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Focusing UCB's Pipeline Strategy

Therapeutic expertise, new molecule discovery, and a U.S. market focus spell success for UCB. p. 20

Roch Doliveux, CEO, UCB

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20 FEATURE: UCB

UCB's CEO, Roch Doliveux, says his company's plan is to target developed nations, like the U.S., with new medicines for severe diseases.

February 2013

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CORRECTION: *In the Jan. 2013 issue article "A Biologics Road Map," the second sentence of the third paragraph should have read, "In November 2012, the FDA accepted its Biologics License Application (BLA) and granted it priority review status."*

Welcome to *Life Science Leader*

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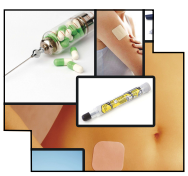

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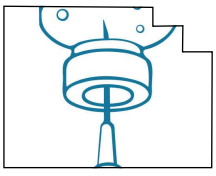

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Why quality by design (QbD) will become an unavoidable necessity for most companies and their suppliers

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EDITOR'S NOTE

FDA Incentives Could Pay Dividends For J&J

In January, the FDA approved Sirturo, a drug developed by J&J (NYSE: JNJ) to treat multidrug resistant tuberculosis (MDR-TB). What makes this announcement particularly interesting isn't the fact that Sirturo is the first new drug in 40 years to be approved to treat tuberculosis. What makes it interesting is the fact that J&J targeted the United States for approval, when fewer than 100 Americans have this potentially fatal disease. Even more interesting is the fact that the drug was granted accelerated approval based on data from a pair of Phase 2 studies. You may be wondering if this is another case of the scientists being too close to the compound, pushing for drug approval where a viable commercial market does not exist. It's no secret that Paul Janssen, founder of J&J's Janssen Pharmaceutica NV, was passionate about finding a treatment for the disease which killed his sister. But there is a method behind what might be viewed as madness. Here is why a $65 billion global pharmaceutical bellwether sought FDA approval for a drug where the commercial market is < .00003% of the population (and, coincidentally, is one of the topics I focus on in this month's feature story on page 20). Basically, if you want success in the global pharmaceutical world, the United States still holds the keys to the pharmaceutical kingdom.

Many countries in the world use FDA and EU opinions as points of reference for approving drugs in their homelands. This makes sense when you consider that the U.S. is the largest pharmaceutical market in the world, and the 27 member-country EU is second. J&J is betting that FDA approval of Sirturo will increase the likelihood of its being approved in China, India, Russia, and Eastern Europe, home to 60% of the world's 630,000 MDR-TB cases. But J&J is getting something else as well, and it isn't just capitalizing on launching a drug which can benefit < .009% of the world's population, or the goodwill created among regulators, governments, and patients around the world for developing a rare disease drug. What J&J gets is a reward, in the form of a voucher from the FDA, for its "commitment to advance innovative medicines that help address serious public-health issues," says J&J spokesperson Pamela Van Houten.

Under the FDA Amendment Act of 2007 (FDAAA), companies receiving FDA approval for a tropical disease treatment (e.g. TB) are eligible to receive a transferrable voucher that allows the bearer to designate a single human drug application submitted under section 505(b)(1) or section 351 of the PHS (Public Health Service) Act, to receive six-month priority review status. So not only did J&J hit the FDA drug approval lottery with this gamble, but also the company did so while the approval process was "on sale." For in September of 2012, the FDA announced a 32% reduction in fee rates for companies wishing to use a tropical disease priority review voucher for the fiscal year 2013. Obviously, J&J sees the benefit of getting another drug in its pipeline a priority review, beyond the $3.6 million bargain fee associated with using the voucher. The idea behind the voucher program is simple and yet brilliant. If you want companies to develop drugs for diseases found primarily in poor and developing countries, provide the appropriate incentive. By developing a nonrevenue-generating and yet lifesaving drug, J&J has the opportunity to accelerate FDA approval of another drug within its pipeline. And if it is approved in the U.S., the world is likely to follow.

Rob Wright
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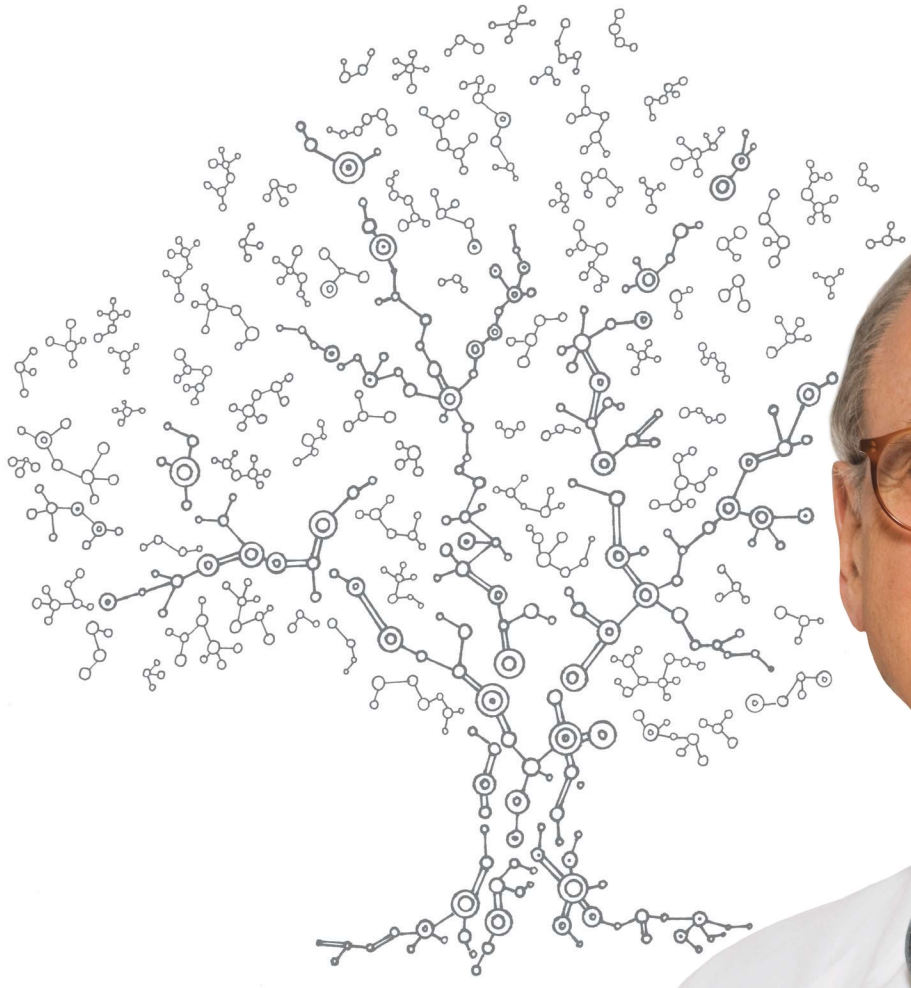

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CHIEF EDITOR'S BLOG

Our Chief Editor, Rob Wright, has been pondering naming his blog. How about "Rob's Rants" or "Wright Writes?" Or, maybe you have a good idea for a name. If so, send him an email at rob.wright @lifescienceconnect.com. He writes about a variety of topics such as recent shows attended, conversations with industry experts, and irritating business buzzwords. And don't forget about your opportunity to pick the brains of our editorial board. Send your questions for our monthly "Ask the Board" section to atb@lifescienceconnect.com.

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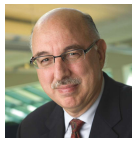
Q: What challenges need to be overcome to increase adoption of single-use manufacturing technologies?

The adoption in large pharma companies is slow for a variety of reasons – extractables and leachables analysis, challenges of vendor change control, and lack of connectivity of equipment from various suppliers which could result in a supply chain manufacturing gap. One of the newest emerging issues is the control of particulates (extraneous matter) that may shed from single-use components during processing. Extraneous matter is a growing concern of regulators and manufacturers alike. The control of particulates is a high-priority topic of the user community of the Bioprocess Systems Alliance (BPSA). Leveraging learnings from other industries (e.g. chip manufacturing) should benefit this cause.

Jim Robinson
Robinson is the VP for vaccine and biologics technical operations for Merck & Co. In this role, he supports the manufacturing strategy, process development, technical transfer, approval, and production of Merck's vaccines and biologicals.

Q: Is the presence of Bisphenol A (BPA) in single-use products a deal breaker?

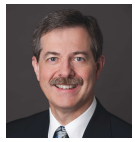
No. Most single-use components are made from polymers that are not made with BPA monomers, and are thus BPA-free. Examples include polyethylene film biocontainers, silicone and thermoelastomeric tubing, polypropylene tubing connectors, and filter hardware and membranes. Toxicity studies have failed to show toxic effect in humans at levels found in food-product leachables. Polymers used for medical devices and single-use bioprocess components made using BPA are from medical-grade resin formulations and processes that do not yield detectable BPA migrants, even under exaggerated extraction conditions. Demonstrated absence of detectable BPA from those components has enabled them to be deemed acceptable by both the FDA and EMA for use in medical devices and biomanufacturing. Public concerns with BPA from food or drink containers does not extend to drug manufacturing and medical devices where BPA migrants are already excluded and where health benefits outweigh unproven risks.



Jerold Martin
Martin is a senior VP of global scientific affairs for Pall Life Sciences and chairman of the Bio-Process Systems Alliance (BPSA) single-use biomanufacturing trade association. He has more than 32 years experience in the biotech and pharmaceutical industry.

Q: What are some of the industry publications you read and why?

I read a variety of journals in order to stay current on the biopharmaceutical industry. For the scientific component, I enjoy the *Journal of Clinical Pharmacology & Therapeutics, Drug Information Journal,* and the *New England Journal of Medicine,* to name just a few. Some of the financially focused periodicals I review include *Forbes* and *Fast Company*. With *Life Science Leader,* I like how the magazine applies lessons and experiences from leaders across the industry, as well as the breadth of stories and editorials. In all of the publications, I prefer excellent content which doesn't have an obvious sales focus, and I personally don't find publications which write about vendors/ advertisers to be of much use.



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

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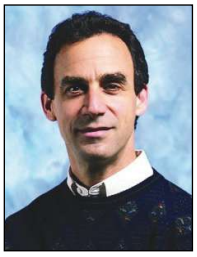
By Wayne Koberstein

Auspex Pharmaceuticals

In a race to create a new space in deuterium-analog drugs

SNAPSHOT

Auspex Pharmaceuticals is a venture-financed company developing a pipeline of deuterium-based drugs in several rare to large disease areas. As analogs to original compounds, formed by substituting deuterium for hydrogen in discrete locations in the drug molecule, the Auspex compounds are new chemical entities designed to improve safety and efficacy, refine dosing and administration, and boost patient compliance over existing therapies. Deuterium forms a much stronger bond with carbon than hydrogen does, and can attenuate the rate of metabolic breakdown of the drug in the body. The company claims the approach lowers the cost and risk of drug development by exploiting the known pharmacological, toxicological, and regulatory paths of existing therapies. Auspex's lead compound is a deuterium-substituted analog of tetrabenazine for treating involuntary movements in Huntington's disease, Tourette's syndrome, and tardive dyskinesia. Other pipeline compounds target idiopathic pulmonary fibrosis, inflammatory diseases, and neuropathic pain.



Larry Fritz, CEO

LATEST UPDATE

• Auspex will use the funds from the Series D Round to advance the development of its portfolio of drug molecules, particularly the Phase 3 development of its lead molecule, SD-809, expected to begin in the first half of 2013.

WHAT'S AT STAKE

Most of the attention given the deuterium approach has so far focused on the supposed race between Auspex and Concert Pharmaceuticals, which is also developing deuterium-based drugs. But neither company has received much attention since 2008, when both achieved major financing, generating a spate of reports that went beyond covering their press releases. Auspex is a small company with novel products in development, years spent mostly in the media shadows, and a recent significant event in its Series D finance round. It has a unique therapeutic focus in the still-tiny deuterium-drug space.

"For decades, scientists had looked at using other atoms in compounds to improve pharmacological performance, and it was recognized that, if you substitute deuterium for hydrogen, you can have very specific effects on a drug's metabolic profile, but no one had employed the method to improve the metabolic properties of an established drug. That was the company's founding concept," says Auspex CEO, Larry Fritz.

The company began in 2006 by doing in-vitro analysis of deuterium analogs looking for a significant "kinetic isotope effect." As a result, it now has a large "broadly patented" portfolio of deuterium compounds and applications. Fritz says the potential and interest in those applications is much stronger these days because the industry is ready to explore opportunities in "the space between generics and branded medicines" with a low-cost, low-risk approach to NCE (new chemical entity) development.

Some deuterium-based NCEs face a simpler regulatory path and lower development risk. Similar to other XR (extended release) forms, a deuterium compound may in some cases follow the FDA's 505(B)(2) application procedure that allows its developer to reference various data in the label of the original drug, which can significantly streamline the development work necessary for drug approval. However, deuterium-substituted analogs must still be tested clinically for adequate safety and efficacy.

Auspex is not waiting entirely for patent expirations or taking old off-patent drugs off the shelf for deuterium applications. Most of the compounds in its pipeline are recently approved brandname products. And although it has orphan indications in its pipeline, other indications could open it to large markets.

So here you have it — a non-public company with arguably strong IP and a largely validated, simple platform and, if anything, a competitor that actually complements the company by expanding the space. What's at stake is many rounds of funding versus potentially large markets for low-risk NCE development. Many good reasons to watch.

VITAL STATISTICS

- Employees: 8
- Headquarters: San Diego
- Finances: Series D (October 2012): $25 M; led by Panorama Capital, with Thomas, McNerney & Partners, CMEA Capital, and Sloan Biotech Fund. Total capital raised to date: $59 M
- Product Deals: Teva Pharmaceutical Industries

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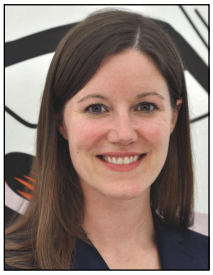


OUTSOURCING INSIGHTS

Competition Yields Benefits For Pharma Companies Outsourcing API Manufacturing

By Kate Hammeke, director of marketing intelligence, Nice Insight

It's no surprise that cost savings motivate outsourcing. However, the affordability of an individual company's services does not necessarily ensure that it will win a project ahead of costlier competitors. Strategic outsourcing tends to bring various benefits to the sponsor organization beyond cost savings, including the ability to focus on core competencies, increased productivity, and access to additional or specialized scientific expertise. Nice Insight surveyed buyers of CMO services to identify the motivations for engaging contract manufacturers, and results showed that the top three reasons for strategic outsourcing are to improve quality (54%), improve time-to-market (49%), and reduce fixed costs (45%).

Beyond probing what motivates these buyers to engage contract manufacturers, the survey asked specifically which products and services respondents acquire from CMOs. Forty-three percent said they purchase small molecule APIs from contract manufacturers, and 30% go to them for potent APIs. While the percentage of respondents who acquire drug product from CMOs (50%) was higher, the large number of innovator pharmaceutical companies that subcontract API production highlights a clear shift from the twentieth century mindset when pharmaceutical companies tended to complete the final stages of API synthesis in-house.

As intellectual property protections improved, the necessity for in-house API production became less imperative. Parallel quality control testing indicated that outsourced API met the same standards as in-house product, and, as a result, CMOs advanced from manufacturing late-stage intermediates to APIs. Pretty quickly, the API contract manufacturing market was flooded with excess capacity and companies competing for business that largely precluded differentiation in capabilities. These issues were compounded by the emergence of low-cost manufacturers in Asia. Yet the result of these problems for CMOs — price erosion — provides an advantage for pharmaceutical innovators.

FOR TOP CMOs, IT'S MORE THAN JUST A GLOBAL PRESENCE

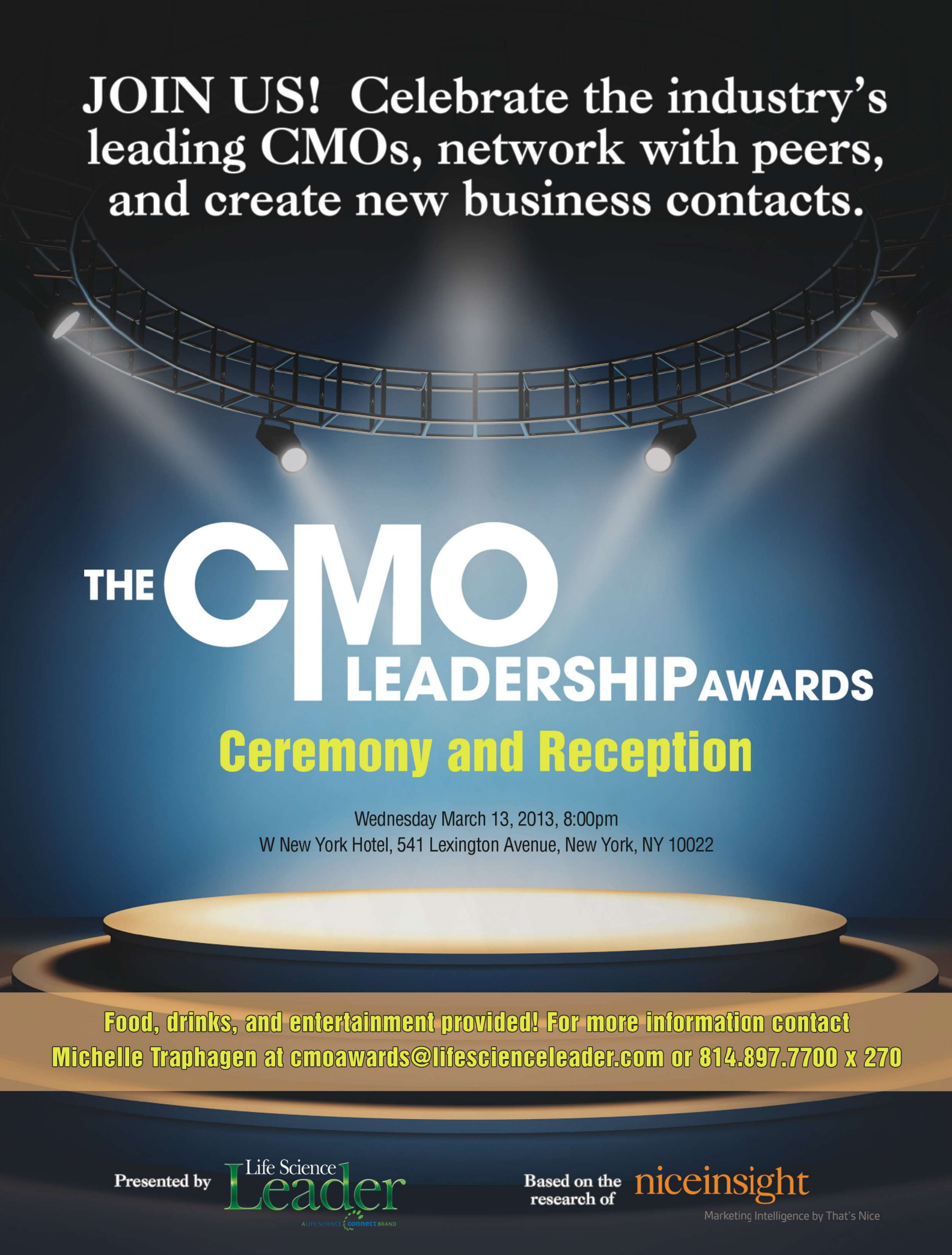
Outsourcing from low-cost labor markets in India and China is not without risk. Offshoring often incurs additional costs, ranging from international travel for site visits to IP violations, quality issues, local legal representation, and tech transfers. Of course, there are ways to benefit from partnering with businesses in emerging markets, while limiting these risks. Working with companies that have a global presence is the preferred method among Nice Insight survey respondents, considering that the top five CMOs (as indicated by the company's project likelihood* score) for small molecule API manufacturing are ones that have facilities in North America, Europe and Asia. Respondents selected BASF, Boehringer Ingelheim, Takeda, Lonza, and Novasep (listed from highest to lowest) as the CMOs they are most likely to engage for small molecule API manufacturing.

It is worth noting that, in addition to global presence, these five companies have several traits in common. Each scored at or above the quality (70%) and reliability (72%) benchmark scores for small molecule API manufacturing. These two traits are consistently ranked as the most important attributes in the CMO selection process, so it's no surprise that exceptional performance in these categories translates to an increased likelihood of winning an API manufacturing project. And with the exception of Takeda, these companies were also perceived as more affordable than other CMOs.

Interestingly, the outsourcing driver where these companies collectively fell short of the benchmark was innovation — perhaps indicating that when it comes to API manufacturing, there is less emphasis on the need for customized solutions. And finally, these leading companies for API manufacturing exhibited a trend that frequently emerges from survey data — those with the highest customer awareness scores were the most likely to be considered for a project.

Not only does outsourcing API manufacturing support the goal of reducing fixed costs — especially under the current market conditions — but also it offers access to scientific expertise beyond the talent of in-house staff, which can help to improve quality and reduce time-to-market. So while CMOs have to find ways to differentiate themselves from the competition in order to win business, outsourcers can take advantage of the consequent pricing conditions.

** "Project Likelihood" measures a company's probability of being selected for a project relative to competing businesses that also offer the service, as indicated by Nice Insight survey respondents.*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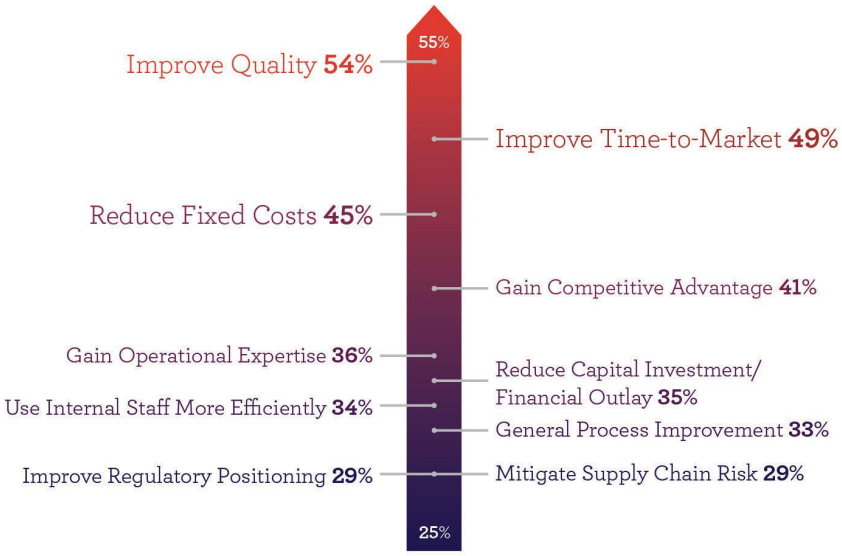
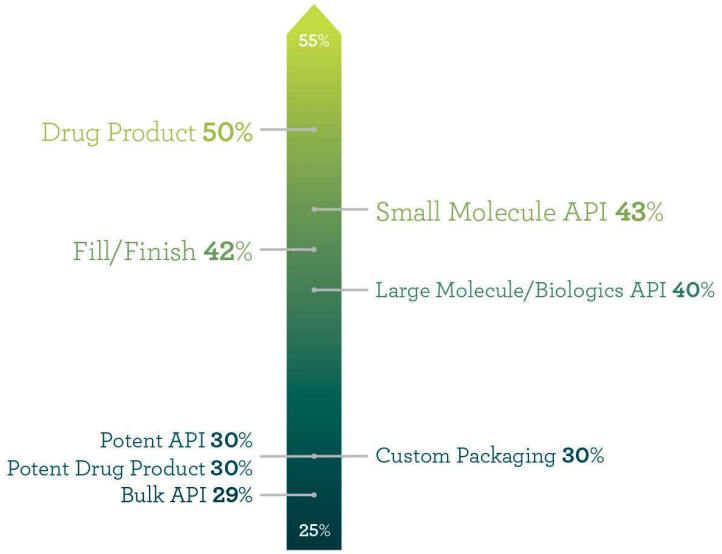
NI Motivations for Engaging Contract Manufacturing Organizations



NI Products & Services Acquired from Contract Manufacturing Organizations



Survey Methodology: The Nice Insight Pharmaceutical and Biotechnology Survey is deployed to outsourcing-facing pharmaceutical and biotechnology executives on an annual basis. The 2012 sample size is 10,036 respondents. The survey is comprised of 500+ questions and randomly presents ~30 questions to each respondent in order to collect baseline information with respect to customer awareness and customer perceptions on 170 companies that service the drug development cycle. Over 800 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.


Walker

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

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BIO INNOVATION NOTES

Is Innovation In Chromatography Losing Steam?

Both end users and vendors are investing less.

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

The biopharmaceutical industry continues to thrive on innovation, new technologies, and product developments that drive efficiencies in a globally competitive market. For several years, BioPlan Associates has measured the industry's attitudes toward new product development, identifying trends in the areas most sought-after by end users and paid the most attention to by vendors.

Preliminary data from our 10th Annual Report and Survey of Biopharmaceutical Manufacturers, to be released in April, shows that many new product development areas of interest (i.e. where end users want suppliers to focus development efforts for new technologies) have gone unchanged over the past few years. However, one area sticks out in the results: chromatography products for downstream processing. Last year, of the 21 new product development areas we identified, chromatography products ranked third in interest by end users (32.2%). The previous year, they ranked fifth on the list (29.7%), while in 2010 they were second (36.7%).

This year, though, among respondents who have currently completed the survey, chromatography products rank as the ninth most-critical area of interest for new product development, cited by 23.7% of respondents (Figure 1). This may be an indication that the pains and bottlenecks involved in current downstream bioprocessing (DSP) continue to moderate. Biopharmaceutical manufacturers are continuing to streamline their DSP operations. And while the need for better solutions continues, the pain appears to be less acute.

SUPPLIERS LESS ENTHUSIASTIC ABOUT CHROMATOGRAPHY INNOVATION

To some extent, the decreased level of interest paid to chromatography innovation among vendors in separate, preliminary results this year may be due to the decreased interest in broad DSP new technologies among end users. This year, we also asked industry suppliers to identify which of 40 different new technologies or new product development areas their companies are working on (Figure 2). Nearly 22% of supplier respondents to date said their companies are working on disposable chromatography (ranking 12th on the list), and 15.6% noted work on chromatography alternatives to protein A.

Our preliminary data appears to be following a downward trend. Looking first at vendor developments for disposable chromatography, the respondents indicating work in this area represent a step down from 2012's results (ranking #5 on the list), but an ever bigger drop from 2011's results (ranking #3). Likewise, alternatives to protein A have followed a similar pattern (Figure 2): The 15.6% of respondents from our preliminary data this year is down from 19.2% last year (#9) and 23.4% the year before (#9).

In comparison, the preliminary data we have received on suppliers' new product development activities shows more variability from previous years. For example, this year, innovation appears to be greater in cell-line optimization and animal-free media components, and there appears to be less interest in disposable bioreactors. It is possible that the numbers will smooth out as further responses come in. Nevertheless, the data appears to indicate a multiyear trend where suppliers are responding to lower demand from end users.

CHROMATOGRAPHY INNOVATION ON HORIZON

There may be various explanations for the apparent drop in interest in chromatography innovation by both manufacturers and suppliers. In recent years, advances in upstream expression improvements have not been met with capacity improvements in chromatography. That has not changed for several years now and appears to remain the status quo for the time being.

That's particularly disconcerting for biomanufacturers struggling with capacity constraint issues. In last year's 9th Annual Report and Survey of Biopharmaceutical Manufacturers, we found that chromatography steps are the chief contributor to capacity constraints — more so than depth filtration or ultrafiltration steps. Moreover, more than half of those experiencing capacity constraints as a result of chromatography steps said those constraints were "moderate" or higher. In all, roughly 1 in 6 respondents said that chromatography column issues were contributing to either significant or severe issues.

Still, it may be simply that while chromatography problems remain, these issues have leveled off, and the industry has learned to "live with it." The percentage of the industry experiencing at least "significant" constraints last year on account of chromatography steps was, after all, down slightly from 21.6% in 2009 and 20.2% in 2008. And since innovation tends to be forward- rather than backward-looking, chromatography innovation may be falling off the industry's radar because capacity issues tied to chromatography steps aren't getting measurably worse.

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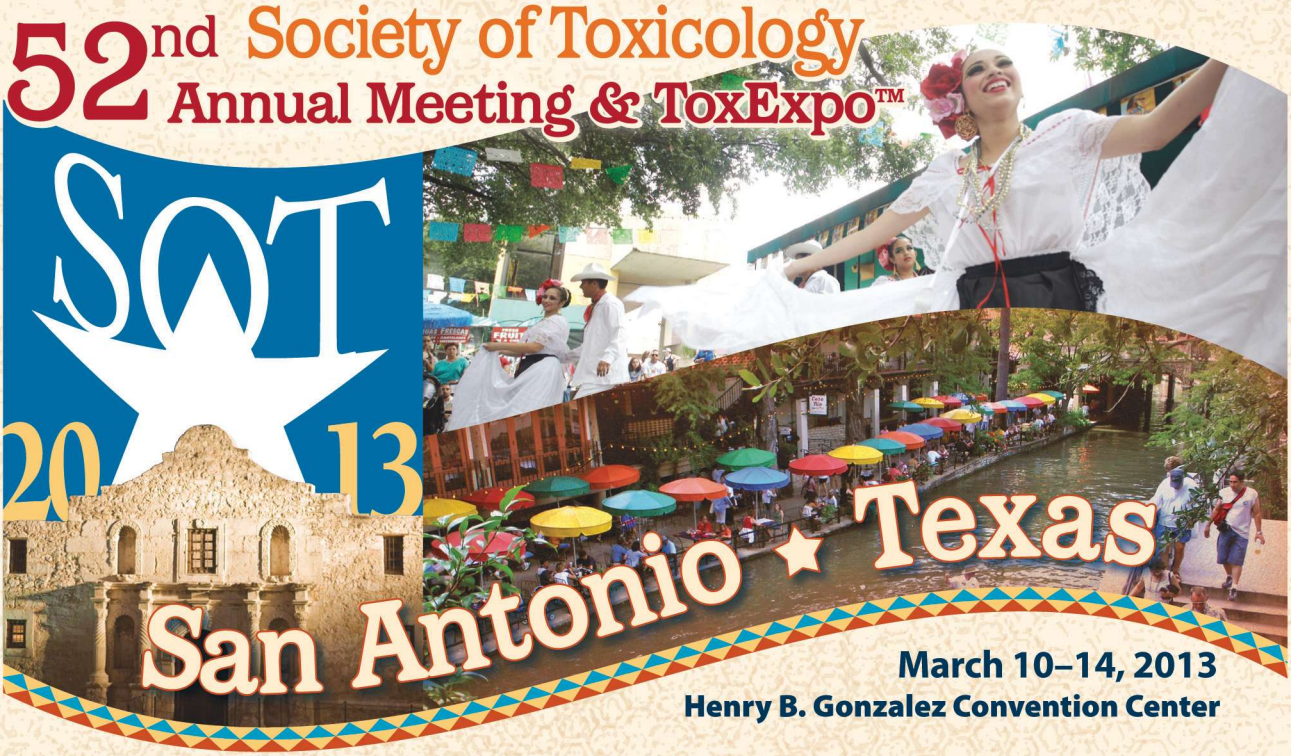

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8:00 AM to 9:00 AM

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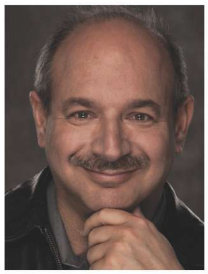


MRC Lecturer

Prof. Jeremy K. Nicholson
Wednesday, March 13
8:00 AM to 9:00 AM

Phenotyping the Patient Journey: Making Systems Medicine Work in the Real World

Photos courtesy of San Antonio Convention and Visitors Bureau. Some photos by Marks Moore, Steve Moore, Richard Nowitz, and Al Rendon.

Figure 1: Selected DSP areas where end users expect suppliers to focus development efforts (preliminary results)

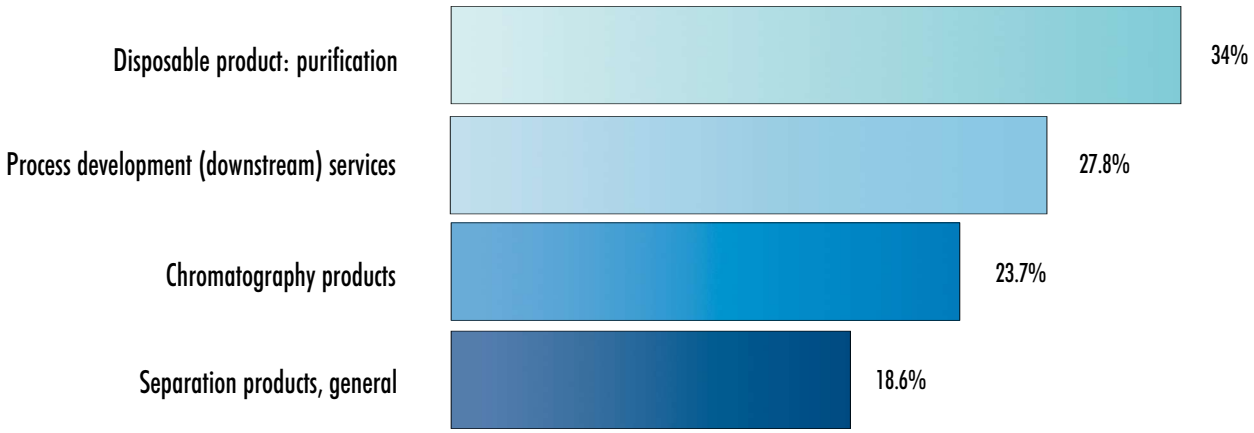
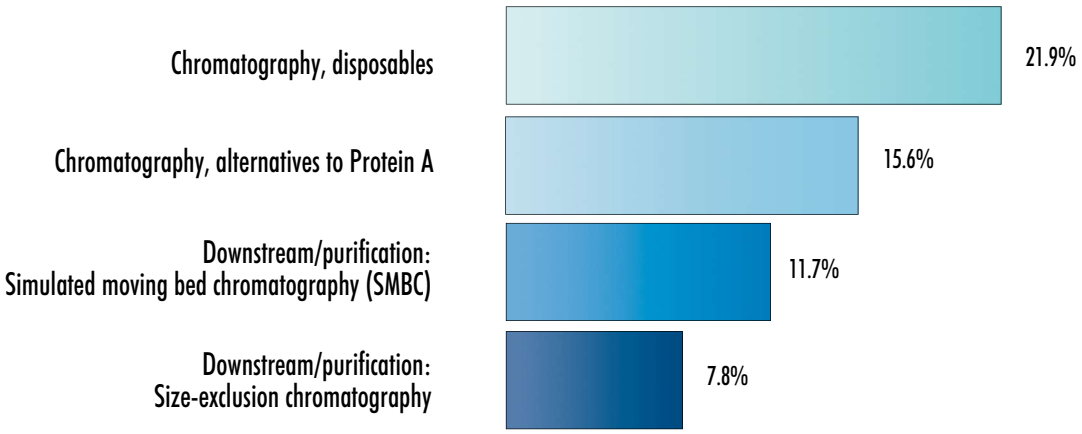


Figure 2: Selected new technology innovations suppliers are developing today (preliminary data)



Survey Methodology: The 2013 Tenth Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production is an evaluation by BioPlan Associates, Inc. that yields a composite view of and trend analysis from 300 to 400 responsible individuals at biopharmaceutical manufacturers and CMOs in 29 countries. The respondents also include more than 185 direct suppliers of materials, services, and equipment to this industry. Each year the study covers issues including 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, and employment. The quantitative trend analysis provides details and comparisons of production by biotherapeutic developers and CMOs. It also evaluates trends over time and assesses differences in the world's major markets in the U.S. and Europe.

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

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"As a CEO, you have to decide on which patient group you can make the most impact," says Roch Doliveux, UCB's CEO.

UCB: Winning In Pharma By Focusing On The U.S.

By Rob Wright

In 2000, I sat in a hotel ballroom at a national meeting for my new employer, Organon — a little-known European pharmaceutical company based in the Netherlands. The company's U.S. president, Hans Vemer, M.D., Ph.D., compared success in the pharmaceutical industry to playing tennis; in order to be successful, you need to play where the ball is. According to Vemer, the United States was "where the ball was" back then. Even now, 13 years later, a successful pharmaceutical company still needs to be successful in the states.

The U.S. remains the largest single-country pharmaceutical market in the world, worth an estimated $300 billion. The European Union, consisting of 27 countries, is second, and China, at an estimated $50 billion, only recently surpassed Japan for third place. And while much has been written about the future of pharma being driven by efficacious drug development in emerging and frontier markets, the fact remains that in order to have the opportunity to capitalize on those future possibilities, present-day success in the developed world, in particular the United States, remains a necessity. Nowhere is this more evident than when you take a close look at the recent success of the 36th largest pharmaceutical company in the world, Belgium-based UCB. Roch Doliveux, UCB's CEO, will tell you, "As a CEO, you have to decide on which patient group you can make the most impact." For UCB, having an impact on treating diseases in the U.S. is having a positive impact on the company's bottom line.

THE U.S. STILL HOLDS THE KEYS TO THE PHARMA KINGDOM

Aside from its approximately 314 million residents, there are many reasons why the U.S. continues to be an ideal place for companies like UCB that want to study, develop, and launch drugs. For starters, the U.S. per capita healthcare spending is about twice that of peer countries like Japan and the U.K. Spending on annual physician visits in the U.S. is about five times that of its peers, driven primarily by the American willingness to seek specialist care, which is reimbursed by Medicare and Medicaid at higher rates. In addition, the U.S. has a higher per capita income than any other large country, which is closely associated with higher healthcare spending. Additionally, one of the largest and wealthiest generations, baby-boomers (people born between 1946 and 1964), is entering peak healthcare-spending age. The U.S. also remains one of only two countries, the other being New Zealand, which allow direct-to-consumer pharmaceutical advertising to the tune to about $5 billion annually. Lastly, whether the rest of the world likes it or not, the FDA remains the first court of approval when it comes to drugs. For example, in 2012, the FDA approved 35 novel medicines, 68% of which were first approved in the U.S., and 77% of which were approved during the first review cycle. If a drug is approved by the FDA, it is likely to gain approval in other countries. The reverse is not always the case, as evidenced by Organon's failing to gain FDA approval of Tibilone, an osteoporosis drug, even though it is currently available in more than 90 countries. Obviously, it pays to invest in discovering drugs for the U.S. market. For UCB, it is not just any drug, however. For Doliveux, this means, "focusing on severe diseases where you have better knowledge and expertise than your competitors, and discovering new molecules, rather than working on something with the same mechanism of action already being worked on by five other companies."

INVEST IN SEVERE-DISEASE R&D

Most major pharmaceutical companies invest in R&D anywhere between 12% and 16% of total revenue. For UCB, the amount is typically in excess of 20%. In 2011, the company invested 24% of its revenue into R&D, up from 21.7% in 2007. During the same period, UCB experienced a revenue decline equivalent to just over a half billion dollars. When I asked Doliveux how he was able to convince company stakeholders of the importance of increasing R&D spending as a percent of revenue, he replied, "There is one thing that is 100% certain in our business — patents expire. And that leads to revenue erosion from generics." For example, when UCB's blockbuster drug, Keppra, an anticonvulsant medication used to treat epilepsy, went off patent in the U.S. in Nov. 2008, the impact was immediate and significant. By the end of 2009, Keppra's global sales declined by a little over $465 million.

According to Doliveux, the key to getting out of a decline is having new medicines which can bring you growth. In the past, this may have meant developing a differentiated molecule that would be fourth or fifth in the class. Case in point, when I worked for Organon, we had an anti-depressant, Remeron, which competed against seven branded anti-depressants, five of which had the same mechanism of action – selective serotonin re-uptake inhibitor (SSRI). One of UCB's previous blockbusters, Zyrtec, a non-sedating antihistamine, competed with similar blockbuster drugs, Claritin and Allegra. UCB made the conscientious decision to move away from the "me too" model. "In 2004," he clarifies, "we decided as a company that we wanted to focus on severe diseases of the brain and the immunology system, focusing on

THE VALUE OF SERVING ON MULTIPLE BOARDS

The late Stephen Covey, author of the bestselling book, "7 Habits of Highly Successful People," was a firm believer in self-rejuvenation, which he termed "sharpening the saw." There are many ways to sharpen your saw. One is through service, something which Roch Doliveux believes makes him a better CEO for UCB. "One of the things that helps me as a CEO is being on the board of another publicly traded company," he states. In addition to serving as a member of board of directors for UCB, Doliveux also serves on the board of Stryker (a +$8 billion medical technology and surgical device company). "Being that it is in the U.S., and also in healthcare, though from the medical device perspective, I find serving on the board to be extremely useful. It makes you see things from a different perspective, it shows you different approaches to similar issues, it confirms or challenges some of the ideas you have; all in all it is a good source of stimulus to do a better job as a CEO," he states. "I would clearly advise any CEO to join at least one board of a publicly traded company." Doliveux would further suggest putting a great deal of thought into the company on which you decide to serve, so that there is some synergy between what you currently do, but different enough to provide you with a varied perspective.

Doliveux serves on a number of other boards as well, such as the European Federation of Pharmaceutical Industries and Associations (EFPIA). "Being on the EFPIA is part of the job as CEO — to contribute and shape the public agenda," he says. The UCB CEO also serves as the chairman and board member of the Innovative Medicines Initiative (IMI) which fulfills his passion for furthering his understanding of the scientific and discovery process of academia and the pharmaceutical industry. He is also a member of Vlerick Business School in Belgium and the founder of the Caring Entrepreneurship Fund (King Baudouin Foundation) which aims to support young entrepreneurs in the health care sector. By serving on a number of boards external to his company, Doliveux keeps his UCB CEO "saw" razor sharp.

first, second, or in any case, best-in-class compounds, so as to be truly innovative." However, when it comes to focusing on severe diseases, which typically impact fewer patients, it is going to take more than just one FDA drug approval to make up for the shortfall of losing U.S. patent protection of a blockbuster. For UCB, it took three (Cimzia, Vimpat, and Neupro) for the company to experience "crossover" in 2012 — the point at which sales revenue of these three core products surpassed the declining sales revenue of Keppra. Focusing on severe diseases and the U.S. market has resulted in the following equation for UCB: 3 + 5 = $545,000,000. Three drugs, with five FDA-approved indications, equal $545 million net sales in just nine months in North America.

> *"Compared to Big Biotech and Big Pharma, we are a midsized company, so in order to compete more effectively, we have decided to focus on specific markets."*
>
> Roch Doliveux, CEO, UCB

FOCUS ON PARTNERING FOR THE LONG TERM

When asked to describe UCB's business strategy, Doliveux lists the following three words — *focus, partnering,* and *long term.* "The term *focus* is quite important to the way we think about UCB," he states. "Compared to Big Biotech and Big Pharma, we are a midsized company, so in order to compete more effectively, we have decided to *focus* on specific markets." Namely, this means developed nations, as well as BRIC countries, Central America, Korea, and Turkey.

With regard to partnering, he views this as a great way to enter a market. "If you want to gain time and expand, rather than try to reinvent the wheel, partnering helps you to learn all the ins and outs, including the culture, of a region," he affirms. "Partnering also helps you to quickly acquire the skills you need to compete." UCB's strategic partnering has helped the company to cover nearly 80% of emerging markets and gain entry into developed markets. Doliveux says, "Partnering is a core strategy of UCB. We think

about partnering everywhere from discovery research to manufacturing, to sales marketing, and even finance." For this plan to be successful, you need to think long term, though. For example, Doliveux notes that the company initially partnered with Pfizer back in the 1960s, which proved instrumental to the successful launch of Zyrtec in the 1990s.

UCB has taken the lessons learned in launching drugs in the U.S. to other markets as well. For example, the company first established UCB Japan in 1988. In 2000, the company acquired Fujirebio. Even with this history, when it came time to launch Zyrtec Dry Syrup in Japan, UCB partnered with Daiichi Sankyo and GSK in order to capitalize on their strengths. Under Doliveux's watch, the company took a similar approach in 2010, deciding to partner with Otsuka, best known for the +$4 billion schizophrenia drug, Abilify, to bring E Keppra to the Japanese market. "We picked Otsuka as a partner because it is the #1 CNS company in Japan, and we didn't have the knowledge and expertise to really maximize the impact of Keppra there," he notes.

"There is one thing that is 100% certain in our business — patents expire."

Roch Doliveux, CEO, UCB

Doliveux advises that when deciding to launch a drug in an unfamiliar market, seek partners that have stood the test of time, are number one or two in the market for the indication you are seeking approval, and most importantly, have had consistent success. "In my experience, many companies are very consistent over time," he states. "Find the best partner that will have the biggest impact with the most expertise in the local market." He also advises seeking stable companies which share similar values and ambitions, so as to be aligned on the fundamentals of a project. "When you enter this type of partnership, they are likely very long term," he affirms.

U.S. FOCUS PAYS DIVIDENDS FOR UCB

In Belgium there is a saying — *experience is the father of wisdom,* meaning, the more that happens to you, the more you will learn. UCB has experienced past success from having drugs approved in the United States. Doliveux demonstrates wisdom in continuing to focus UCB on the U.S., as evidenced by the company's successful R&D, FDA approval, and subsequent launch of three drugs in the U.S. — Cimzia, Vimpat, and Neupro. Cimzia received FDA approval for Crohn's's Disease (CD) on April 22, 2008 and Rheumatoid Arthritis (RA) on May 13, 2009. CD falls into the category of irritable bowel syndrome, one of the five most prevalent gastrointestinal disease burdens in the United States, with an overall healthcare cost of more than $1.7 billion. There is no medical cure, and it commonly requires a lifetime of care. About 22% of the U.S. population suffers from arthritis, with two million falling into the category of RA. Consider the fact that Cimzia is presently available in 31 countries. That being said, through nine months of 2012, Cimzia sales were +51%, with 69% of its sales attributable to North America, the bulk of which is obviously the United States.

Vimpat, an anti-epileptic drug, received approval October 29, 2008. And though it is available in 33 countries, UCB's sales figures reveal how much the U.S. patient is benefitting from this drug, to the benefit of UCB, which in my opinion, is quite okay. Because, though it is important to develop drugs to meet an unmet medical need, companies are not doing so as a charity. For the first three quarters of 2012, Vimpat sales were +54%, with 75% of the drug's sales coming from North America. The company is anticipating big things from these two drugs over the next several years, with peak global sales forecast in excess of $1.5 billion each.

Lastly, Neupro, indicated for Parkinson's disease and Restless Leg Syndrome (RLS), received FDA approval on April 3, 2012 and has been available in the U.S. market since July 16, 2012. However, sales for the drug in the U.S. are already more than double those in the rest of the world, excluding sales in the EU. UCB estimates peak global sales of $527 million during the next few years, but I believe that number will be much higher. Here's why. For starters, Parkinson's typically impacts people over the age of 50. Remember, most of the baby boomers are already past that age. Next, consider that approximately 50,000 Americans are newly diagnosed with the disease each year, with more than half a million affected by Parkinson's at any given time. In addition, in the United States the disease is highly visible, thanks in large part to Michael J. Fox and his foundation.

UCB seems to have mastered the art of survival. Established in the 1920s, the company has survived, among other things, two blockbuster patent cliffs. Its approach seems fairly simple — think long-term, strategically partner, and focus on markets such as the United States where you will not only have an impact on people living with disease but also have a positive impact on your company's bottom line.

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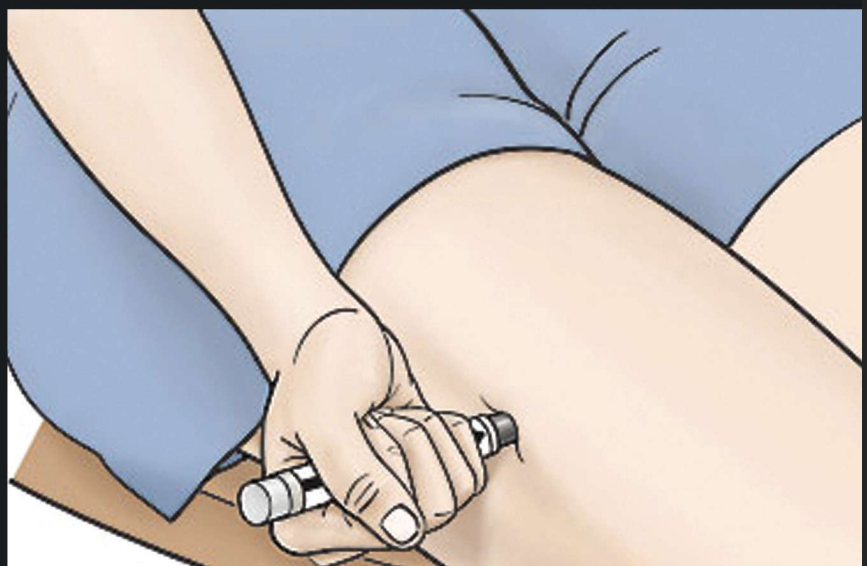


Drug + Device + Best Practice = Development In Parallel

Lessons from Janssen, Allergan, and Boehringer Ingelheim show how successful drug-device development begins at the earliest possible stage.

By Wayne Koberstein,
Contributing Editor

Drug-device combinations generally have two alternative purposes: to enable a new use, indication, or effect; or to extend a product's life cycle. Each alternative brings a particular set of technology choices and influences the timeline in product development. But both demand a level of coordination and planning — starting at the earliest possible point — that companies often cannot or do not achieve. One large pharma company addressing the challenge is Janssen Research & Development, LLC, one of the pharmaceutical companies of Johnson & Johnson, where Douglass Mead, director of regulatory affairs and medical devices and combination products, leads the regulatory strategy for a drug delivery device team dedicated to parallel development of drug-device combination products.

Janssen recruited Mead in 2006 from the device industry to navigate the regulatory pathways for its new auto-injector combined with large molecule drugs such as monoclonal antibodies (mAbs). As combination product regulations evolved, he recognized the full extent of the Janssen portfolio — about 30 drug-device combinations either on the market or in the pipeline. These included everything from prefilled hypodermic syringes and auto-injectors to transdermal patches, as well as kitted devices such as oral syringes and vaginal applicators. In short order, he was working closely with a new drug deliv-

ery group that has grown to about 40 people, consisting equally of medical device and drug delivery/packaging experts, as an operating unit within the company's drug-development program.

"We recognized early on that we needed to devote resources and expand competencies in delivery device technology — its development and regulatory pathways," says Mead. "Patients are prescribed a drug but they rely on a device to administer some of them. We consider this premise now as we design, test, and manufacture the device component of the drug combination products. We also focus on understanding the applicable regulatory requirements for drug-device combinations and how to structure the dossier for submission in the U.S. and the rest of the world. Combination-product regulations are evolving rapidly, but in many countries, regulations lack specificity, giving local authorities more regulatory discretion, which often requires more negotiation."

ORGANIZATION & PROCESS: LINEAR TO PARALLEL

By its very mission — to focus on combination-product development — the Janssen device group breaks from the past, when companies typically delayed thinking about how a new drug therapy might benefit from or even require a device component. Another experienced drug-device developer, Sesha Neervannan, VP of pharmaceutical development at Allergan, describes the industry's shift from the traditional paradigm:

"Most of the time, it has been a pharmaceutical company developing the drug-device combination, with the drug being the primary mode of action, so the company would not think of the device until much later in development; its main concern was whether the drug was safe and effective. But now, in many cases you cannot have a drug without the device and vice versa. So more and more companies are thinking about devices and the delivery approach very early on."

Neervannan says companies are learning this basic lesson in drug-device development: "Don't wait until it's too late, because the drug will have certain properties and those properties can be optimized to a certain device. And if you know them ahead of time, you can develop the drug and device together."

By creating a separate unit for combinations, Janssen implemented parallel development of their drug and device components. Formally, Janssen established two development processes, one for drugs and one for devices, that work in tandem. The ideal approach is to consider the physical characteristics of the drug and the planned device component initially and then bring them into alignment at the right moment for studying the product performance and the pharmacokinetic (PK) comparability questions that may arise — anytime between the first PK study to some part of the Phase 3 program, he says. "You need to plan the timing very carefully for each product."

Formerly at Janssen, when research discovered a molecule, developers began preclinical testing to establish its safety profile and look for efficacy signals to the degree possible, at least with a monoclonal antibody. Then they produced a useable formulation to study the molecule in humans — say, a lyophilized or liquid-in-vial compound. Only later, typically before Phase 3, would they move from the liquid-in-vial to a prefilled-syringe formulation and begin to look at certain issues of usability, such as the influence of silicone on the compound, viscosity, and needle-gauge selection.

Now, says Mead, the team develops two or three formulations for a compound with representative viscosities and physical stability and tests them with delivery devices to assess, very early, any challenges that occur from the combination of the products. "For example, an auto-injector has a fixed spring force, and we want to make sure that the viscosity of the drug is appropriate when used together and working as a delivery system. We can make adjustments to the formulation or change the needle gauge, for example, to optimize combination-product performance before we lock down a formulation for Phase 2 or 3."

PRACTICE-BASED INNOVATION

Besides earlier testing of formulation and device in combination-product development, companies have also focused more attention on predicting how drug-device combinations will work in practice, not just therapeutically but ergonomically. Low-cost, efficient human factor studies with health workers and the intended patient population, using candidate products, now guide much of the innovation in drug-device development.

Janssen has adopted the concept of "design controls" from the device industry — a formal FDA regulation for planning, design, and development of medical devices. "Design controls look at all activities within the development sphere, including design inputs such as user needs and technical requirements, and follow them through design validation — ensuring that the device's intended uses are met," Mead says. "We consider the drug formulation to be a design input to the delivery device, and then we carry that through

THE CROSS-HYPHENATION OF DRUGS & DEVICES

Words are easily hyphenated — unlike the concepts and realities behind them. A case in point is the hyphen-joined phrase "drug-device." It has become common enough parlance that for regulatory purposes the FDA has distinguished four different types of drug-device combination products: drug and device combined into a single entity; separate drug and device packaged together; investigational drug or device and approved product to be sold separately for use together under amended labeling; and investigational drug and device to be sold separately under new, original labeling. (21 CFR 3.2[e]) All combinations must require both components to achieve the intended use, indication, or effect; however, one usually contributes more than the other, creating a further distinction between "drug-device" and "device-drug" products. New compounds and delivery technologies arising from the swarm of small life science enterprises have especially swollen the ranks of products in the first two FDA categories, but also represent a growing portion of the other types as well.

"Every pharma company has some focused effort to look at drug delivery."

Douglass Mead, director of regulatory affairs and medical devices and combination products, Janssen Research & Development

specification, bench testing, and ultimately design validation in trials or human factor studies." The ultimate criterion for a successful drug-device combination is often "ease of use" coupled with a minimum of use errors.

When the Janssen team needed an auto-injector technology, it found no 510(k)-cleared device or platform available that it could marry with its own prefill syringe without extensive customization, so it developed its own auto-injector. In other cases, it has adopted off-the-shelf devices, such as the needle guard installed on every prefill syringe for user protection. "We were able to find a state-of-the-art needle guard from a third-party provider that worked successfully and required no customization, which is the perfect solution."

Neervannan observes that, with sufficient planning and protocol design, delivery concepts can be tested early in clinical development. "We can design a Phase 1 or Phase 2 study, applying innovative but preliminary device or delivery concepts that simulate how a final product might work (such as remote-controlled capsules for site-specific oral delivery). It doesn't require pathology up front but just answers to questions, such as, 'Do we need to deliver the drug in certain parts of the target tissue for best absorption?' Or 'Is the drug efficacious and safe at a level that can be delivered at a maximum dose or delivery rate for intended route of administra-

tion?' We can answer those questions quickly without investing in a full-fledged formulation and manufacturing effort."

Janssen evaluates combinations with small, cost-effective nonclinical studies. Bench testing examines the reliability of delivery and performance attributes such as how hard one must press a button to actuate a device or length of delivery time with a particular drug. Focus groups and other ergonomic experiments test how the product actually works in use with patients — down to how the devices feel in hand and where controls should be placed. Beginning with the prototype, Mead says the team conducts "formative human factor studies" with representative users to make these assessments.

"They might be nurses or patients who've never experienced a particular technology before or who are hand-impaired if we're dealing with a rheumatoid arthritis indication. We will study the performance of the device with patients, along with the proposed instructions for use, to evaluate deficiencies that we would then want to mitigate with design changes to improve the product or choose among alternatives," Mead says.

"Certainly, if you are in a therapeutic area where a device is a must, especially if you're coming in second or third in the market, you better have a device that's at least as good as other marketed devices and generally better, to have some competitive advantage — and for that you must establish the design early, based on patient feedback."

Keith Horspool, VP of pharmaceutical development at Boehringer Ingelheim, echoes Mead's advice. "If you overlook those aspects, it can be very expensive and time-consuming — in some cases, costing you the product. That is another reason for early development: to get patient feedback on how they're using the product, what they like or don't like about it. Otherwise, something that looks technologically exciting to an engineer or a scientist may not necessarily be appealing to a patient, and market adoption may suffer."

Also emphasizing the "critical issue" of packaging, Horspool says, "With many combination products/devices, how the formulation is packaged and presented in the product is very important to the ease of use and acceptance by patients. Another critical factor is understanding and control of materials that come into contact with the formulation during storage and use. Some device technologies can contain materials that are unprecedented and may not be approved for pharmaceutical use, which requires additional investment and effort for regulatory acceptance. Often, the formulation, packaging, and device engineers work separately. But all three need to be developed in concert, and that's an area where I've seen gaps."

WHERE IS THE CUTTING EDGE?

Future drugs may create even more demand for new delivery technologies. Mead, Horspool, and Neervannan expect most future innovation to come from the small labs and companies that have pioneered most device development in the past.

"Academia is very good at creating new drug-delivery technologies at the molecular or formulaton level," says Mead. "But with devices, most innovation comes from small medical device companies, and that's really been true with some of the injector systems, for example. They can make and design unique products. Our role

FORMULATE FOR THE DELIVERY MATE

Two participants in this article — Sesha Neervannan, VP of pharmaceutical development at Allergan, and Keith Horspool, VP of pharmaceutical development at Boehringer Ingelheim — have extensive experience in the drug side of drug-device development. They stress the importance of matching drug characteristics to the chosen delivery device. One or the other, or both, may need to change to make a safe and effective match.

NEERVANNAN: When you develop a new drug for a new therapy, you must determine early whether to give it to patients orally, intranasal, or by injection — each formulation has its own quirks, so drug properties must be optimized. But if you first decide to give orally, then a few years down the road decide on intranasal or through the lungs, you know the original formulation may not be the optimum one, and you have to go back to the drawing board and start all over. That's where a lot of time, money, and opportunities are wasted.

HORSPOOL: Formulation can be even more critical to success than the API. If certain API aspects are suboptimal, in some cases that's not a problem; the formulation can be adjusted quickly to compensate. But when you make poor decisions on the formulation design and have problems with it later on, it can be extremely expensive to correct. Changes to the API and formulation will naturally be more feasible when the device enables a drug action or use because the device aspects have to be addressed early in development. But when the purpose is line extension, it will typically be too late (or very undesirable) for changes to the API because of the need to show equivalence with the original compound, forcing new tests for stability, toxicology, and so on, as well as other steps to optimize the formulation for the device.

More often, it's the other way around — companies tailor the device to the compound. But most developers now understand that particular devices and therapeutic areas demand optimization of certain drug characteristics. With injector systems, the critical issues include viscosity, aggregation, and drug-device compatibility factors such as drug absorption into plastics. With certain routes of delivery such as nasal and respiratory, a pharmaceutical salt that is acceptable orally may not be tolerated by these other modes of administration. Similarly, certain formulation or API aspects that are acceptable for certain modes of delivery and certain devices may be incompatible with other device designs. For example, a more hygroscopic formulation might be challenging to develop for certain inhaler devices where exposure of the product to moisture during storage, or even during use, could adversely affect delivery performance.

is with larger combination-product development, where we utilize technologies developed by other groups or develop our own, working with outside design firms."

Mead no longer considers the Janssen device group an exception among pharma companies; Pfizer, Roche, Amgen, Merck, and others have similar units dedicated to drug-device development. Horspool believes even companies that have no dedicated unit now coordinate their drug and device activities.

"Every pharma company has some focused effort to look at drug delivery, typically a group or several groups constantly evaluating the technology, and some have dedicated functions," Mead says. "But it is a very multidisciplinary type of development, and often pharma just doesn't have the full capabilities needed. So that immediately is a challenge for drug-device development: You need all sorts of extra capabilities and a lot of engineering input, and it is quite different from going to a third party for a device, which takes a lot of negotiation up front."

Allergan uses an "open innovation" model to find solutions for some of its drug-device challenges, according to Neervannan. The company starts with a large anonymous search for people who can solve the problem at hand, people it may otherwise not know about. "They may not be in delivery technology, but in some component of a manufacturing process or even in another industry. They are not in our network. When we find the right people with the technology solution, we take them as a partner and develop the technology through partnership in research."

Mead says pharma companies developing combination products need to adjust to how the world of devices works. "You can expect that devices will constantly evolve, unlike the drug world where you don't want your drug to change very much over its patent life. In the device world, you want it to change, you want to improve it, and you can look at a delivery-device technology now and ask yourself, what are we going to have five years from now? What are we going to have 10 years from now, to improve our product for patients and be competitive?"

Executives in the pharma industry only rarely have a device background. But Mead believes incorporating combination-product leadership into a biopharma company is the first step toward combining the power of two disparate technologies — one stable but flexible, the other dynamic and ever-evolving. The next step is investing in the early development needed to marry the optimum drug formulation with the most complementary delivery device.

BY WAYNE KOBERSTEIN, CONTRIBUTING EDITOR

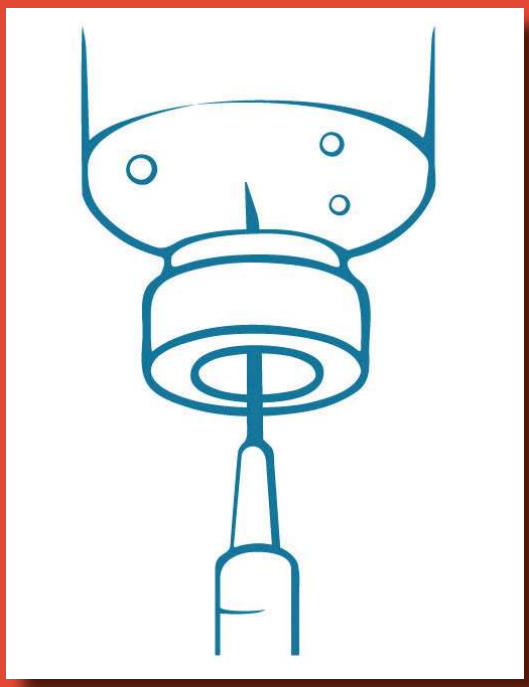
THE RACE IN DIABETES R&D

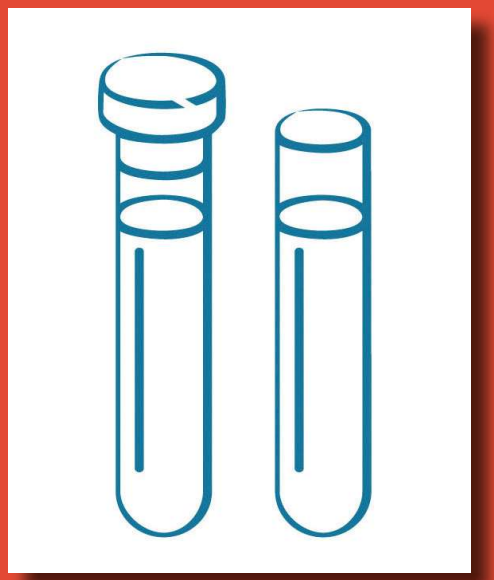
GSK and other drug discovery and development companies are taking new aim on the global diabetes explosion — sometimes alone, sometimes in league together.

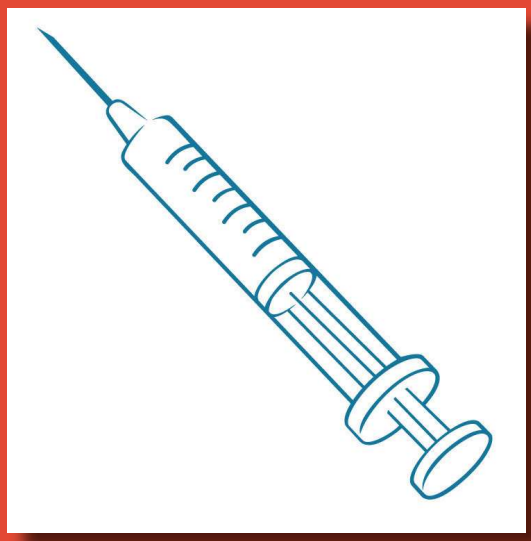
For decades, patients with diet-related (i.e. Type 2) diabetes have relied on drugs that improve insulin sensitivity and actions, such as metformin and the thiazolidinediones (pioglitazone and rosiglitazone). Drugs that stimulate insulin secretion (sulfonylureas) have been in use since the 1950s. But the treatments are far from perfect in safety or efficacy. Type 2 is about nine times more prevalent than Type 1, the autoimmune form of diabetes, for which insulin replacement is still the main therapy.

There are many contenders for the next blockbuster in diabetes, and it is easy to see why — a truly gigantic global market awaits. After efficacy and safety, which will determine the market leader, other products will have to compete on price, and who wants to do that? So, in discovery and development, the race is primarily scientific. Alliances at all scales, between companies far apart or equal in size, as well as academic innovators, will continue to form around diabetes R&D at an accelerating rate.

Here we focus on GSK as a company that can share insights from its long experience, challenges, and new approaches to diabetes prevention and therapy — speaking with Murray Stewart, head of GSK's metabolic pathways therapy area unit.







MARSHALLING METABOLICS

GSK has changed its mode of operations to speed products from discovery through development and on to commercialization, organizing R&D by therapeutic areas, rather than by functions as it was in the past. Heading the metabolic pathways area, Stewart says he oversees the "end-to-end development" of diabetes drugs — from the earliest targeting of disease and drug mechanisms to the marketed product ready for all the regulatory, reimbursement, and other reality-based challenges of the competitive landscape.

"Historically in R&D, there were all these handovers between what the GSK scientists were discovering and what the GSK salespeople were selling. From one end of that continuum to the other, the story — everything the product was intended to address — might have changed completely," says Stewart.

Scientists in diabetes drug discovery are now encouraged to keep a clear picture in mind of the patients who will be at the receiving end of new medicines, including the effects of their condition and how they manage them, specific treatment needs, and the particular elements of drug administration that affect their compliance and response. Such patient visualization is also practiced by all the teams responsible for early development, later clinical trials, and market access. Stewart's unit conducts focus groups out in the field to capture patient experiences with the disease, standard treatments, and new products in development.

GSK's therapeutic area (TA)-based organization is only a few years old, and it precedes further integration of product development on a world scale. In the company's "next evolutionary step," Stewart says a new network of global franchise leaders, each one overseeing commercial strategy of a therapeutic area worldwide, will "partner" with the respective R&D unit leaders. Each TA will then have a global R&D strategy combined with a global commercial strategy.

"This will be particularly important in diabetes, which is growing rapidly around the world, including the Middle East, the Western Pacific region, and Asia. Although our research is driven by the research groups in North Carolina, Philadelphia, and the United Kingdom, our clinical trials are actually global; we conduct them wherever there are significant pockets of diabetes. And with the global franchise leaders, we will be thinking in terms of true global development."

A global strategy in diabetes, however, is not a homogeneous one, says Stewart. Distinct differences exist in how the disease manifests itself in different regions. Type 1 diabetes is genetically more prevalent in Scandinavia. Type 2 diabetes, mostly related to a combination of genetics, family history, and obesity, is on the rise in the Middle East and Indo Asia, where contemporary changes in diet have caused weight gain in traditionally thin people. "When you think globally, you have to take the cultural differences into

FROM DISCOVERY TO DEVELOPMENT – THE FIRST HURDLE

It is important to know that, while the big developers like GSK break down the "buckets" that separate all the discovery and development functions, many smaller companies play a key role by toiling away in discrete cubbyholes to support the total effort. Each one makes a business from doing things a large company sees as only a cost item, operating leanly but with the efficiency that comes with practicing its special talent. One such niche is "*in vivo* modeling," i.e. establishing and using animal models for proof-of-concept and safety studies on early drug development candidates – a niche inhabited by MPI Research.

After speaking with three top scientists at MPI Research – Jim Laveglia, EVP and director of research; Dale Mais, director metabolism and endocrinology; and Thomas Vihtelic, director of experimental therapeutics – I realize how critical it is for drug developers to know whether their development candidate is likely to be safe or cause a positive response in humans, long before they commit precious resources to further drug development in clinical trials. Even after the *in vivo* proof-of-concept testing the lab conducts, a drug has a long way to go in generating the additional preclinical data sufficient to qualify it for further development and be acceptable for regulatory validation. But the early *in vivo* testing can eliminate many weak contenders and thus narrow the field before more expensive pivotal studies begin.

At such an early stage, diabetes drugs are handled much like drugs in any other category. But what is apparent at the *in vivo* testing stage are the changes in drug mechanism and dosage form as new diabetes treatments enter the field. For example, MPI Research has recently worked with glucokinase activators, which stimulate removal of glucose from the blood independent of insulin, as well as the glucagon-like peptide 1 (GLP-1) compounds discussed elsewhere in this article. MPI Research has also witnessed the transition from injectable to oral insulin sensitizers now on the market.

Each new drug mechanism or form may require a different animal model to test it – probably the most significant way diabetes drugs particularly challenge MPI Research. But the basic drill, measuring the common effects of a drug, both positive and negative, still serves most cases well. "In Type 2 diabetes, there are many different animal models: animals with different gene mutations that acquire the disease as they age or if you feed them a high-fat diet. In fact, even normal animals fed a Western diet get obese and develop Type 2 diabetes. Companies come to us to see if their drug, by whatever mechanism, works, and we've dealt with many different types of mechanisms, but it doesn't take many biomarkers to measure the control of glucose or insulin; glucose and insulin suffice in most cases," says Mais.

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account — diet, exercise, genetics, and so on — and that may affect the approaches you take in discovery and development of treatments."

STRATEGIC COURSE OF DIABETES R&D

"In diabetes, we have two main scientific challenges — one, halting the progression of the disease, and two, tackling its complications," Stewart says. The first challenge, halting or even curing diabetes, begins with the earliest signs of metabolic disease. Again, the pathways to the two main types of diabetes are different but related. In both, the problem is that the pancreas stops producing insulin, but in Type 1, the insulin-producing beta cells are destroyed by autoimmunity; in Type 2, the sensitivity of beta cells to insulin is reduced and thus their ability to increase insulin production to needed levels. Consequently, the therapeutic strategies for the two types have been and will continue to be quite different.

For Type 1, Stewart says, "You may ask, why aren't we looking at autoimmune therapies to prevent the destruction of beta cells in the pancreas? But the data published on preventing the destruction has been disappointing, probably for two reasons. One, there are multiple causes for autoimmune destruction, and the industry has tried to focus on single components. Some say successful drugs must tackle the B cells; others, the T cells. But we probably need a combination of therapies. Another reason we struck out trying to preserve beta cells is we were trying too late. For Type 1, by the time you're diagnosed, 90% of the beta cells have been destroyed, and we should probably look at relatives of Type 1 diabetics, the people at risk, and treat them before they *get* diabetes."

Type 2 diabetes presents a more varied and practical therapeutic picture. Like Type 1, the disease rates are higher in some families, suggesting a genetic component; anyone who has a relative with Type 2 stands an 80% chance of getting it eventually, according to Stewart. Being overweight and having high blood pressure also increases risk, but clinical obesity is the largest risk factor of all.

"In discovery in Type 2 diabetes at GSK, we believe that, if we tackle obesity, we will actually be tackling diabetes at the same time," says Stewart. To that end, the company is following a big clue from an entirely different form of medical intervention for obesity, bariatric surgery. "Research shows that bariatric surgery has been very successful in getting people to lose weight — but it's also been very successful in some cases of curing diabetes."

Some obese patients with diabetes not only have lost weight following the surgery but their diabetes has disappeared, with glucose levels returning to normal, all within a few days after the procedure. Scientists theorize a switch or trigger mechanism exists in the surgery that halted the diabetes even before significant weight loss occurred. The trigger may reside in the actual fat cells removed. In the so-called "centralized adiposity," fat cells produce

hormones that, along with stimulating appetite, suppress beta-cell insulin sensitivity and trigger the disease. GSK and other companies have thus opted for a strategy with the catchy but somewhat awkward name, "mimicking bariatric surgery with a pill."

Another key to strategy is likely the body's release of other biochemical factors in the absence of the excised fat cells and their insulin-desensitizing hormones. "One of our discovery units is looking at the polymers and peptides that influence appetite and might help weight loss and improve diabetes. You can't give bariatric surgery to everyone. But if we could prompt the release of the same hormones, chemicals, and peptides the surgery does, we can then start to tackle not only obesity but diabetes."

DEDICATED TO DIABETES R&D – PROFIL PURSUES EXCELLENCE

Profil Institute for Clinical Research is a "center of excellence" in diabetes and obesity drug development, having run pivotal Phase 1 to 2a trials for "every clinically promising drug class and device development in diabetes and in more than 175 clinical studies since the company's inception in 2004." More recently, PICR has launched a new subsidiary, the Profil Institute for Translational Medicine, to codevelop compounds for diabetes and obesity. I spoke with President and CEO Marcus Hompesch about Profil's changing role as it moves into translational medicine with the new subsidiary.

WHAT HAS BEEN THE MAIN FOCUS OF THE PROFIL INSTITUTE SINCE ITS INCEPTION, AND WHY?

HOMPESCH: We do Phase 1 to Phase 2a clinical research – first-in-human studies for proof-of-mechanism and proof-of-concept in diabetes and obesity. That's the focus, and the focus exists because that's what we know best. That's where we have our scientific expertise, that's where we can create value. At the end of that process is the meaningful time to make a "Go/No Go" decision for a compound, which is critically important before committing to a Phase 3 trial, because if you get it wrong, it's a big-dollar failure. We do that as a service to the biopharma industry.

IS ALL OF YOUR WORK ONLY FOR BIOPHARMA COMPANIES?

No. Although the majority of our study sponsors are today's largest pharma companies, we also perform studies for midsize and smaller biopharma, academic institutes, and clinical research organizations that outsource their sponsored metabolic-related studies to us for our specialization in this disease area. We are looked at as a quasi bridge between the clinical research industry and academia, combining distinct academic intellect specific to metabolic diseases with the means to efficiently complete clinical trials.

HOW IS THE NEW SUBSIDIARY (PITM) DIFFERENT FROM THE PARENT CLINICAL RESEARCH ORGANIZATION?

The business model there is to build on the strengths of the parent company – the scientific expertise, disease focus, and technical capability – and apply them to preclinical through early-stage clinical trials for promising compounds that might otherwise languish due to lack of funding or lack of focus. PITM takes in leads that are all out there, but shelved for portfolio reasons or sitting idle at biopharma companies or academic institutions because they require a partner to move the compounds on through development. We will apply our research methods, science, and quality to mature those leads to a point where they are qualified and thus have a higher probability of success, because the data that we are generating is more meaningful and more conclusive. We lower the risk of further investigating the compounds – a significant upside when it comes to a licensing deal with a large pharma company.

WILL THE TRANSLATIONAL MEDICINE INSTITUTE HAVE ANY OWNERSHIP OF THE COMPOUNDS?

In most cases, we would want to structure a deal with the originator where we would not be involved in the negotiating of any deal with a commercial company later on. That would be a potential conflict of interest. So we would most often want to structure our deals in a way that we don't take ownership in a promising compound, but have a very clear and strict agreement about what we will do and what we could expect in return from the owner of the compound. A popular term used for this today is risk-sharing.

WHAT ARE SOME SPECIFIC PROJECTS THAT YOU'RE STARTING WITH, AND HOW WILL YOU OBTAIN MORE?

We have already built a premium pipeline around four specific leads, but we are approached on almost a weekly basis with other codevelopment opportunities. At this point in time, our pipeline includes an intranasal insulin peptide delivery platform and a nontemperature-sensitive insulin injectable, which would be a very relevant product particularly for emerging markets, such as Asia, where a refrigerator is not a common household item; and we have two GPCR (gene protein coupled receptor) compounds that represent a new class of drugs for diabetes. Those leads came to us without us scouting for them. Because of the nature of our business and reputation, we have exposure to many leads, in contrast to the big pharma scouting teams, which are typically rather small. We are also about to open another facility in Orlando, FL, in partnership with Florida Hospital, which will give us access to an interesting portfolio of additional methods for what we want to do in translational medicine. Long term, we want to move from a project-by-project approach to being a systematic hub known for its ability to qualify compounds for drug development.

WHAT ARE SOME OF THE MOST IMPORTANT HURDLES THAT REMAIN FOR COMPANIES IN DEVELOPING DRUGS FOR DIABETES?

The challenge for pharma companies is not the number of compounds from which they have to select, but the ability to narrow down the most promising compounds early in the clinical research process. A lot has changed fairly recently. The industry now performs early trials using first-in-patients studies, meaning clinical trial volunteers have the specific disease or illness for which the drug candidate is meant to treat, as opposed to only "healthy" volunteers, essentially skipping a step in the process of establishing drug efficacy. There have also been advances in technologies that simulate disease physiology, drug action, and patient variability to assist with study design. But the challenge still exists for pharma companies to obtain the best possible conclusive data on their compounds early in the clinical trial process to ensure the therapeutic's most efficient and least costly path.

Currently, the GSK unit has produced some animal data on a number of peptides in various combinations. But out in front of other candidates is "one of the biggest advances in the past five years," glucagon-like peptide 1, or GLP-1. Once food enters the gut, GLP-1 is released into the circulation, and it then goes to the Islets of Langerhans in the pancreas and stimulates the beta cells, one of multiple islet cell types, to produce insulin. In patients with Type 2, GLP-1 levels are low, directly accounting for low insulin production insufficient to maintain normal glucose levels.

With the discovery of GLP-1, companies rushed in with GLP-1 analog drugs to mimic its function, including exenatide (Byetta, Lilly/Amylin) and liraglutide (Victoza, Novo Nordisk) now on the market. GSK's once-weekly albiglutide is in Phase 3 trials, and Sanofi and Lilly have similar products in development. New approaches are already close behind.

"The biggest advances in diabetes therapies have been the introduction of incretin therapies which include the DPPIV (dipeptidyl peptidase 4 inhibitors) combined with GLP-1," Stewart explains. "The DPPIV cause only modest efficacy by stopping degradation of GLP-1, whereas the GLP-1 part gives a supraphysiological increase in insulin, which results in greater reductions in glucose than the DPPIV alone — and also weight loss. Besides GLP-1, there are other peptides such as peptide YY (PYY) that have been associated with weight loss, and therefore one of the future developments in drug discovery is to combine peptides such as GLP-1 with PYY and other peptides to cause even greater weight loss and a reduction of glucose."

"When I evaluate a drug in development, the first thing I say is that it must be 'glucose plus,' that it doesn't cause weight gain, and that it does not raise cholesterol."

Murray Stewart, GSK

DIABETES INNOVATION – BEYOND THE BEACHHEAD

Following the best science is a logical strategy, but never enough to bring a drug to market. Companies must still face the external challenges of regulation, reimbursement, and recognition by patients and physicians that a new drug is worth adopting. Too much is at stake for drugs with only modest benefits to succeed.

"You need plenty of evidence to show your drug works," says Stewart. "It has to do more than glucose control. One of the main complications of diabetes is heart disease; 50% of patients will have heart disease related to diabetes and die from a cardiovascular event, a heart attack or stroke, so the drug has to be beneficial for cardiovascular morbidity and mortality. Now, how can we do that without doing a 20,000-patient study?"

The answer, Stewart says, is hopefully to start in discovery looking at risk factors for heart attacks and stroke. "When I evaluate a drug in development, the first thing I say is that it must be 'glucose plus,' that it doesn't cause weight gain, and that it does not raise cholesterol. And if anything, we want to see an improvement in those parameters, and if we do, we will invest heavily in development, as we did with albiglutide, our long-acting GLP-1 inhibitor."

For Type 1 diabetes, the main advances will continue to be new forms of insulin replacement. But for both Type 1 and Type 2, more sophisticated approaches are on the horizon that may come close to the holy grail — curing the disease completely. The top contenders, Stewart agrees, are beta-cell transplant and/or rejuvenation. Some recently published studies suggest that beta cells lost to diabetics are not actually dead but only "dedifferentiated" into more stem cell-like states. If that is true, it might be possible to "redifferentiate" such cells back into working beta cells. But Stewart advises caution.

"We might be able to shake up the beta cells and stop the destruction or, if they're quiescent, revive them. That is worth looking at, but I'm not hopeful. I am more hopeful of finding a way to grow the cells or give patients a fresh supply. So I do like the stem cell approach." Obtaining human beta cells, or islets, is quite difficult, and performing the transplantation surgery requires immunosuppression, he says. "The exciting thing is that if you take islets and you give them to someone who doesn't have any functioning islets, providing you have the right environment, you can make some Type 1 diabetics insulin-independent."

Stem cell therapy may be an even better option than transplant in 5 to 10 years, Stewart believes. In theory, the stem cells would differentiate into islet cells, so that Type 1 patients could grow their own islet cells in the pancreas and be free from insulin injections.

If the field were to go in the direction of stem cells, GSK would still be involved. "We've got a discovery group, we've got a clinical group, and I spend quite a bit of my time looking at business development opportunities because I think the future is partnership. So GSK is willing to partner with smaller companies, and perhaps with larger companies, to find the answers to diabetes, wherever the search leads us."

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Are Suppliers Ready For Quality By Design, Or Should They Be?

By Wayne Koberstein, contributing editor

Quality by design, oh my … is it salvation or mere vexation for manufacturing and other suppliers to pharma and biotech companies — or something else entirely?

I came out of a USP (United States Pharmacopeial Convention) meeting last October with the strong impression that QbD was surging across the globe as the ultimate solution in risk management for the bio/pharma supply chain. Now I'm not so sure. Despite declarations, conventions, and even extensive guidelines from regulators who want to see it happen, QbD is not quite the tidal wave I first envisioned. The innate conservatism of Big Pharma and the persistence of Byzantine regulatory disincentives are two key reasons; another, the lack of a clear payoff for smaller companies. Because it largely comes down to a product-by-product decision, the case for more universal adoption of QbD over conventional QA remains at least equivocal.

For large companies, the QbD proposition is naturally scary. It would bring an unprecedented transparency to their relationship with regulators, essentially "opening the books" on production even in clinical development. For some companies and compounds, the shared openness could offer advantages, such as collaborating with regulators for smoother process selection. But for most companies — where clinical trials are notoriously messy with false starts, discarded protocols, less than perfect data, and so on — such transparency has little or no appeal.

Still, I believe new regulatory pressures for change will eventually prevail, and QbD will become a core capability for companies and their suppliers. In that case, it will profoundly affect most if not all players in every conceivable aspect of drug manufacturing, from the bench — where molecules are first characterized — to end product, packaging, and distribution — where QbD covers stability. QbD is not a tsunami but a rising tide, yet one strong enough to sink some boats as it raises others.

Are CMOs and all the others potentially affected ready for that tide? Or should they even want to be? QbD will likely become ubiquitous, but not universal. Many well-characterized molecules may be produced with no more than the time-honored methods used in legacy systems. Lower-cost QA and risk-management options must remain available to smaller companies with limited budgets. But those are the exceptions that prove the rule. For most companies and their suppliers, investment in QbD will be an unavoidable necessity.

WHAT IS QbD, REALLY?

QbD is not just about producing a consistently high-quality product or avoiding regulatory oversight — it is about having systems in place supported by data that can assure regulators (or clients) that you will consistently produce high-quality product. That assurance may allow you to forego some reporting requirements or to make you more competitive, but not to escape end-product testing for purity, strength, and stability.

Quality standards are not static; they evolve as science and technology advance, mainly with new drug products, but also with new approaches to older drugs. Qualities such as aggregation, concentration, and potency continuously increase in importance along with the flow of advancements in pharmacokinetics, physiology, and precision measurement. For many new products, especially in biotech, new standards may become increasingly unreachable by the old methods.

QbD is not an all-or-nothing option. It consists of countless possible configurations of innumerable parts and processes, many of which are still in development. Depending on client demand, a supplier might implement a QbD system partially or incrementally, from the simplest in-line tests to a complex "design space" for an entire robotically controlled production line. The industry is abuzz with new production models to measure and control critical quality attributes (CQAs), using tests and testing procedures at multiple stations along the process flow. Such models, used widely in other industries, could boost output quality, and thus efficiency, in state-of-the-art processing. Manufacturers also shared their experience with applying analytic techniques to entire processing systems. It seems, at least at this point, that every QbD system is unique, the sum product of product

attributes, manufacturing standards, and negotiation with regulators. Some experts see increasing standardization or indefinite customization in QbD's future. But here's one thing all the experts agree on — the pharmaceutical industry has heretofore always steered clear of the quality-improvement stream, resisting all moves to update its QA management tools. The most important benefit of QbD might be to force the industry off its collective behind to make improvements it could otherwise never bring itself to make.

Suppliers such as CMOs are meanwhile stuck with a hard choice: whether to stay with the old ways or help lead the way to QbD. If seen only as a decision about technology — whether to invest in new equipment and instrumentation as a new industry standard — adoption of QbD among suppliers will likely be slow. But there is another way to look at the choice: no change versus the chance to gain a competitive advantage in risk management and quality output. There is no need to sell clients a QbD "package" — your design space or process technology. What counts is the confidence in your ability to meet product specifications based on proof of consistent results. In short, QbD could enable suppliers to give their clients the same assurance of quality that regulators need and ever more frequently demand.

If you're not ready to take the plunge into QbD just yet, you should at least do some homework to learn the basics of what it is you're postponing. The International Committee on Harmonization (ICH) offers some great background documents or Guidelines on Quality Risk Management (QRM) that include Guidelines Q9, Q10, and Q11, all dedicated to the essentials of QbD:

- Guideline Q9 looks at the principles of QRM including risk assessment, control communication, and review, as well as risk management tools such as failure mode, effects, and criticality analysis and fault tree analysis, and potential QRM applications at key stages in the supply chain.
- Guideline Q10 applies QRM principles to pharmaceutical quality systems, from creating a product profile to methods of testing the compound against its profile for safety and quality. It examines models for continuous improvement of systems, processes, and product quality over time, including QbD.
- Guideline Q11 takes QRM into preclinical and clinical drug development and manufacturing, covering production of raw materials, steps to manage impurities, meet GMP standards, and so on — again, including the use of QbD approaches throughout the production line.

Special thanks to Tony Stefano at the USP for his extensive input and ideas reflected in this article.

One Solution For Managing Pharma Supply Chain Risk

By Pedram Alaedini and Birnur Özbaş, Ph.D.

In most industries, changes to manufacturing processes or delivery modes are usually internal decisions that can be easily and quickly implemented. However, our industry is highly regulated, and any modifications that could potentially affect product safety or efficacy require expensive and lengthy qualifications and validations in addition to meeting rigorous and lengthy regulatory and approval processes.

Risk management is one way to help safeguard the quality and supply of product to customers and ultimately the end user. It helps anticipate dangers and control risk through an ongoing process of risk awareness, reduction or acceptance, and review. It also helps justify improvement and investment where needed and prevents both potential problems for customers and loss of business.

As part of a risk management approach, a simulation model for supply chain management can be utilized where it is too expensive or risky to do live tests. Simulation provides a relatively inexpensive, risk-free way to test changes ranging from a simple revision to an existing production line or redesign of an entire supply chain.

WHAT IS SIMULATION MODELING?

Simulation is a tool for managing and accelerating change which provides more than an answer: It shows how the answer was derived and allows you to generate explanations for decisions.

A simulation model is a mathematical representation of a system or process that includes key inputs which affect it and the corresponding outputs that are affected by it. For example, a model can calculate the impact of uncertain inputs and decisions one makes on outcomes that are deemed important, such as manufacturing costs, quality matrices, investment returns, and inventory or safety stock levels. A simulation model includes inputs which are changed by the user and a set of relationships between elements of the modeled system in addition to the model outputs that summarize the behavior of the system for different inputs.

Simulation modeling can be utilized in many areas of the life sciences supply chain to measure and improve outcomes. These include reducing manufacturing costs, product portfolio analysis, network modeling, quality and compliance level measurement and improvement, facility and process design, and customer satisfaction levels. It also helps to analyze and identify poorly performing links in the chain by comparing them to best practices.

A PHARMA CASE STUDY

A midsize pharmaceutical company with one manufacturing facility in the U.S. expects approval of its new drug — a tablet — in about 12 months. Marketing projections for this product are one million tablets per month, equal to 1,000 kg of bulk finished product.

To prepare for the new product launch, the supply chain group decided to take a systematic approach to determine the required systems, personnel, and procedures to ensure successful launch and uninterrupted supply of product to market. As part of the exercise, the team assigned one of its existing production lines in addition to dedicated manufacturing and quality control personnel exclusively to this new product. The team's overall objectives were:

- ensure no product backorder for longer than seven days at any time;
- keep cost of goods and inventories at the lowest possible level without jeopardizing product supply or quality.

To achieve these objectives, a discrete event simulation model is developed to gain an understanding of the supply chain processes. To simplify the model, the team limited the supply chain to only include the manufacturing line, quality control and assurance, warehouse, order processing, and the three main raw material vendors.

The model involves several parameters that allow the user to test a variety of risky or resource-intensive scenarios. These parameters include product demand, production and inventory plans, lead times, analytical testing durations, inventory levels, and production times. As an example, as part of this simulation exercise the validated batch size is changed in the model, and its effect on the entire system/performance measures was observed. In addition, the inventory policy was modified in different ways, and its effect on required production rate and budget were analyzed. Obviously in real life, such modifications would require significant investments and, in many instances, lengthy regulatory approval processes.

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Upon completion of the model, the simulation is run 25 times, each representing the same one-year period. Replication of the simulation provides a complete statistical description of the model variables since there are many uncertain parameters in the model. In other words, it represents a good sample of all possible events that may occur. The results are obtained through averaging the results of 25 replications. Thus, the simulation model provides not just an average value, but also 95% confidence interval and minimum and maximum values.

SUPPLY CHAIN BACKLOGS

The model showed that the current supply chain policy would result in an average of 16 backlogs with 12 of them lasting longer than seven days. On the manufacturing side, production was disrupted 39 times on average because existing raw material inventory did not meet the requirements. The average finished product inventory was 450 kg throughout the year with $12,620 in holding costs. Similarly the average raw material inventory was 439 kg, 198 kg, and 69 kg for API, and two different excipients respectively with the total inventory holding cost of $22,375 over a one-year period.

Statistics also showed at least one QC test failed for a total of 140 kg of the finished product, 20 kg of excipient 1 and 196 kg of excipient 2, but never for API over an average one-year period in this particular simulation. During this simulation exercise, the company produced 40 batches of the new product at the cost of $4,814,400 and shipped 48 shipments resulting in $18,135,000 in transfer pricing gains. It is important to note that in this model manufacturing batch sizes and lot shipments are of different size, and the simulation started with 750 kg of initial inventory.

As seen, base case results show that the initial plan would not meet the supply chain objectives. The product backlog is quite high, and the production plan is often disrupted by raw material scarcity.

The team assigned to this project decided to determine and present several possible scenarios where the objectives of the assignment could be fulfilled. The following scenarios were chosen as the ones to control supply and cost of product in addition to inventory levels of both raw material and finished product.

Scenario 1: Production duration is shortened to 4±1 days instead of 5±1 days. As a result, production cost is decreased to $106,000. Although this scenario required overtime payment to operators, the indirect costs were accrued over a shorter time period, hence reducing the total cost.

Scenario 2: Changing the production plan and producing in batches of 600 kg every two weeks instead of the original weekly 300 kg batches. This can be achieved by validating a larger batch size, placing products on stability studies, and filing a supplement with the regulatory agencies. In this scenario, production cost increased to $150,000 per batch.

Scenario 3: In the base case, the average excipients 1 and 2 inventory levels seemed too low compared with production requirements. Therefore through negotiations with the vendors, delivery lead times for excipients were reduced from 1.5±0.5 months to 30 to 45 days.

This scenario analysis showed that shortening of the production time (scenario 1) with other things the same — *ceteris paribus* — is not useful since production is disrupted resulting in a back-order situation, again primarily due to the shortage of raw material. However, in this scenario, production costs are considerably reduced.

In scenario 2, although changing the production plan decreases production disruption by 57% and production cost is decreased by 38%, the backlog problem still persists.

Scenario 3 shows that the most significant bottleneck in the system is raw material availability, especially of excipients. When the upper limit of lead time is decreased by 15 days, backlog of more than 7 days completely disappears and less than 7-day backlogs are rarely observed, hence overall total production disruption is decreased by 46%. Although in this scenario the average inventory level for finished product and the excipients in addition to inventory holding costs increase, this is compensated by the increase in total earnings.

This case study presents only three distinct scenarios. In a real simulation analysis, many scenarios and combinations of them are usually run to achieve better results.

SIMULATION MODELS ARE THE FUTURE

Life sciences supply chain management is a complex and risky process because of the level of uncertainty at its multitude of stages. Historically, high operating margins in the life sciences industry have supported a "better-safe-than-sorry" approach to supply chain activities and, in particular, production and inventory planning. And many companies knowingly overstock excessively to avoid back-order situations. However, now there are significant pressures to reduce working capital without disrupting high service levels or risking compliance issues. In addition, there is intense pressure to reduce costs and improve efficiencies in the fiercely competitive life sciences industry.

Computer simulation, since it can be applied to operational problems that are too complex or difficult to model and solve analytically, is an especially effective tool to help analyze supply chain and logistical issues and help control and improve the systems.

For more info on simulation modeling, see the video at http://youtube/WxIZ57nxNig.

About the Authors

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The Intersection Of Business Decisions With Quality Risks

Effective business strategies accurately weigh opportunity against risk. Life sciences companies, in particular, often overlook a key factor that can easily unbalance the opportunity/risk balance: How will bottom-line business decisions affect product quality?

More than one CEO, confident in the company's compliance policies and practices, has been blindsided by a product recall, safety alert, or curt warning letter from the FDA citing quality failures. A common denominator among these organizations is a narrow focus on compliance rather than a broad emphasis on quality. Compliance and quality are not synonymous, a point vigorously promoted by the FDA in its "Case for Quality" initiative, which calls for companies to adopt a view of compliance as one part of achieving overall quality rather than the ultimate goal. To do that, companies need to recognize the interrelationship of product quality and business decisions — and then take practical steps to address the potential risks created by the intersection of the two.

RISKY BUSINESS

Strategic business decisions — mergers, acquisitions, market expansion, outsourcing, cost-cutting, corporate restructuring — are all developed under the gun of a pitching global economy, regulatory twists and turns, legal and illegal competition, and social upheaval. The opportunity/risk balance is identified and analyzed by teams of experts in a variety of departments/areas. Yet, even though the success of any decision is inescapably tied to the quality of its products, the Quality Department is often missing from this roundtable of experts, called in only after the decision has been made. Tearing down the silo that separates "quality" from "business" is the first clear step in achieving the FDA's goal of a quality-based viewpoint. The second step is factoring the potential that quality impacts into the decision itself.

Product quality can be affected by virtually any business decision, but consider the potential impacts created by just three:

- Mergers and Acquisitions: Investigations of quality-based risks are often guided by past events such as product recalls, warning letters, safety alerts, or patient litigation. Instead of looking backward, quality questions must focus forward. Are there adequate resources committed to integrating the two organizations? Is there adequate manufacturing capacity for new product lines? Will additional production lines introduce potential contamination, climate control, sterility, or handling requirements? Will consolidated supply chains add single-source risks?
- Cost Cutting: Quality issues are attached to virtually all cost-cutting proposals. If one plant is closed, can production be moved to another plant without major structural, environmental, or operational changes to the facility? Will a shift of production require new, potentially unfamiliar suppliers for transportation and warehousing? Will quality be a priority, and will there be adequate resources despite cost-cutting measures?
- Headcount Changes: Major layoffs have been blamed for quality failures, often because of shrinking quality assurance resources and fewer trained employees, but a rapid increase may also signal concern. Whether or not the new employees are adequately trained is the obvious issue, but a rapid increase may also suggest a too-quick expansion of production or products. Is production increasing more rapidly than new employees can be integrated into the system?

Ellen Leinfuss

Ellen Leinfuss serves as SVP, Life Sciences, at UL. She is responsible for the company's worldwide life sciences strategies, alliances, thought leadership, and program development.

ECONOMICS OF QUALITY

Historically, medical product quality has been assumed if compliance is maintained. Companies can no longer afford that assumption. In its "Understanding Barriers to Medical Device Quality," the FDA pointed out, "The costs of negative quality events have risen due to increasing regulatory, legal, and media attention." Supporting that point, the study provides data that shows an average drop of 16.8% in company share prices due to quality issues. While the FDA report refers specifically to medical devices, the same risks and relative costs could apply across the life sciences industry.

The FDA's "Case for Quality" picks up where "Understanding Barriers" left off. So far, the initiative simply illustrates the FDA's plan to encourage more quality-centered thinking in the life sciences industry. With product recalls and questions of quality rattling patients, prescribers, and payers, the industry has good reason to embrace a strong quality-based perspective toward its operations.

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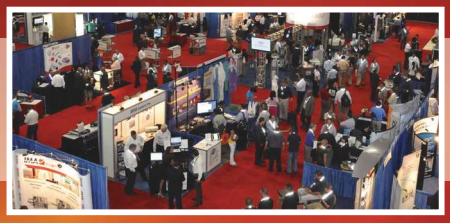

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How A U.S./Japan Partnership Provides Pharma Potential

Over the past decade, U.S. pharmaceutical companies have expressed a steadily rising interest in partnering with pharma companies headquartered in Japan, now the second-largest pharmaceutical market in the world. That's because virtually all of the major pharma companies are watching their revenues decrease because of weak pipelines, patent expiries, and the rise of generics. Japanese companies, which are experiencing these forces more severely than most, are now also more actively seeking alliances with partners in foreign countries.

In a January 2012 interview with The National Bureau of Asian Research, B.T. Slingby, who is the director of global partner solutions at Eisai, noted an "interesting trend" in Japan pharma at this time: proactive globalization, in which Japanese companies are actively examining how they can open up and expand into other markets. He added, "To move forward means ... new business models — organic growth. New business models have to be integrated, they have to be innovative, they have to look at volume instead of profit margin, they have to address the unique needs of the healthcare system as a whole, and they have to look at how patients in each country access healthcare and medicines." Thus a golden opportunity seems to be apparent for U.S. pharma companies that are interested in partnerships.

INSIGHTS FOR SMALL/MIDSIZE PHARMA COMPANIES

Considering that the bulk of headlines to date regarding partnerships between the U.S. and Japan have involved Big Pharma, executives at smaller-to-midsize pharma companies in the U.S. might be wondering about their own chances for success. If so, consider the following pieces of advice:

1. Fostering a sense of trust between your company and your prospective partner is by far the most crucial element in determining the overall success of the partnership — even more so than the exact financial details involved. Trust is the key to any long-term relationship, especially in one that involves shepherding a new drug through a successful marketing campaign.

2. If you do not already have one, set up a company representative in Japan who is tasked with evaluating compounds currently under development within the country.

3. Instead of focusing solely on drug development at the largest drug companies in Japan, it is important to play close attention to smaller companies, which are just as involved with the next wave of innovative drugs as are their larger counterparts.

4. If you choose to become a publicly traded company in Japan, be mindful of the differences in the way that the market operates in that country as compared to the U.S.

Yuichi Iwaki, M.D., Ph.D.

Yuichi Iwaki, M.D., Ph.D. is founder, president and CEO of MediciNova, Inc., a biopharmaceutical company founded upon acquiring and developing novel, small-molecule therapeutics for the treatment of diseases with unmet need.

5. Consider attending the monthly meetings in Tokyo of the Japan Pharmaceutical Licensing Association, which addresses topics relevant to the industry.

It is tough to tell what the future will hold. However, competition within the pharma industry for new sources of revenue is slated to increase and may serve as a greater incentive for U.S./Japan partnerships among even smaller companies. A "snowball effect" might even occur as insights regarding such partnerships, and the challenges they present, become better defined and better known throughout the industry.

There are considerable rewards for U.S. pharma companies, both large and small, that wish to partner with pharma companies in Japan. Success, however, will depend on many factors, including a clear understanding of how the Japanese pharma industry operates, an ability to navigate the Japanese markets (if you opt to list your company on a Japanese exchange), and the ability to gain the long-term confidence of your new partners. The future belongs to the bold.

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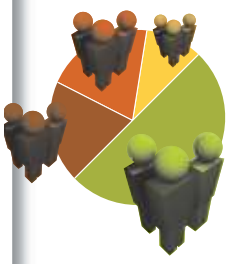

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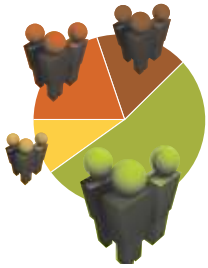

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7 Steps To Becoming — *And Staying* — Relevant

By Kare Anderson

Apart from honing their top talent, guess what Atul Gawande and Richard Branson have in common? They have two vital and intertwined traits in this increasingly complex world where we are drowning in information. They've sharpened their ability to be quotable and to be deeply connected to notable people in worlds apart from the one in which they work. In so doing, they are likely to see trends early and be considered thought leaders on a broader stage, thus being able to attract more opportunities and secure support. Namely, it keeps them sought-after.

Here are seven specific behaviors that are vital if you want to stay relevant and become sought-after, especially for those of you who are involved in science in which both innovation and regulation are speeding up:

1. Become a connective listener

Be genuinely curious by asking follow-up questions that relate to what a person just said, rather than what interests you. Keeping the focus on the other person enables you to get closer to their underlying interests, better remember what they said, and be able to discuss the world their way.

2. Make your message almost as vital as oxygen

Label yourself before someone else does. Some topics are widely discussed in first conversations, such as what you do or what you most care about. Give A.I.R. to those messages by including three elements: Make them Actionable, involve an element of Interestingness, and be Relevant.

3. Seek out the most left-out person in the situation

When in a lively gathering, pull in the most overlooked person and thus alter the dynamic of the conversation and earn an ally. Plus it will feel good.

4. Look to another's positive intent, especially when they appear to have none

When you act as if the other person means well, you are likely to turn around potentially divisive situations and sidestep conflicts, and sometimes even turn potential critics into unexpected friends.

5. Speak soon to the strongest sweet spot of mutual benefit or interest

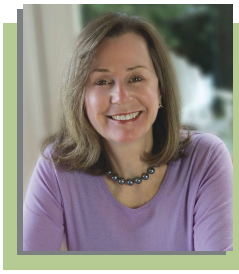
Start deeper and you may be surprised by the desire others have for meaningful conversation.

6. Cultivate Unexpected Allies

It pays to seek out individuals who are vastly different from you in temperament, life experience, and perhaps even values. Out of these meetings you may find the right ally to co-create a new product or organization, enter a new market, or to simply cross-consult.

7. Praise individuals in front of those who most matter to them

Specifically, vividly describe the admirable thing someone did when you are around their most valued colleagues or friends, either face-to-face or by sending a descriptive note or email to them, copying others. Do it soon while the event is fresh in your mind and before the opportunity slips away.



Kare Anderson is an Emmy-winning former NBC and *Wall Street Journal* journalist, and "Connected and Quotable" *Forbes* columnist and author of *Moving From Me to We*. She is now a professional speaker and consultant with clients as diverse as Novartis, Google, and the San Diego Padres.

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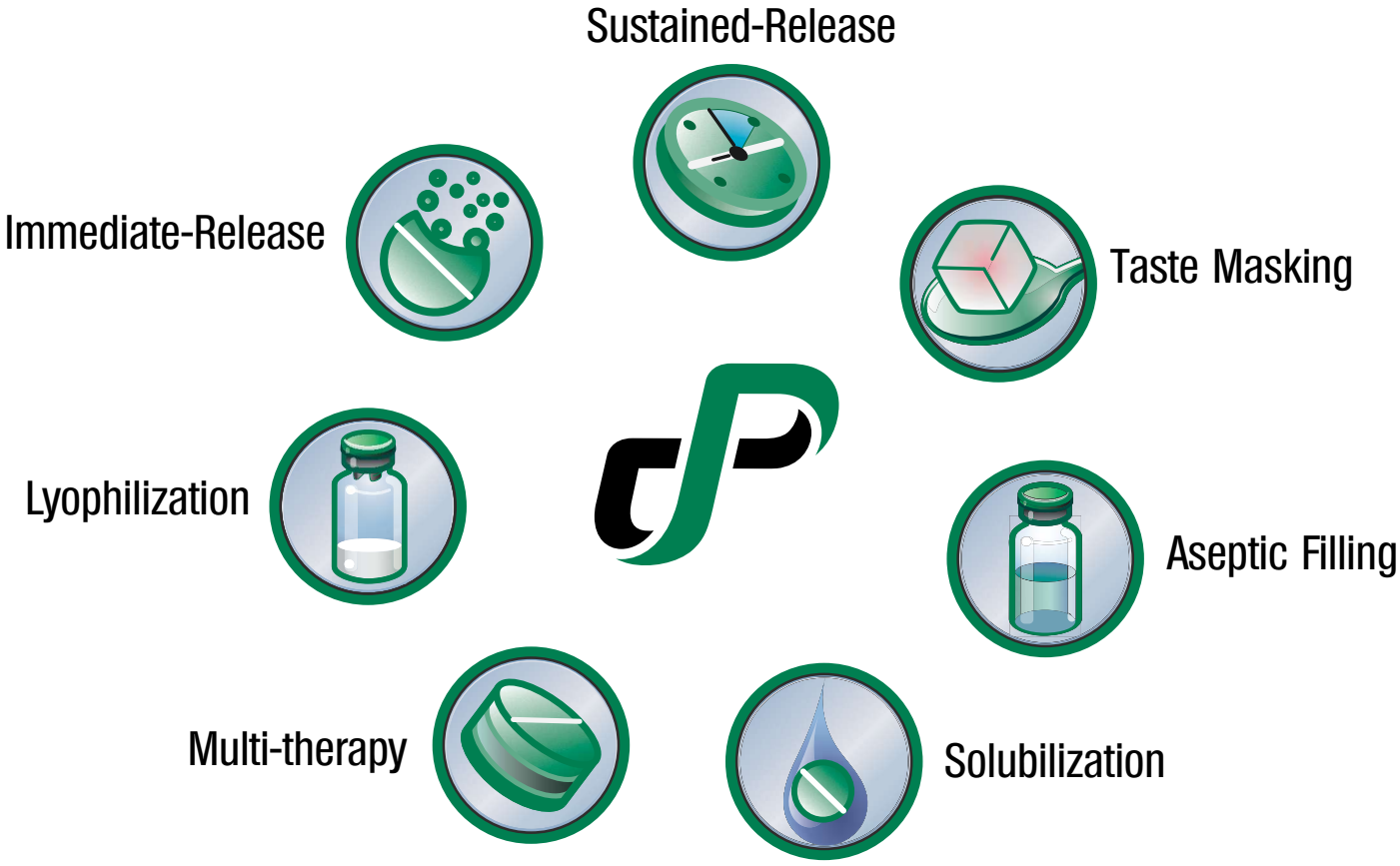

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