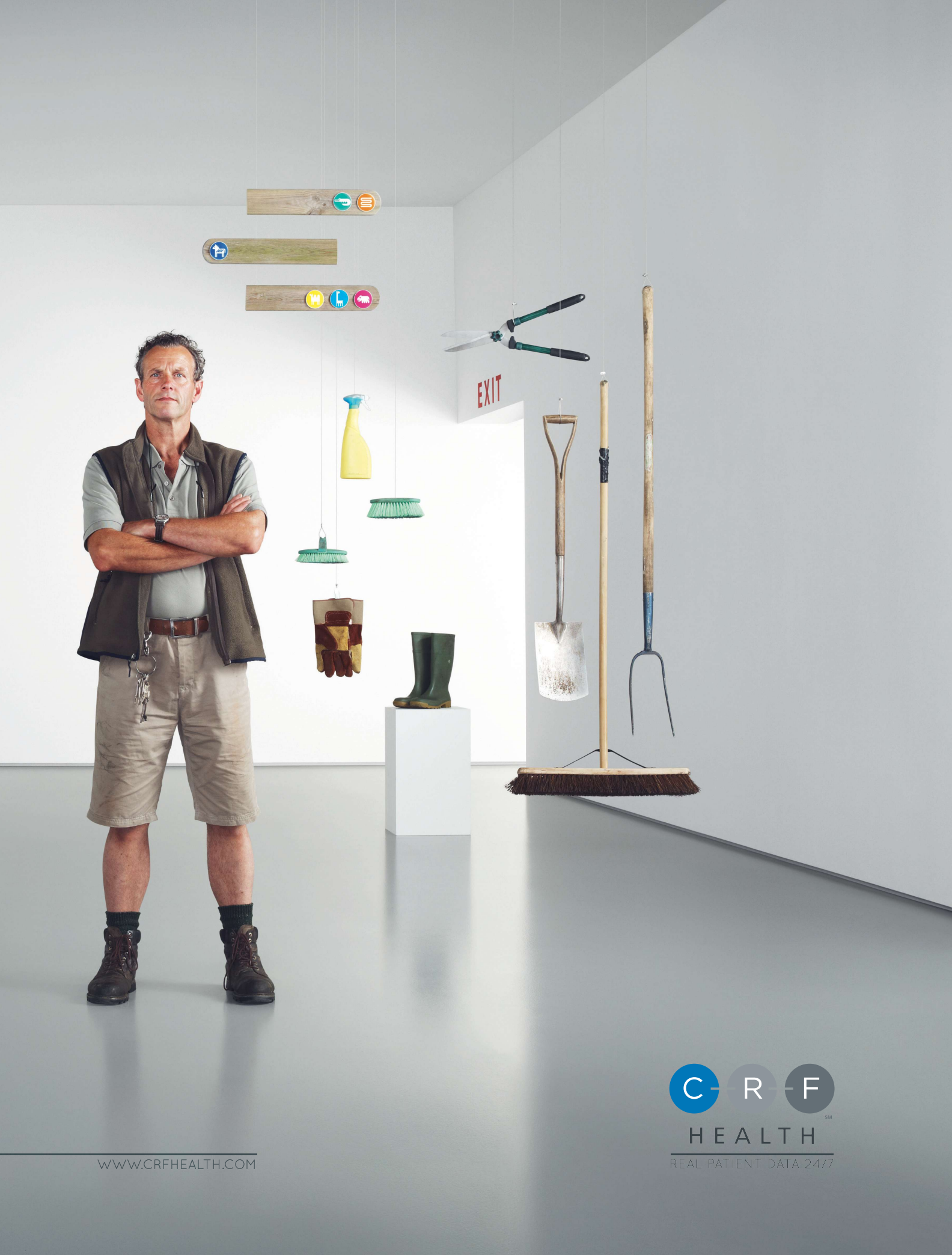

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"We have learned a lot from Genzyme's patient-centric culture and hope to continue to draw on those characteristics as we move Sanofi forward."

Anne Whitaker, president of Sanofi North America Pharmaceuticals

Genzyme and Chattem and is very careful to not smother what is unique and beneficial about them as they are integrated into the Sanofi culture.

Question: What are your views on the current trend of outsourcing pharmaceutical R&D?

Whitaker: While R&D is not part of my purview, it is worth noting that Sanofi does and will continue to maintain its own strong in-house R&D capabilities. It is important to point out that, although the company is actively pursuing more collaborations and partnerships, we are committed to our R&D functionalities. Our external R&D collaborations rely on the internal expertise of our R&D teams to evaluate opportunities and successfully work with our partners to develop patient-focused healthcare solutions and treatments.

Question: Much has been written on personalized medicine. Does Sanofi have plans to enter the personalized medicine market?

Whitaker: We believe personalized medicine will have a significant impact on patients who use our products. Diabetes is an example of a therapeutic area that we think personalized medicine can help to improve the lives of patients.

To that end, in 2010 Sanofi entered into a research alliance with Scripps Genomic Medicine and more recently announced an agreement with Joslin Diabetes Center to advance R&D in personalized medicine to address the challenges of insulin resistance faced by many people living with diabetes.

Question: Like other Big Pharma companies, Sanofi is eying opportunities in emerging markets like China, India, and elsewhere. What are your thoughts on growth opportunities in developed versus emerging markets?

Whitaker: Emerging markets are clearly part of Sanofi's overall business strategy and represent a key growth opportunity for the company. However, while great opportunities exist in emerging markets in China, India, Brazil, and elsewhere, North America still represents about 30% of the world's pharmaceutical market and will continue to be vital business and innovation hubs for us moving forward.

Chris certainly views the U.S. as a place that still rewards innovation, and we can continue to learn a lot in the U.S. and Canada to take to the emerging markets. Likewise, we can learn many things from emerging markets and take advantage of them in North America!

Thanks to our diversification strategy, unlike some of our competitors, North America still represents an enormous opportunity for Sanofi.

Question: Why do you think Big Pharma has lost the ability to innovate, and how will the industry innovate in the future?

Whitaker: When we talk about "innovation," it's tempting to only think in terms of drug development and filling pipelines. After all, historically, that's what success has been based on in our industry. But, as we continue to move to become a company that places patients first, we will be forced to define "innovation" more broadly. To that point, we need to look beyond innovative new drugs to innovations in patient services and other healthcare products.

The demand for this kind of innovation is driven by our operating environment. For example, as our population ages and becomes more and more urban, incidences of chronic disease will increase. Technology will continue to drive consumers' connectivity and their demand for medical information. Payers will increasingly look at outcomes to measure the value of their investments. And innovations in medical technology, not only drugs and biologics, will continue to expand what is possible for patients.

At Sanofi, our approach to healthcare is becoming increasingly patient-centric. To that end, Sanofi is constantly pursuing innovative, entrepreneurial, and commercialization partnerships and strategies that will help patients succeed in our new healthcare environment.

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MORE THAN MEETS THE EYE

Can Rapid Mobile Diagnostics Speed Up Clinical Trials And Regulatory Reviews?

By Wayne Koberstein, contributing editor

No industry trend is more promising, and yet more conflicted, than personalized medicine (PM). In its rationale, PM is almost logically invincible; who can argue with matching individual patients with medicines to which they are most likely to respond? But in practice, despite citable though qualified successes, the rationale often breaks down. Expensive and complicated tests, gaps in companion-diagnostics regulation, meandering business models, tiny patient segments, and record-high prices as the apparent trade-off for volume sales all tarnish the beauty of PM logic.

So, it is natural to be a bit skeptical when a new voice comes on the scene to proclaim another technological revolution in the PM sphere. That voice belongs to Dr. Anita Goel, CEO of Nanobiosym, who combines her business message with a grand vision of global medicine transformed by what she calls "nanodiagnostics."

Nanodiagnostics is an accurate term in Goel's case, because her company's Gene-RADAR chip, developed so far primarily through U.S. defense and other federal grants, probes DNA molecules at the nanometer scale. "What we are doing in our Gene-RADAR is using a very high degree of precision control with nano-scaled schemes to control DNA molecules, and the nano motors that read and write information into the molecules enable controlling them on very precise scales to achieve faster, better, cheaper readouts of the DNA."

But the "nano" label does not apply to all single-unit, nonlaboratory diagnostic tools now in development. Thus, here we use the more widely applicable term "rapid mobile diagnostics" (RMDx) to encompass all the micro, milli, and other portable-scale Dx technologies. (Another, less-specific term in general use is "point-of-care" diagnostics.) And, as a new technological space containing all the alternatives, the most practical and immediate application for RMDx may be in clinical trials.

Beyond portability and speed, many RMDx technologies also claim higher accuracy than current lab-based, ELISA (enzyme-linked immunosorbent assay) tests. Some of the new technologies, like Gene-RADAR, vie to replace the old light-sensing, antibody-targeted assays with much more accurate but ephemeral DNA detection, thereby also dethroning PCR (polymerase chain reaction). Other RMDx devices measure non-DNA indicators of drug response and disease status, such as oxygen molecules. Microfluidics is a popular platform, but new modes, such as MRI or LCD technology, are always popping up. In an ideal world for all RMDx developers, their technologies would spread across the entire clinical spectrum, from research to mainstream treatment.

Goel and others in the RMDx space maintain the technology could speed up trials and regulatory reviews by quickly selecting ideal patients and expediting the collection and analysis of patient response data. For regulators, the review process would operate in a higher gear thanks to the higher-quality data and higher benefit-risk ratios as predicted by the patient selection. "You find patients in a target population before you enroll them in a clinical trial, and you accelerate the drug development process, decreasing the cost and time in getting FDA approval, because you've focused your patient population in such a way, based on their biomarkers, that they will be more likely to show increased efficacy and decreased toxicity," says Goel.

A WORLD OF PLAYERS

In a nutshell, Nanobiosym's initiative spans all the possible fields of play in the RMDx game, from research to fighting the world's worst epidemics. But its Gene-RADAR technology has plenty of competition from other companies, platforms, products, and applications. In addition to an untold number of small, entrepreneurial companies, large medical-device makers like Roche, Abbott, and Siemens are developing RMDx. To gather a core sample of the lesser-known startups, we spoke with several other companies for this report — Rheonix, T2 Biosystems, and SuperNova Diagnostics — each with its own unique platform.

Although every new technology may have its own list of initial disease targets, most aim for maximum flexibility in customization, so it is likely many of them will overlap in promise and in practice. Some developers share Goel's vision that RMDx use in the developing world will lead to its adoption in the developed world; others do not. But essentially all players agree that commercial competition in the major markets will ultimately shrink the field.

Clinical trials logically present the first large competitive space for RMDx technologies. Diagnostics in general already have wide use in clinical development; a simple search for "diagnostic test AND

"There are two big trends in medicine. One is the personalization of medicine, and the second is the mobilization of medicine." Dr. Anita Goel, CEO, Nanobiosym

drug" on ClinicalTrials.gov yields 2,979 trials, with the top areas being Infection (e.g. HIV, malaria, tuberculosis), Cardiovascular (CHD, COPD), Gastrointestinal (IBS), Renal (transplant rejection), and Cancer. One RMDx-specific study, "Introducing Rapid Diagnostic Tests Into the Private Health Sector," aims to show how the technology can reduce overuse of anti-malarial drugs in Uganda.

Because most of the trials involving diagnostics are early to mid-stage, it is impossible to know how many of them will eventually lead to commercial drug/diagnostic combinations. But the gap between the number mentioned above and the mere 44 studies listed when "companion" is added to the search term — even allowing for the vagaries of text-string searches — suggests many more Dx tests are in use as adjuncts to trials than as part of a commercial combination in development.

Adopting RMDx to replace lab tests in clinical studies is arguably the next logical step. It is easy to see how handheld Dx devices, perhaps entrusted to the patients during a study's active phase, could bring vast improvements over current tests in patient selection and monitoring alone — thus a huge potential exists for their use in trials. Similarly, RMDx could help investigators screen patient candidates more quickly and, maybe, less expensively. So the case for its superior efficiency, speed, and cost savings seems to rest on solid reasoning, if only in potential.

Yet, here as in proverb, the devil may reside in the details. Given the great range of testing targets, methodologies, and data types among all the competing platforms, the future for RMDx companies, users, regulators, insurers, and targeted patients remains unclear. Meanwhile, somewhat ironically, the most impeding factor in RMDx progress may be the imposing variety of alternative technologies it presents.

Certainly, faster, cheaper, more accurate diagnostics could be a key component of personalized medicine, starting in clinical trials. But according to Dr. Vicki Seyfert-Margolis, the FDA Commissioner's senior advisor for regulatory science and innovation, the greatest challenge in PM is understanding disease causality — matching therapeutic mechanism-of-action with patient-specific mechanism-of-disease through accurate interpretation of the related biomarkers.

Where those relationships are well understood, some advanced diagnostics are already in use; however, a vast area remains where diseases continue to confound us and thus RMDx may find use mainly as a research tool. Many conditions may never yield to personalized targeting. Still, much the same could be said for many supportive technologies meant to speed drug development; applying them more widely and effectively will require greater understanding of disease mechanisms.

Promisingly, many of the RMDx platforms in development offer advanced immunoassays — one possible key into the great unexplored territory of immune/inflammatory response to disease. Signaling a shift in the PM model, Seyfert-Margolis stresses the need to "go well beyond genes and gene variance" to understand the immune system's role "not only in the initiation, but in the maintenance" of diseases.

SPICE OF VARIETY

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PREACHING THE GLOBAL RMDX GOSPEL

Rapid mobile diagnostics may take root in the developing world before spreading to the developed world, according to Nanobiosym's CEO Anita Goel. She says her company's nanodiagnostics could be adopted by the developing world before the developed world. But the low cost and rapid results of such tests would presumably fuel parallel adoption of the technology in the leading global markets.

"It is important to start to see global health as a truly global phenomenon that's an issue for both the developed and the developing world, and the solutions that cut costs in the developing world also cut costs in our developed worlds," Goel says. "There are two big trends in medicine. One is the personalization of medicine, and the second is the mobilization of medicine, which is taking the ability to diagnose disease out of the centralized hospital or pathology lab, and bringing it out into the field — doctors' offices, people's homes, and even remote villages where they lack basic infrastructure."

Nanobiosym's website gives little information about the company or its "nanodiagnostics" technology, Gene-RADAR. Instead, it mainly serves as a link to Goel's related public campaign and "global initiative," the Nanobiosym Global EcoSystem. But the company has developed a platform technology on a dual track: mobile medicine and personalized medicine. The mobile medicine track focuses on the developing world and infectious diseases such as HIV, TB and malaria and could be adopted there first because of the lack of legacy healthcare infrastructure. The personalized medicine track focuses on the developed world markets and can be used as a companion diagnostic to cut the costs of clinical trials. Meanwhile, the company is building an "ecosystem of partners" for further development and refinement of its platform.

Goel believes RMDx technologies will evolve, eventually producing the contemporary equivalent of the "Star Trek" tricorder. Yes, a medical tricorder — now an official X-Prize target. Goel apparently inspired the new X-Prize initiative, and her company is one of the first entrants. Meanwhile, if you want to know more about the global network, you'll have to join it (www.nanobiosym.com).

Not everyone sees such a close connection between the developed and developing worlds for RMDx, however. President Tony Eisenhut of developer Rheonix sees flaws in the concept. "Third world or developing world systems are usually focused on a specific disease, and most of those systems can only be brought to market at a low price point. When you look at putting systems in place in the developed world, where you may be running 5,000 to 50,000 tests a year, to make a large capital investment for a specific test is not feasible. There you want a system that has more of what they refer to in the molecular diagnostic business as menu. You want to be able to run more assays on a single piece of equipment as opposed to a special piece of equipment. Even if it's low cost, there's still maintenance and operator knowledge that goes along with it, and the healthcare industry wants to minimize that through our market feedback."

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of RMDx. The company is developing "a highly customizable diagnostic platform that can run both user-designed and FDA-cleared assays" for infectious diseases, cancer, pharmacogenomics, and water testing. Rheonix claims its "milli-fluidics" Encompass platform, a portable work station, and its CARD system, a disposable multi-sample cartridge, "provide significant cost-savings, allowing for universal adoption of mobile diagnostics."

RMDX: THE FDA'S VIEW

To get the FDA's perspective on the future use of rapid mobile diagnostics in clinical trials, we spoke with Dr. Vicki-Seyfert-Margolis, the Commissioner's senior adviser for regulatory science and innovation.

DO YOU BELIEVE RMDx TECHNOLOGIES CAN SPEED UP CLINICAL DRUG TRIALS AND FDA REVIEW BY IMPROVING PATIENT SELECTION AND MONITORING?

These devices could clearly have an advantage in the field, in particular in medical practice in the developing world, but it depends on the application and if it presents advantages over other tests that can be or are deployed in different clinical settings, particularly if there is no advantage in quality or accuracy. It is possible that these types of devices would allow more diffuse trials, i.e., that patients would not necessarily have to come to a medical center to be in a trial. This could be an advantage where people most appropriate for the trial are not able to travel, for whatever reason, e.g. economics, disability, location. Also, the "rapid" aspect of the device could benefit in allowing a patient to know right away whether they could enroll in a trial, and this probably has some value in more agile enrollment.

WHAT PROBLEMS OR CHALLENGES MIGHT HINDER THE USE OF RMDx IN CLINICAL TRIALS?

Depending on the accuracy, measures performed, and validity of the methods, there may or may not be an advantage to small mobile devices. It would be critical to see how these devices would or would not integrate into the overall management of the patient. For example, would they add significantly to the methods and diagnostic tests currently in use in a hospital setting, particularly if the tests are not as accurate?

If the device couldn't do the right type of test in a valid way, then it wouldn't be very useful in trials. We also like to see testing done in the same way as it would be deployed in the "real world setting." So if the expectation was that if a rapid mobile device were to be a companion diagnostic, then we would want to know that physicians who were going to treat patients could use it. We often see some fundamental differences between test results when the technology is different.

(See also, "Speeding Up The Evolution Of Personalized Medicine," June 2012.)

RMDX REGULATORY ROUTES

It is beyond the scope of this article to detail all the regulatory pathways that RMDx products and platforms might traverse. Although companion diagnostics grab all the attention these days, the use of Dx in clinical trials, involving a much larger variety of tests and technologies, has mainly proliferated off the radar, trial by trial. Pathways vary greatly, depending on each trial's protocol, biomarker targets, patient sets, and so forth. And the regulatory authorities, like everyone else, are caught in the flux as the old wall between drugs and Dx devices wears away. Currently, diagnostic tests meant to replace similar assays or tests on the market go through the 510(K) route through the FDA. But tests for life-threatening diseases or with new applications or indications must obtain a pre-marketing approval (PMA), equivalent to the CE Marking designation in Europe. Some products may qualify for a CLIA (Clinical Laboratory Improvement Amendments of 1988) waiver from the FDA. But only simple tests that "use unprocessed specimens (whole blood or oral fluid), be easy to use, and have little risk of an incorrect result" because of good failure alerts, fail-safe mechanisms, traceable methods to ensure accuracy, and adequate labeling may obtain the waiver. Applying advanced Dx tests in clinical trials still requires close case-by-case collaboration with regulators.

The FDA publishes the In Vitro Companion Diagnostic Devices guidance, and it is now composing a draft guidance outlining strategies for clinical trial design and regulatory considerations for co-developing a novel companion diagnostic and therapy simultaneously. The draft guidance contains recommendations for the use of biomarkers for patient selection and screening, as well as clinical trial designs that allow ethical patient selection strategies. The FDA says it is also producing an "internal plan for how it will review applications using co-development strategies for product development to accompany both guidances and ensure the agency meets the special needs of these types of products in a timely way."

The Center for Drug Evaluation and Research (CDER) has started a partnership program for qualification of new drug-development tools (DDTs). A company may apply to qualify a tool or a marker for clinical use, and if qualified, the tool will be put into the public domain. It can still be patented but must be shared. The company gains the ability to use the tool — say, a specific biomarker or other patient-rating instrument — in developing its products. An FDA guidance, "Qualification Process for Drug Development Tools," furnishes the details of application, evaluation, and terms of the program.

In configuration, the Rheonix system typifies most of the RMDx systems at this point. Rather than the single "Star Trek" tricorder-like unit envisioned for the future, it consists of several separate units, including a briefcase-sized base station. But, like most other RMDx developers, Rheonix has a self-contained desktop device in prototype to replace its larger but still portable system. Again, it is in prototype — the word indicates the real state of the technology at this point. Further miniaturization to handheld scale, albeit along an uncertain timeline, could

expand use beyond doctors and nurses to patients or others with little or no medical training.

The question is, which RMDx platform is best suited to leading the charge? Opinions depend, of course, on each developer's interest and viewpoint. Yet a comparison of developers' competing positions can be informative.

One critical issue in the race, maintains Rheonix President Tony Eisenhut, is sample size. Not all conditions are amenable to nano-scale measurement, he says. "To catch or identify an infectious agent or cancer biomarker early, you're looking for the needle in a haystack, and the likelihood of finding the target in a nano-size sample is highly unlikely. So from a clinical standpoint, there are often times where you want a large sample in hopes of capturing the actual agent or marker you're looking for."

Eisenhut also emphasizes the need for RMDx systems to be easily customized for various biomarkers and disease indications, to deliver significant cost savings over current systems, and to take advantage of electronics-industry style production of expendable components. Given those constraints, he sees room for more than one platform in the field.

"My personal belief is that there'll be multiple players, perhaps up to six players, in the marketplace," he says. "A couple will be very specialized, maybe oncology-focused, a couple infectious disease-focused, and a couple will bridge infectious disease and oncology, pulmonary, cardiac, or anything that involves molecular-genotyping assays."

T2 Biosystems addresses another potential differentiating factor in the RMDx field: sample preparation for maximum efficiency and speed. To challenge the mainly optical-based tests currently in use, the diagnostic tool in development by T2 Biosystems uses tiny magnets in a miniature MRI device to measure how oxygen molecules react in the presence of magnetic fields. Detecting unique signatures within complex bioreactions, the T2 system delineates pathogens, genomics, and protein and small-molecule immunochemistry. It may be unique or at least among the few systems that handle raw samples, eliminating expensive purification.

Such refinements, which primarily serve to speed up the process, will be most useful in the PoC environment, where the technology must be conducive to physician or patient use, as in clinical trials. Yet some in the business question the handheld concept, at least to a degree.

"Although we have a preproduction prototype to address the shortcomings of PoC, the current problem is if you want to do PSA for prostate cancer or biomarker tests for other cancers and infectious disease, you can't do those types of tests in a handheld format to the standard of the central lab," says Neil Campbell, president and CEO of SuperNova Diagnostics. "What we're finding is that the majority of the tests that physicians, nurses, and patients really want in a PoC format can't be miniaturized or made into a clinical-care format because of limitations with current PoC technologies."

Still, with its portable set of sample collector/processor, analytical disposable, and the readout device, the company still aims to "move the laboratory into the palm of your hand." Its system returns to an optical approach, measuring antibodies, antigens, or DNA samples, but with a new twist: tiny LCDs inside its AmpCrystal system enable a "direct detection method" without signal or target amplification.

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Neil Campbell, president and CEO of SuperNova Diagnostics

"We're looking at wellness, infectious disease, chronic and acute infections initially where there's a sense of urgency, not necessarily life and death in every case, but where the medical intervention would be changed dramatically to improve the results," Campbell says.

UNIVERSAL SELECTION

For companies, developing a technology solely for use in clinical trials involves a degree of unpredictability even surpassing that of commercial development. Markets may be moving targets, but they are at least visible. In contrast, the aims, protocols, and support needs of clinical trials are only generally as predictable as trends in therapeutic areas or scientific knowledge. Often, the details of how a given trial needs to use diagnostics may be entirely unique — perhaps beyond any technology's ability to customize.

Thus, even more than the market, clinical trials will tend to winnow down the players to the precious few that offer the most flexibility for drug developers. Short of building a new test from scratch for every trial — still the current practice in most cases — eventually the best individual solutions may prove to be the most universal ones.

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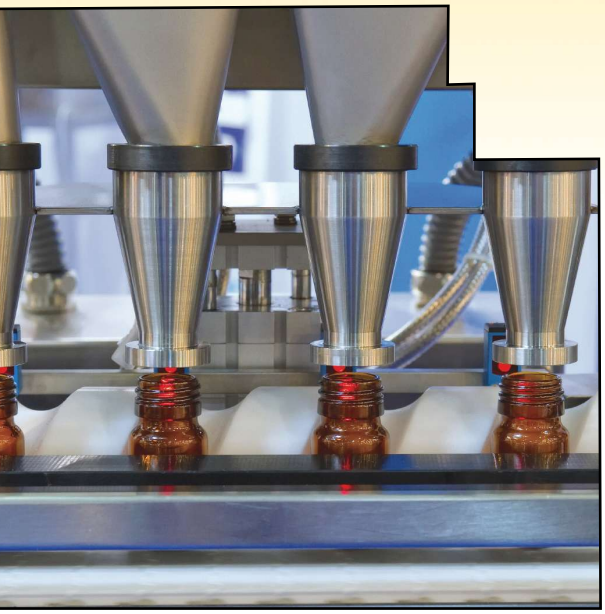

Comparing China's And India's Pharmaceutical Manufacturing

Jim Zhang, Ph.D., JZMed, Inc.

The pharmaceutical markets of China and India have been experiencing such rapid growth in the past decade that they are widely recognized as two of the world's most dynamic emerging markets. Consequently, they have attracted many drug companies around the world. Similarly, the pharmaceutical industry in these two countries has also experienced rapid advancements in recent years. The technical capabilities, production skills, and regulatory knowledge of the local companies have accordingly been greatly improved and reached acceptable levels for global companies. These features, coupled with the still-low costs of their services and/or products compared with those of the developed countries, have made these two countries the primary choices of global drug companies for sourcing raw materials and finished products or outsourcing of manufacturing work.

However, despite a number of similarities between China and India, there are still a larger number of differences between these two countries in the areas related to pharmaceutical manufacturing. The strengths and weaknesses of each country and their advantages and disadvantages to certain sourcing/outsourcing projects have become the key differentiators. Many sourcing/outsourcing companies are, however, still not clearly aware of these differences.

We recently conducted an in-depth study and analysis on the pharmaceutical manufacturing industries in both China and India. Our study focused on the growth and development history of 200 major pharma companies in each country. The study revealed some interesting results, such as similarities and differences regarding their capabilities, capacities, market sizes, cost structures, strengths, and shortcomings. The research also indicated future development potentials, as well as the strategies of multinational companies in these two countries. This article summarizes our results.

GENERAL COMPARISON OF PHARMACEUTICAL INDUSTRY BETWEEN CHINA AND INDIA

In many aspects, China and India are very similar. Both countries are located in Asia with similar sized populations, and both belong to the group of emerging markets with fast-growing economies. Both countries also have low wages for most workers in many industries.

There are, however, also significant differences between these two countries. For example, generally speaking, China has a better general industrial infrastructure than India because the Chinese government has put enormous efforts and investments in this during the past two decades. The logistic service in China also is better developed and less expensive than in India. These advantages have made China attractive to foreign companies looking for a country where doing business is relatively easy.

However, India has its advantages, too. It has a better infrastructure in information technology (IT) than China, which is significant since IT skills play an important role in data management, bioinformatics, and clinical trials. The business philosophy and operating culture in most Indian companies are closer to Western traditions than their Chinese counterparts. This makes Indian companies easier to negotiate and reach business deals with their Western partners.

Analyzing further, to some extent, China has a better education system in biology, molecular biology, and other life science–related fields, resulting in, generally speaking, a better biotech industry in China than in India. However, India has paid attention to promoting its pharmaceutical industry a lot earlier than China. This has directly resulted in a stronger pharmaceutical industry in India than in China. For example, India currently has a substantial number of key players whose capabilities are strong enough to compete full-scale in the international market; whereas so far none of the Chinese drug companies has reached the same level or even come anywhere close.

At present, to global pharma companies, China and India possess the best ratio of cost to product/service quality among all emerging countries. However, the current labor and raw material costs in the Indian pharmaceutical industry are gener-

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ally about 25% to 30% higher than in China. That fact makes China more attractive than India to pharma companies when they source bulk materials or outsource long-term, large-scale manufacturing projects.

COMPARING CHINA'S AND INDIA'S API MANUFACTURING

Unlike their Chinese counterparts, the majority of Indian pharma companies began with simple dosage forms and then gradually moved to novel and/or complex drug delivery systems, and later decided to expand their business scope to include APIs. This development model is commonly called reverse-engineering. To a large extent, this development pattern has resulted in the shortage of APIs in India. At present, only about 70% of the APIs the Indian pharma industry needs are made domestically. The rest are imported from other countries, mostly from China. Many Indian drug companies have thus been sourcing APIs from China for many years.

Compared with its Indian counterpart, in the global pharmaceutical manufacturing industry, China has been well recognized as the world largest API producer. For example, among the total of 2,000 or so APIs in the global market, China can make close to 1,600 of them. As a comparison, the Indian pharma industry is currently able to make about 400 APIs. However, at present, most Chinese API makers still do not have sufficiently good technical or R&D capabilities. They are mostly engaged in only low-tech manufacturing. Currently, the most popular Chinese-made APIs are still those for the medications of bacterial infections. As a comparison, the APIs in the therapeutic areas of oncology, cardiology, diabetes, and tropical diseases are the main products of most Indian pharma companies.

APIs are also the largest class of products among all Chinese-made pharma-related products marketed overseas. China currently has about 1,000 API makers that market their products in the international market. The export value of the Chinese-made APIs reached $22 B in 2011, accounting for about 49% of the total export value of all Chinese-made pharma-related products. From 2005 to 2011 this Chinese pharma sector successfully maintained a CAGR of around 13%. As a comparison, the current export value of the Indian-made APIs marketed overseas is only about $6.7 B. From 2007 to 2011, this Indian pharma sector has successfully maintained a CAGR of about 15%.

Currently, there are about 150 Chinese API manufacturers that have various numbers of APIs registered with the international regulatory agencies; and about 30 of them have API production facilities that are cGMP-certified by the regulated countries. As a comparison, there are a total of more than 120 Indian pharma plants that have passed FDA's cGMP inspection. More than 800 manufacturing units in India are also in compliance with WHO's standard.

COMPARING DRUG FORMULATION AND MANUFACTURE OF DOSAGE FORMS

For a number of years, China has been well-known for marketing APIs in the global market, but less recognized for any of its dosage-form drugs. Although a large number of Chinese companies also produce dosage forms, only a handful of them are currently able to market a limited number of their finished products in the regulated markets. To a large extent, this has determined the low-end position of the Chinese-made pharma products in the international market and the long value chain of global pharmaceutical supply.

Collectively, the Chinese pharma industry is able to produce more than 60 dosage forms with a total of about 5,000 medicines. Among all dosage forms, the powder for injection is the largest group, followed by oral solids. As a comparison, India is currently able to make almost all types of dosage forms with a total of more than 60,000 medicines. A large number of Indian companies has even gained the formulation and manufacturing capabilities for difficult-to-make forms, including injectables and soft gels. Attracted by their capabilities in formulation, a number of major pharma companies have collaborated with Indian companies on codevelopment of generic drugs or licensed the sales rights to them.

Currently, an increasing number of Chinese pharma companies are aggressively improving their production facilities and aim to get them certified by the regulated countries. Compared with their Chinese counterparts, a larger number of Indian pharma companies possess large manufacturing facilities that have already been certified by the regulated countries.

Currently, China markets finished drugs in more than 170 countries and regions. But the largest markets are still the developing countries. The current total export value of dosage forms is only a little more than $2 B. Sales of the Chinese-made finished drugs in the developed countries account for about 40% and are mostly marketed by the Chinese divisions of major multinational pharma companies. In comparison, the current total export value of India's finished drugs is about $11 B. About half of the Indian-made finished drugs are marketed in the well-regulated markets, mostly by the Indian companies themselves.

WHERE TO SOURCE OR WHAT TO OUTSOURCE

India has been playing increasingly important roles in the global pharmaceutical manufacturing industry. Its recognized capabilities in formulation development, finished drug manufacturing, and

product marketing in the regulated markets have made it a trusted source for global pharma companies when seeking partners for codevelopment and/or comarketing of generics.

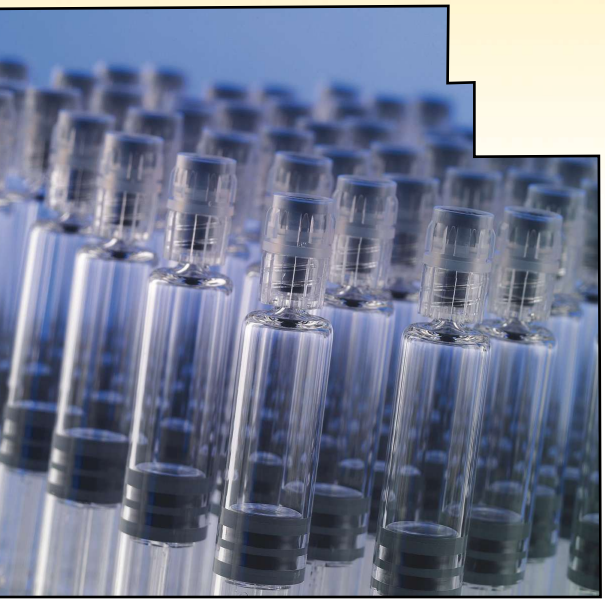
China's current strengths reside in its better industrial infrastructure, large-scale manufacturing capabilities of raw materials, and relatively low labor and material costs. India's current strengths include its stronger capability in process development, drug formulation, dosage form manufacturing, and marketing in well regulated markets.

Thus, it can be concluded that, at present, the Indian companies are the better choice for formulation development, manufacturing, and marketing of dosage form drugs. In contrast, Chinese companies are a better fit for upstream work, such as contract manufacturing (and sourcing) of advanced pharma intermediates and APIs. Also, Chinese companies charge less than Indian counterparts for the same type of services/products, thereby offering better cost-reduction benefits.

On the other hand, as our research results have revealed, even though China and India are presently the hotbeds for global pharmaceutical manufacturing, they still play much less significant roles than developed countries, in particular in the high-end areas such as the special formulation techniques and the manufacture of APIs and finished drugs that are still under patent protection. The situation is largely determined by the intrinsic weaknesses of these two countries in low R&D investment in pharmaceutical industry.

About the Author

Jim Zhang, Ph.D., is president and managing director of JZMed, Inc., a market research company specializing in research on the Chinese pharmaceutical outsourcing industry. The company also provides consulting services for pharmaceutical outsourcing in China.



Prefilled Syringes: The Next "Big Thing"?

By Cliff Mintz, Ph.D.

Until recently, most injectable drugs were mainly supplied to end users in sterile vials and syringes. However, the growing use of biologics and biotechnology drugs, coupled with a staggering increase in the number of patients who self-administer drugs to treat chronic diseases, has forced drug manufacturers to reconsider the vial-and-syringe format, which is prone to dosing errors and low patient-compliance rates. Because of this, prefilled syringes — single use, disposable syringes filled with a prescribed unit dose of medication — are rapidly replacing the traditional vial and syringe format to deliver protein-based drugs, sustained release formulations, and other parenteral medications.

Typically, prefilled syringes are made of glass and use a conventional plunger-barrel delivery mechanism. These syringes come in a variety of sizes with the 1.0 ml syringe being the most popular. Glass is the material of choice because it is strong, chemically inert, dimensionally stable, and easy to sterilize. Further, it is transparent, which allows visible inspection of a dosage form before it is injected. In recent years, syringe manufacturers introduced plastic prefilled syringes, mainly in response to the possibility of breakage and plunger failures. Nevertheless, "Glass is still the gold standard," said Brian Lynch, program lead, health science & technology, immunization, BD Medical-Pharmaceutical Systems.

Needle options for prefilled syringes include staked-in (needle is manufactured as part of the syringe) and luer cone or luer lok designs. Staked prefilled syringes are primarily used in medical and emergency situations (where treatment speed may be vital), whereas luered-prefills are mainly used for self-administration purposes. Because of growing concerns about needle stick safety and prevention, many commercially-available prefilled devices offer automatic needle shielding or retractable needle options. "Needle safety and prefilled syringe disposal continue to be an issue," said Joanne Jacobs, manager of drug product technical services at Cook Pharmica.

Prefilled syringes are filled aseptically; sterile plungers are inserted, and individual units are packaged in blister packaging before shipping. To facilitate the filling process, sterile prefilled syringe barrels are usually shipped to filling facilities in nested carriers or tubs and then filled aseptically with automated fill-finish machinery.

WHY THIS MARKET IS POISED TO GROW

Patty Kiang, former head of device development at Genentech and currently a pharmaceutical consultant, estimates that more than 50 drugs, including antithrombotic agents, vaccines, blood stimulants, interferons, and rheumatoid arthritis treatments, are now available in prefilled syringe formats. She indicated that more than 2.5 billion prefilled syringes were used in 2011, and the prefilled syringe market will continue to grow well over 10% per year for the foreseeable future. "The prefilled syringe market is poised for expansive growth mainly because of the ease-of-use factor that these syringes offer to patients and healthcare professionals," she said.

Like Kiang, Tony Pidgeon, Patheon's senior manager of global science and technology, believes the convenience offered by prefilled syringes is what is mainly driving their uptake. Also, he stressed that "prefilled syringes help eliminate dosing errors, improve patient compliance, ensure greater sterility, and reduce the likelihood of contamination during the injection process."

Healthcare reform, cost containment, and changing medical practices are also driving the uptake of prefilled syringes. To cut costs, patients are increasingly self-administering drugs, especially biologics, rather than traveling to physicians' offices or infusion centers. Also, BD Medical's Lynch added that the "retailization of immunization," a growing trend where people are being vaccinated outside of traditional medical settings such as pharmacies, schools, retail

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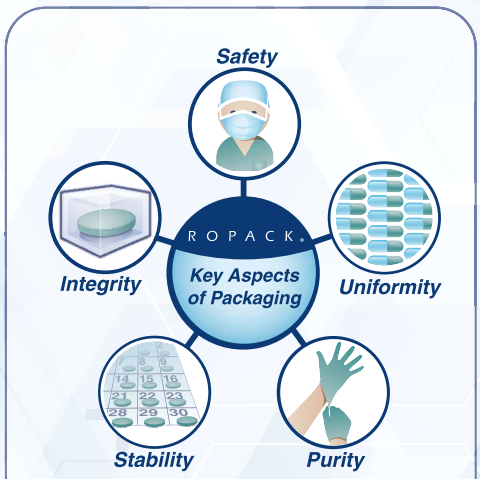

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outlets, and even airport kiosks, is driving the prefilled market. He said, "Because many other people besides healthcare professionals are administering vaccines, prefilled syringes offer a simple, convenient, and efficient way to meet burgeoning patient demand."

THE ADVANTAGES TO DRUGMAKERS

While prefilled syringes offer many advantages to end users, they also offer a variety of benefits to drugmakers. First, according to Jonathan Arnold, VP and general manager of sterile technologies at Catalent Pharma Solutions, prefilled syringes usually offer drugmakers lower overall cost-per-dosage-unit as compared with syringe and vial formats. This is because prefilled syringes contain an exact amount of drug to be delivered whereas vials are typically overfilled 10% to 25% to account for any drug that may be lost during injection preparation and administration. To that point, Mahesh Chaubal, senior director of drug development at Baxter BioPharma Solutions, said, "Elimination of vial overfills can result in substantial cost savings, especially for biologics manufacturers whose products are very expensive to produce."

Second, Cook Pharmica's Jacobs offered that from a logistical and supply chain management perspective, prefilled syringes are easier to handle, store, and ship than vials. She explained that prefilled syringes weigh less and take up less space than vials, so they cost less to ship. She added, "Prefills occupy less shelf space at distributors and pharmacies, which makes them easier to store than vials, which can also help to reduce costs."

Finally, prefilled syringes can help drug manufacturers with brand differentiation and life cycle management for their products. For example, according to Kiang, many biotechnology companies typically launch new products in a standard vial-and-syringe format and switch to prefills for second generation products to better differentiate themselves (because of ease-of-use) from competitors. Also, Baxter's Chaubal added "Prefilled syringes offer biopharma companies more flexibility for brand differentiation

"Elimination of vial overfills can result in substantial cost savings, especially for biologics manufacturers."

Mahesh Chaubal, senior director of drug development, Baxter BioPharma Solutions

and lifecycle management of their products."

THE CHALLENGES OF MANUFACTURING PREFILLED SYRINGES

Because of the plunger-barrel design of prefilled syringes, syringe barrels must be coated with silicone to ensure sufficient glide force for the plunger to easily deliver a drug during injection. Storage of proteins in silicone-coated prefilled syringes can sometimes result in silicone leaching into the product. Also, protein-based drugs (especially those formulated at low or high pH) can leach or extract contaminants from prefilled syringe rubber stoppers. To overcome these challenges, many syringe manufacturers developed new silicone coating techniques and specialized silicones to reduce the likelihood of silicon leaching. Moreover, Patheon's Pidgeon and Baxter's Chaubal suggested that some of the extractable concerns with prefilled syringes might be overcome by replacing rubber stoppers with less chemically-reactive substances like Teflon.

While glass remains the industry standard for prefilled syringes, there have been recent concerns over pharmaceutical glass quality and the possibility of delamination — a process (especially at lower pH) in which microscopic shards of glass can be shed into solution over time. These concerns have led to the development of cyclic olefin polymers and copolymers (e.g. COC, COP, and CZ) that are "glasslike" in appearance; have low extractable, leachable, and protein surface adsorption properties; and are stable over wide pH ranges. While plastic prefills may help to reduce drug manufacturers' anxiety about

breakage and delamination, their higher cost may hinder adoption.

Another concern with prefilled syringes is drug stability and product shelf life. According to Kiang, products in prefilled syringe formats cannot have a shelf life of less than two years. She said, "Anything less than a two-year shelf life does not make economic sense because it may take as long as six months for the product to make it through its distribution chain." Kiang added, "Product stability and shelf life are extremely important factors that must be considered before adopting a prefilled syringe format."

"There is a perception out there that it costs more to deliver biologics or a vaccine in a prefilled syringe," said Lynch of BD Medical-Pharmaceutical Systems. "However, recent studies show that when you compare the administrative, personnel, and ancillary costs typically associated with administration of biologics and vaccines using a conventional vial-and-syringe system, prefills offer real cost advantages and savings." In fact, she, as well as Catalent's Arnold, offered that several time/motion studies conducted at Johns Hopkins and other academic institutions showed that flu vaccination with prefills offered substantial cost savings over conventional vial-and-syringe administration.

AUTOINJECTORS, NEEDLELESS DEVICES, AND OTHER INNOVATIONS

Autoinjectors, spring-loaded glass syringes that keep needle tips shielded or hidden prior to injection, are becoming increasingly popular for patients who self-administer injectable drugs. These devices offer patients who self administer a "one-click solution" — pressing a button releases the needle, which is inserted a predefined depth into the skin, and the drug is subsequently delivered.

Paul Whyte, CEO of United Kingdom-based Future Injection Technologies, believes that autoinjectors will become the optimal choice for self-administering patients suffering from chronic diseases like rheumatoid arthritis (RA). He said, "Many patients with RA simply lack the manual dexterity or hand strength to use conventional prefilled syringes to self-administer. Autoinjectors are ideal for these patient populations."

Needleless injectors were initially designed to overcome "needle phobia" and the hesitation commonly associated with injection via needle-based systems. While several different needleless devices have been developed over the years, they are not widely used because many patients report that injections with these devices are more painful and sometimes cause more injection site injury than those administered with needles. Nevertheless, development of a safe and effective needleless device still represents something of a "holy grail" for the syringe manufacturing industry.

Finally, as previously mentioned, the standard plunger-barrel design of commercially available syringes continues to present many challenges (e.g. drug stability, shelf life, leachables, extractables, and rising costs) for drugmakers that want to offer their products in a prefilled syringe format. To attempt to overcome these challenges, Artemes Technologies, a Boston-based medical technology start-up is developing

Joanne Jacobs, manager of drug product technical services at Cook Pharmica, says, "Prefills occupy less shelf space at distributors and pharmacies, which makes them easier to store than vials, which can also help to reduce costs."

> "Product stability and shelf life are extremely important factors that must be considered before adopting a prefilled syringe format."
>
> Patty Kiang, former head of device development at Genentech and currently a pharmaceutical consultant.

a plungerless injection system that uses magnetic principles to dispense medication/fluids from uniquely constructed disposable, single-use sealed cartridges. Boris Zubry, an Artemes cofounder and inventor of the device, offered, "Magnetically-propelled fluid delivery is currently used in many industrial applications. By applying these principles to a new syringe technology, we can remove the plunger from the syringe design and thereby eliminate the multiple negative issues of the barrel-plunger system altogether." Further, Michael Dudley, Artemes' CEO added, "Sealed cartridges can help to dramatically increase product shelf life and better contain the escalating manufacturing, shipping, and storage costs commonly associated with most conventional prefilled syringe formats."

ROOM FOR GROWTH?

Despite the commercial availability of a plethora of prefilled syringe design options, many syringe manufacturers and drug delivery experts believe there is still plenty of room for innovation in the prefilled syringe market. For example, Catalent's Arnold thinks that microneedle transdermal patches and needleless auto-injectors may represent promising areas of innovation. However, for the foreseeable future, it appears that conventional prefilled syringe formats will remain the method of choice for self-administer biologics and other parenteral drugs.

Sunshine Act Compliance: Are You Prepared?

By Animesh Gandhi,
director of information management, Alliance Life Sciences

In 2011, CMS (Centers for Medicare and Medicaid Services) published the draft rules for Sunshine Act implementation and then collected comments until Feb. 17, 2012. The organization plans to issue the final rules "sometime" in late 2012. CMS is also considering a preparation period of 90 days after the rules are finalized.

In light of the above development and timeline, we suggest companies start to capture data as soon as possible to ensure its accuracy and integration with the reporting system.

It should be noted that although the dates have changed, the majority of Sunshine Act requirements will be expected, minus a few exceptions in the draft rules:

1. CMS has confirmed the use of NPPES (National Plan and Provider Enumeration System) or NPI (National Provider Identifier) to identify covered recipients.
2. Applicable manufacturers are defined as those organizations that manufacture at least one "Rx Only" drug or a PMA (premarket approval) device.
3. Privately held manufacturers and Group Purchasing Organizations (GPOs) that have physician ownership must submit two separate reports: one for transfers of value to a covered recipient, and another detailing the physician investment/ownership interests.
4. The provisions for allocation of group spend are as expected and should cover cost per individual recipient.
5. CMS proposes that manufacturers report transfers to group practices (GP) compared to the physician(s) who make up the GP.
6. Reports for payments directed to third parties should include both the third party and the primary recipient.
7. The entire amount should be reported, not individual payments for research.
8. CMS proposes to publish a list of teaching hospitals that are covered.

Companies should proactively navigate through the complex set of requirements by focusing on three areas:

SPEND GOVERNANCE: Proactive compliance is more than simple data collection. You need to:

- Create a framework to promote awareness and help educate various stakeholders regarding the importance of governance and the focus required to successfully implement structure.
- Define a spend governance operating model including key roles, responsibilities of the working group, timing, and improvement of data quality.
- Establish high-level policies and guidelines.
- Define the roles and responsibilities and responsibility assignment (RACI) matrix for the spend governance and data stewardship functions.
- Define goals and success measures, establish monitoring and metrics for goal attainment, and define scorecards to report on capability performance.

POLICIES AND PROCEDURES: You may need help with:

- spend disclosure compliance communication to employees on transparency obligations
- standardizing spend definitions and classifications ("nature" and "purpose") categories across the organization
- finance/payment policies for handling of payments to entities that veil a reportable end recipient
- business rules customization including data entry requirements, triggers, warnings, etc.
- third-party contract requirements and SOP for payment reconciliation
- spend determination SOP for submitting a new or unreported spend events
- disbursement reporting SOP for establishing new reportable disbursable items, work instructions to classify nature and purpose category.

TRAINING: Develop training curricula and materials for aggregate spend program components such as:

- Sunshine Act implementation and ongoing state disclosure requirements
- data stewardship protocol, including the roles, responsibilities, and coordination among compliance/business data stewards and technical data custodians
- spend policies and business rules
- spend disclosure compliance and employee obligations
- third-party spend data governance and reconciliation
- post-implementation best practices such as fair market value (FMV) policies and procedures.

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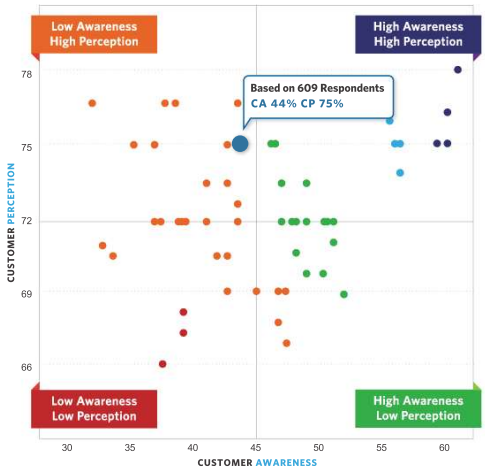
Customer Perception: CP describes how a potential or current buyer has rated the company based on the information to which they have been exposed, from marketing materials to word-of-mouth influence, as well as personal experience with the company.



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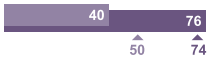

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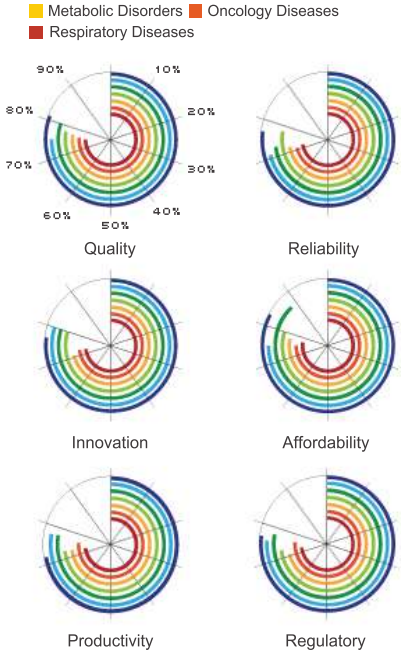
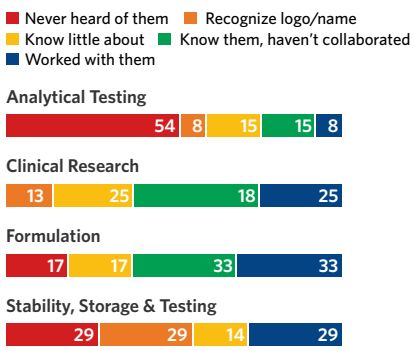
Cardiovascular Diseases

BY SERVICE CATEGORIES
Fill & Finish

CUSTOMER PERCEPTION OUTSOURCING DRIVERS BY THERAPEUTIC CATEGORY



CUSTOMER AWARENESS BREAKDOWN



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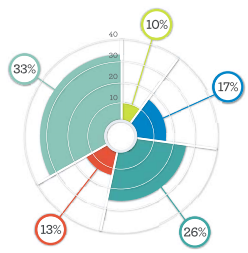

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5 Reasons For Using Integrated EDC/EHR Platforms

By James Rogers

With the fast pace of technological advancements, life science researchers are regularly presented with a wealth of new tools that can potentially bring life-saving drugs to market quickly and economically. One development that is generating a lot of industry buzz is the integration of platforms offering electronic data capture (EDC), traditionally used to manage clinical trials, with platforms used within the healthcare industry to create and maintain electronic health records (EHRs).

The federal government's spotlight on EHRs, and the lucrative incentives it offers today through the 2009 HITECH Act to entice organizations to deploy them, have had a profound effect on both the healthcare and life sciences R&D industries. In healthcare, where most records have traditionally been "physical" media such as film (x-rays), paper (notes), or photographs, an EHR is now streamlining record storage and retrieval, easing billing issues, improving data input accuracy, and most importantly, increasing the quality of care for patients.

As the healthcare industry's adoption of EHRs has widened, it has created a ripple effect in the life sciences industry, generating excitement among those who understand how EHRs might offer potential access to previously untapped patient population pools and significantly lower investigative study costs. Most researchers today are already using an electronic data collection (EDC) tool to help manage even early-stage clinical trials. Because the collection methodologies for EHRs are similar, could a single system simultaneously be used for patient care in both the hospital/clinic and clinical trial settings?

Data models to enable this type of integration are quickly evolving with support from industry groups on both sides. Some examples include the Integrating the Health Enterprise (IHE), Retrieve Form for Data Capture (RFD), and HL7's Continuity of Care Document (CCD).

ELIMINATE DUPLICATE DATA ENTRY AND WORKFLOW ISSUES

Outside of high profile, staged interoperability demonstrations, there has been significant progress in the deployment of integrated platforms since 2009. Nextrials and its partner, Greenway Medical Technologies Inc., conducted a multisite retrospective study in which patients were enrolled in real time, and patient data was collected through a single interface. The participating sites included facilities experienced in conducting research, as well as small medical clinics in their inaugural clinical trials. One of the outcomes of this pilot project was the successful resolution to two major problems long noted by industry leaders — duplicate data entry and workflow issues — that had been traditionally associated with disparate EDC and EHR systems.

With EDC/EHR platforms moving beyond the theoretical realm, why should life science drug discovery and development professionals care? What are the benefits? Here are five reasons to consider choosing an integrated EDC/EHR product for an upcoming study:

1. An integrated EDC/EHR platform can pre-identify sites with appropriate patients for even the most tightly focused study. This, in turn, fosters fewer enrollment delays — an important consideration from not just a cost standpoint but from the implementation requirements of a competitive, go-to-market strategy.
2. Research costs are considerably lower due to certain economies. For example, study monitors and research associates do not need to travel to sites as often for source data verification because 80% to 90% of the data is typically taken directly from the EHR.
3. There is a greater pool of potential sites, even those that have never participated in drug research, because the start-up requirements are significantly lowered through an integrated EDC/EHR platform. The potential patient pool is also increased, as those living far from large medical centers can now enroll through smaller, more localized clinics.
4. By removing the potential for transcription errors, data quality is improved.
5. Information that isn't normally collected within a site's EHR can be collected on eCRFs (electronic case report forms) that are displayed in the EHR interface.

About the Author

James Rogers is the co-founder and CEO of California-based Nextrials, Inc. With more than 25 years of life sciences experience, he is a frequent speaker at webinars and conferences. He can be reached at jrogers@nextrials.com.

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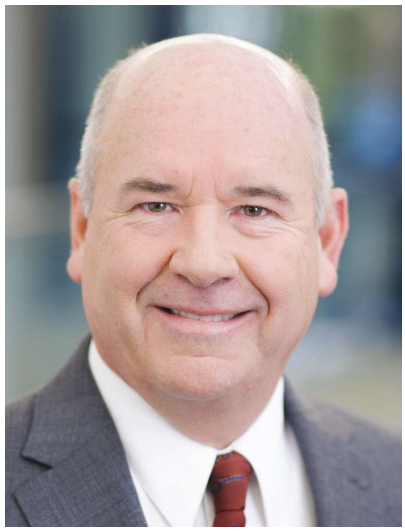

Brian Bollwage, JD

Brian Bollwage is vice president, strategic regulatory affairs at Theorem Clinical Research, which provides a variety of clinical trial services.

NIH's Office of Rare Diseases estimates there are more than 6,000 diseases that meet the FDA's criteria for orphan conditions. A list of these candidate diseases can be viewed at http://rarediseases.info.nih.gov. As of July 2012, the FDA has granted orphan designations for 2,617 products, leaving a large number of research targets yet to be pursued.

THE ORPHAN DESIGNATION PROCESS

In order to obtain orphan designation for a disease, a sponsor must submit an orphan designation application to the FDA's Office of Orphan Products Development (OOPD). The required information is described at 21 CFR 316.20(b). Of the nine elements required, there are two particularly critical items — the scientific rationale (item 4) and a convincing demonstration of population prevalence (item 8). The requirement for demonstrating an appropriate scientific rationale has evolved since the 1980's, when a mere hypothesis for patient benefit was often considered to be sufficient to qualify. Recently, the FDA has become more demanding regarding the scientific rationale. OOPD now requires data validating the clinical benefit, either via a relevant preclinical model of the disease or with actual clinical data. To qualify as an orphan product in the U.S., the patient population must fall below 200,000.

MARKET EXCLUSIVITY, TAX CREDITS, AND RESEARCH GRANTS

The Act includes two significant rewards, which Congress intended to promote the development of drugs to treat rare disease. Most prominent of these is the grant of seven-year market exclusivity and tax credits for certain clinical testing expenses. Regardless of a product's patent status, market exclusivity begins on the date the FDA approves a designated orphan drug, assuring the exclusive market for a full seven years. Tax incentives allow up to a 50% credit for certain clinical testing expenses from the date of the orphan designation to the date of FDA approval. A marketing application for a product that has been designated as a drug for a rare disease is typically exempt from the standard prescription drug user fee, which is $1.84 million in FY 2012.

There is other help, too. For example, OOPD administers a grant program that underwrites the costs of clinical trials for drugs intended to treat rare diseases. The FDA subsidizes about 70 programs with grants ranging from $200,000 to $350,000. Typically, OOPD funding grants run for three years. Grant applications are solicited via a Federal Register Request for Applications (RFA), published in August each year.

FDA PROTOCOL ASSISTANCE

The Orphan Drug Act provides formal protocol assistance upon sponsor request. Protocol review responsibility rests with the center and division holding responsibility for the relevant therapeutic area, but OOPD personnel act as advocates for the sponsor during the protocol review process.

The approval of an orphan designation request does not alter the standard regulatory requirements or process for obtaining market approval. However, the smaller patient populations involved generally justify reliance on data from smaller clinical trials. As a result, orphan applications are reviewed faster on average — 6 months — than the standard 10-month review time.

The FDA has approved more than 400 orphan drugs in the U.S. In 2011 alone, 10 of the 35 new drugs approved were for orphan diseases. There remain substantial opportunities and significant incentives for development of the more than 5,500 rare conditions yet to be addressed. Orphan drugs are estimated to account for 7% of the world pharmaceutical market. With an estimated global market size totalling 1 trillion dollars in 2012, the potential market for orphan drugs approaches $70 billion worldwide.

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A Forgotten Majority: Diversity In Clinical Trials

Robert A. Beltran, M.D.
President, Quality Health Care Management

Sara Tolsky, M.B.A.
President, Farma Consulting

Owen Garrick, M.D.
President & COO, Bridge Clinical Research

What is the future of medicine and healthcare now that Obamacare is the law of the land, especially now since the forgotten majority-vulnerable populations will be covered under the Patient Protection and Affordability Act?

No one can deny the essential role that clinical trials have played in the progress of medicine and healthcare. Clinical trials are as fundamental to medicine as baseball and apple pie are to America. The quality and outcomes of clinical trials continually contribute to excellent care delivered in the majority of our major medical centers throughout the United States.

Even though we recognize the importance of patient diversity in clinical trials, along with the racial/ethnic differences in the causes and responses to the treatment of various diseases, recruitment of both physicians and patients in clinical trials remains a challenge. In 2001, Congress mandated that minorities should be included in government sponsored clinical trials to elicit relevant information, yet Hispanic participation rates still remain low, relative to the 50.5 million known Hispanics living in the U.S. (16.3% of the U.S. population). So why is the ethnic diversity of clinical trial participants so limited?

Today, typical patients entering a clinical trial are middle-class, affluent, well-educated Caucasians. This patient population is well-established in site databases and responds well to messages geared to the upper end of Maslow's Hierarchy of Needs, such as self-actualization and altruism. These traditional recruitment methods are not aimed at lower socio-economic groups, many of which are underserved medically, representing *more than* half (52%) of uninsured Americans in the U.S. who have *no* regular source of health insurance.

WHAT ABOUT HISPANICS AND LATINOS?

One focus group, held in 2011, explored why Hispanics and Latinos did not participate in clinical trials. While there were a number of misperceptions about participation in clinical trials (i.e. "I don't have health insurance so I can't participate" [35%]), the main reasons were lack of information and lack of (a) Hispanic physicians or (b) walk-in/emergency clinic physicians who recommended and referred patients to clinical research trials. Sixty-nine percent stated, "It's important to have a Hispanic/Latino healthcare professional who understands the language and/or culture," and 46% said they would be more likely to participate in trials if the information came from a Hispanic/Latino caregiver.

Research shows that a bottom-up, "a las calles" approach is more successful in recruiting these patients to clinical trials. This approach includes outreach programs, walk-in clinics, independent pharmacies, and social work departments that deal directly with patients. Additionally, messages used to promote participation in clinical trials must focus more on the benefits of participation such as "free" regular medical assessments, multifaceted diagnostic evaluations, free drug, and reimbursement commensurate with fair market value.

Patient management must also be more targeted towards patient satisfaction (i.e. "good customer service") and deal with the practical realities of day-to-day living for those with little or no disposable income (e.g. arranging for transportation that does not require the patient to up front the cost and ensuring prompt payment for each medical visit).

WE NEED SUPPORT FOR CLINICAL TRIALS DIVERSITY

We believe two critical supporters in the endeavor for clinical trials diversity are the policy makers and clinical researchers. If clinical researchers are to have more responsibility in supporting greater patient diversity in clinical trials, then our policy makers must provide resources that enable action and accountability for such diversity.

Exploring new ways to reach out to the less advantaged U.S. patient populations can be an adjunct to traditional recruitment methods and a way to enhance the new pending regulations for increasing care for the underserved, forgotten majority.

The "new" law of the land now provides a foundation for this necessary change for greater diversity in clinical trials to become a reality.

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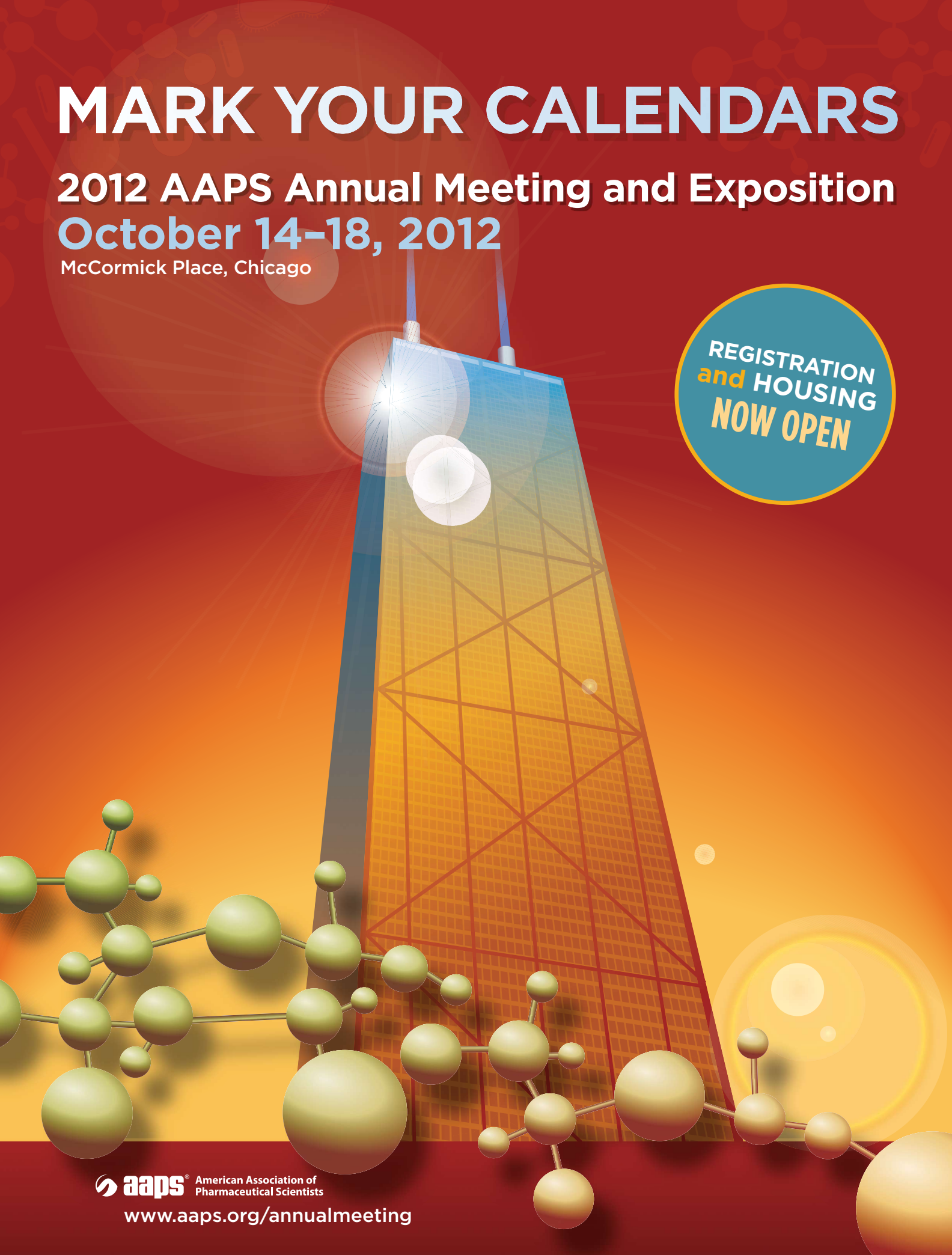

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The Need For Actionable Data

Enabling The Intelligent Cold Chain

In these turbulent times, pharmaceutical manufacturers, 3PLs (third party logistics), and couriers are searching for ways to maximize profits while facing mounting challenges in their cold chain logistics operations necessitated by the rapid growth of the biologics and other temperature- and time-sensitive biopharmaceuticals. It's estimated that at least 25% of all pharmaceutical products are temperature-sensitive, and that number is expected to grow to 80% by 2016. These products typically require 2° to 8°C refrigeration and temperature control throughout shipment. Beyond the critical importance of these medicines to the patients, many of these products are often the most expensive products that a manufacturer produces, furthering the need for strict diligence at every step in the cold chain from manufacture to healthcare provider. The loss of these products due to supply chain issues immediately and directly impacts the bottom line. One failure in any part of the shipping process — in a truck, on a tarmac, in the air — means lost revenue, lost product, and most importantly, patients that will not receive the drugs and medications they need.

Facilitating an efficient, effective, and documented temperature-control process is an increasingly essential part of the transit process. What's equally important is monitoring the temperature of the actual product in the package, in transit. Monitoring the ambient or external temperature isn't sufficient to ensure the safety and efficacy of the product throughout the cold chain where weather conditions, shipping delays, and a variety of other factors can create problems that impact the quality and efficacy of the products.

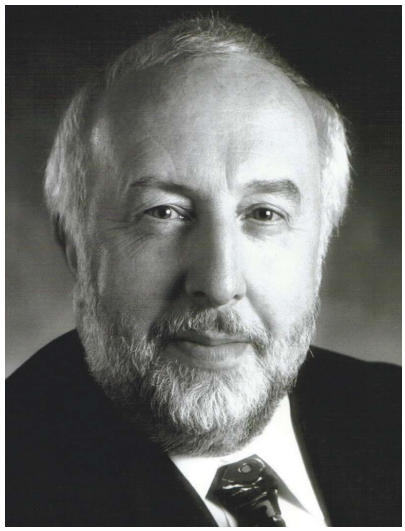
Because of this, it's critical to go beyond monitoring your cold chain; you need to actively manage your cold chain, and that requires having access to actionable data — data that provides the ability to know when a problem is likely to occur before it actually occurs. Actionable data implies that the entire journey must be monitored and documented because each step of the cold chain is equally critical for time-and-temperature control. With actionable data, available on-demand throughout the cold chain, you can anticipate when action needs to be taken when the products in the carton are at risk of being compromised or experiencing an excursion. In-transit temperature monitoring — at every step of the cold chain — provides this capability by providing the ability to "see" inside the carton without opening or unpacking it.

A NEW APPROACH

Traditionally, many types of data loggers have been used to monitor the cold chain including chemical, USB, and active RFID data loggers. Each of these types of data loggers, however, has limitations in today's rapidly evolving cold chain. They either provide no detail about what happened (chemical loggers), they can't be used inside aircraft (active RFID tags), or they can't be accessed and read in transit without opening and tampering with the container (USB-based loggers). These tools simply weren't designed to address today's rapidly evolving cold chain.

Fortunately, new solutions are becoming available. A new breed of RFID technology known as battery-assisted passive (BAP) RFID offers advantages over legacy temperature monitoring and recording devices for the shipment of temperature-sensitive products from the manufacturer to the healthcare provider. With on-tag memory, BAP RFID maintains a complete record of the in-package conditions with the product, which can be read at any point in the shipping process, as well as providing a documented record at the end of the shipping process. Because BAP RFID tags do not transmit or beacon, they are FAA-compliant for use in airplane cargo holds. But, perhaps most importantly, because of the performance of BAP RFID, temperature-monitoring tags can be read through pharmaceutical packaging without opening or tampering with the container, helping to reduce counterfeiting and grey market diversion of products. Together, these capabilities provide the ability to capture actionable data about the condition of the product and identify issues before they occur, as well as document proper shipment throughout the cold chain. They provide you with actionable data to enable an intelligent cold chain.

Only by providing manufacturers, 3PLs, couriers, and providers with actionable data can the pharmaceutical industry maximize quality and profitability in the cold chain. Forensic or historical data can only document their losses.



Peter Norton

Peter Norton is a senior consultant for Cold Chain Solutions at Intelleflex, advising clients on more efficient approaches to monitoring and managing cold chain logistics. Previously, Peter was at Genzyme Corporation and GSK.

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10 Tips To Maximize Your Conference-Networking Experience

By Thom Singer

One of the top reasons people cite for attending conferences, seminars, and conventions is the networking opportunities they provide. Unfortunately, many fail to make many legitimate, meaningful, and long-lasting connections. Why? They don't position networking as a priority. Having an event-networking plan is equally as important as planning which educational tracks to attend. Here are 10 tips to maximize your conference-networking experience so you get more out of the "hallway conversations" than a business card exchange.

1. Have a plan. Know in advance the type of people you want to meet, which speakers you want to hear, and what booths you want to visit.

2. Bring plenty of business cards. In today's digital world some argue against the importance of business cards. But having a card is not for you, it's for the other person. Some people forget names quickly, and asking for a card helps their recall. Telling someone "Google me" is making them work to keep in touch.

3. Do not focus on meeting celebrity speakers. Meeting famous authors and speakers can be fun. But you are one of hundreds who will come up and shove a business card in their hand. Instead, place your focus on meeting other people in attendance. These are the folks with whom you will create long-lasting and mutually beneficial relationships.

4. Talk to the people sitting next to you. Take the time before the presentation begins to say hello to people seated around you. I call this the "power of hello." A simple hello makes it easier to strike up a conversation with this person when you see them later in the week. Also, never lead with your "elevator pitch." People are more interested in talking about themselves. So ask questions to help get them talking.

5. Put your technology away. Do not run to your phone or laptop at every break. When you are working on electronics you send the message, "I am unapproachable and busy."

6. Do not automatically send a LinkedIn or Facebook request. Too often people immediately send social networking link requests to people they just met. However, different people have different policies about whom they link with. If they believe in only connecting with those whom they have established relationships with, you make it awkward by sending them a link too early. It is best to ask people if they would welcome such a link at this time.

7. Read their stuff. Many people are active bloggers, tweeters, and authors. If people create the written word, seek out their work, and read it.

8. Introduce others. When you meet cool people, be the conduit that connects them with others who might be beneficial to them. This includes others at the conference, as well as other people you might know back home.

9. Follow up. Own the follow-up after you meet people, send them an email (or better yet, a handwritten note) telling them how much you enjoyed talking with them, and plan for future discussions.

10. Do more than others expect from you. Bring more to a new relationship than the other person expects, and they will always remember you as someone who is a giver.

Thom Singer is a corporate trainer and professional speaker. He is the author of eight books on the power of business relationships, networking, and presentation skills. He regularly consults with companies to enhance their decision-making skills in regard to human-to-human relationships and finding better sales results.

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

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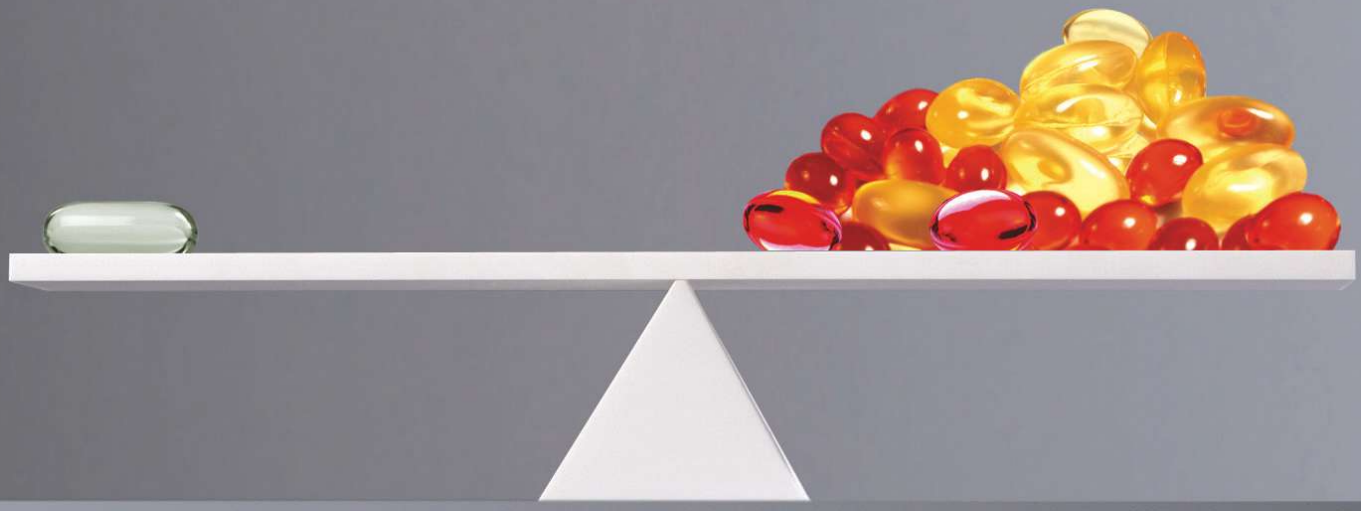

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