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December 2012
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20 FEATURE: MERCK

"We don't serve by creating technology. Merck doesn't sell technology. We sell product, and if our technology doesn't make product better, then it's not good technology," says Jim Robinson, VP of vaccine product & technical operations at Merck.

December 2012

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EDITORIAL DIRECTOR: Dan Schell
(814) 897-9000, Ext. 284
dan.schell@lifescienceleader.com

CHIEF EDITOR: Rob Wright
(814) 897-9000, Ext. 140
rob.wright@lifescienceconnect.com

VP OF PUBLISHING: Jon Howland
(814) 897-9000, Ext. 203
jon.howland@lifescienceleader.com

ASSOC. PUBLISHER/BIOPHARM & LAB: Shannon Primavere
(814) 897-7700, Ext. 279
shannon.primavere@lifescienceleader.com

PUBLISHER/CONT. MFG. & INGREDIENTS: Cory Coleman
(814) 897-7700, Ext. 108
cory.coleman@lifescienceleader.com

GROUP PUBLISHER/OUTSOURCING: Ray Sherman
(814) 897-7700, Ext. 335
ray.sherman@lifescienceleader.com

BUSINESS DEV. MGR.: Mike Barbalaci
(814) 897-7700, Ext. 218
mike.barbalaci@lifescienceleader.com

SR. ACCOUNT EXECUTIVE: Scott Moren
(814) 897-7700, Ext. 118
scott.moren@lifescienceleader.com

ACCOUNT EXECUTIVE: Tim Bretz
(724) 940-7557, Ext. 123
tim.bretz@lifescienceleader.com

ACCOUNT EXECUTIVE: Becky Brown
(724) 940-7557, Ext. 164
becky.brown@lifescienceleader.com

ACCOUNT EXECUTIVE: Bill Buesink
(814) 897-7700, Ext. 119
bill.buesink@lifescienceleader.com

ACCOUNT EXECUTIVE: Sean Hoffman
(724) 940-7557, Ext. 165
sean.hoffman@lifescienceleader.com

ACCOUNT EXECUTIVE: David Ruler
(814) 897-7700, Ext. 157
david.ruler@lifescienceleader.com

PRODUCTION DIRECTOR: Lynn Netkowicz
(814) 897-9000, Ext. 205
lynn.netkowicz@jamesonpublishing.com

DIRECTOR OF AUDIENCE DEV.: Mindy Fadden
(814) 897-9000, Ext. 208
mindy.fadden@jamesonpublishing.com

Life Science Leader
2591 Wexford-Bayne Rd. Bldg. II, Level 3, Ste. 305
Sewickley, PA 15143-8676
Telephone: (724) 940-7557 ● Fax: (724) 940-4035

LIFE SCIENCE LEADER (ISSN: 21610800) Vol. 4, No. 12 is published monthly by VertMarkets at Knowledge Park, 5340 Fryling Road, Suite 300, Erie, PA 16510-4672. Phone (814) 897-9000, Fax (814) 899-5580. Periodical postage paid at Erie, PA 16510 and additional mailing offices. Print PP. Printed in the USA.
SUBSCRIPTION RATES for qualified readers in the U.S. $0. For non-qualified readers in the US and all other countries $97 for one year. If your mailing address is outside the US or Canada, you can receive the magazine digitally if you provide a valid email address. POSTMASTER: Send address corrections (Form 3579) to Life Science Leader, Knowledge Park, 5340 Fryling Road, Suite 300, Erie, PA 16510-4672.

EDITOR'S NOTE

What's Wrong With Big Pharma?

At this year's CPhI (Convention on Pharmaceutical Ingredients) worldwide event, I sat down with CARBOGEN AMCIS' CEO, Mark Griffiths. When I asked him to share what he sees as some of the challenges currently facing the industry, he gave me an earful. For example, he told me that in the last 18 months he spent significant resources on procedural matters, such as filling out questionnaires. Mind you, these questionnaires are from companies which CARBOGEN AMCIS has worked with for years. For one company, he completed two separate questionnaires which were asking for the same thing. When he pointed this out to the company's representative, he was told that they needed to have it in this particular format. I understand the need and benefits to standardization; frequently I have argued in favor of it for single-use technologies. However, perhaps companies should get their ducks in a row prior to having their supposed strategic partners' waste time duplicating work.

Another issue Griffiths mentioned involves competing merely on price. He says his company works on a number of very complex projects, and he often faces the challenge of explaining to price-conscious customers that quality comes with a price. He has sat in front of customers who told him he was too expensive and that, as a result, they were opting to take their business elsewhere. But then, maybe six months later, these same companies would return, because the competitor that had the lowest price failed to deliver.

During the past 10 years, CARBOGEN AMCIS has responded to the changes in the marketplace by diversifying its customer base and embracing small biopharma companies in addition to big pharma clients. Griffiths sees these smaller companies as not only being faster and more aggressive, but also more willing to strategically partner. Since they don't have the bandwidth of their larger counterparts, they need more support — that is where strategic partnering comes in.

Griffiths stressed that now it is more important than ever to build relationships with a variety of functions within big pharma companies in order to achieve strategic partnerships, acknowledging that decision making has shifted from technical and scientific people to folks with a purchasing orientation (i.e. driven by cost). A more streamlined process for sharing information and a commitment to dialogue can go a long way in building mutually beneficial partnerships.

Having worked in both big and small pharma, I can certainly empathize with Griffiths' opinions and insights. However, big pharma is getting plenty of things right. Just look at some of the past articles I have written on Pfizer, Lilly, Genzyme, or even this month's feature on Merck's Jim Robinson, VP of product and technical operations. Not only did Robinson educate me about process intimacy — see page 20, he also enlightened me on accountability via John Miller's book, *The Question Behind The Question — QBQ*.

Rob Wright
rob.wright@lifescienceconnect.com
@RFWrightLSL

WAYNE KOBERSTEIN

Wayne Koberstein is the former editor in chief of *Pharmaceutical Executive* magazine and was the founding editor in chief of *BioExecutive International magazine*. He is a 25-year veteran of the publishing industry, with extensive experience in publishing, communications, and business development. During his business journalism career, mainly focused on the pharmaceutical and biotechnology industries, he interviewed and profiled more than 200 top executives in pharmaceutical companies, as well as major regulatory and healthcare leaders around the world.

CATHY YARBROUGH

For over 25 years, Cathy Yarbrough has written about biomedical research and medical care as a journalist for *The Atlanta Constitution*, *Kidney News*, and *DocGuide* and as a communications strategist for Rockefeller University, Singapore's Biopolis and Fusionopolis, the American Society for Cell Biology, and other leading research organizations. She is a member of the National Association of Science Writers.

CLIFF MINTZ, Ph.D.

Cliff Mintz, Ph.D., is a regular contributor to *LSL*. He has degrees in microbiology and bacteriology and 15 years of experience as a life science freelance writer with a focus on topics such as regulatory affairs, bioscience career development, and social media.

CINDY DUBIN

Cindy Dubin has been reporting on the pharmaceutical industry since 2003, with a particular focus on executive decision making regarding formulation, delivery, development, and commercialization. She is the former editor in chief of both *Pharmaceutical Formulation & Quality* and *Specialty Pharma* magazines.

GAIL DUTTON

Gail Dutton has covered the biotech industry since soon after its inception, focusing on the intersection of business and science.

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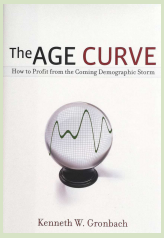

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Q: What is the best way to match mentors and pupils for leadership development?

There are many factors to successful mentoring, three of which I will spotlight with regard to matching up mentors and pupils:

1. clear objective for what the pupil wants to accomplish
2. mentor with expertise on the target objective
3. chemistry of the relationship.

Mentoring varies from a brief interaction to a lifelong relationship. Mentors can be found within your company, your association, your community, or your family. They can be either senior or junior to you and be in person or on the other side of the world. The consistent thread in all of these scenarios is the foundation of a successful pairing. Building a personal board of mentors is a critical tool in supporting your leadership advancement, so don't shy away from adding mentors with subject matter expertise nor discontinuing a relationship if the chemistry is not right.

Laurie P. Cooke
Laurie P. Cooke, B.S., RPh, PGDip, CAE is the CEO of the Healthcare Businesswomen's Association (HBA), the leading nonprofit professional association in the women's leadership space in healthcare globally.

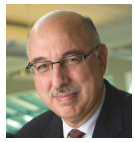
Q: What is your opinion on the CMS/FDA proposed parallel review process?

CMS (Centers for Medicare and Medicaid Services) and the FDA have proposed creating a parallel review process in which CMS would begin its national coverage determination review process while the FDA completes its premarket review and play a role in discussions regarding investigational products under development. BIO does not believe that the existence of separate FDA and CMS review processes has resulted in significant problems in the review and coverage of drugs and biologics and questions whether there is any need for a new parallel process. Sponsors who wish to involve both the FDA and CMS in clinical development and premarket review discussions may do so voluntarily under current practice, and we encourage both agencies to continue to provide opportunities for early consultation. BIO understands and fully supports the need to minimize the length of time between marketing approval and commercial availability of new drugs and biologics.

Alan Eisenberg
Alan Eisenberg serves as executive VP for emerging companies and business development at the Biotechnology Industry Organization (BIO). In this role, he manages and directs BIO's services and advocacy efforts for BIO's emerging companies.

Q: What advice would you have on creating single-use industry standards?

The first step is to define what is meant as a "standard." Is it a consensus practice, a formulation or design specification enabling interchangeability of components, or a fixed single-use system (SUS) dimension and design? For practices, users have called for standard extractables data packages from suppliers. While reasonable for new products, suppliers do not want to see the value of costly prior studies invalidated due to minor changes in methodologies. Standardization of components and systems is more challenging, as many components are either proprietary formulations (films) or are covered by IP (sterile connectors). For these to become true standards, sterile connector patents need to expire and users must come to agreement on what formulations and designs to standardize. Those interested in developing standards should develop consensus within their own company first, then work with trade groups, professional societies, and standards organizations to reach a consensus across the industry.



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

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By Wayne Koberstein, contributing editor

Serina Therapeutics

A positive push beyond PEG with POZ — developing a new platform, products, partnerships, and progressive public financing

SNAPSHOT

Serina Therapeutics has billed its POZ (polyoxazoline) platform as the next generation of polymer-aided drug delivery, following logically from PEG (polyethylene glycol) and PEGylation, the drug delivery platform Serina's founders first helped commercialize. POZ is designed for a wide variety of applications and therapeutic areas and may offer substantial advantages in terms of drug safety and efficacy. Serina has three drug-POZ conjugates in preclinical development, with the lead candidate, POZ-rotigotine (SER-214), a weekly injection for Parkinson's disease and restless leg syndrome, headed to the clinic in late 2013 or early 2014 ahead of the other two candidates, both in cancer.

Randall Moreadith, M.D., Ph.D., president and CEO

LATEST UPDATES

• March 2012: U.S. Patent Office grants two broad patents on the company's polymer drug-delivery technology. The patents cover all classes of molecules for attachment and targeting. (Composition patent awarded May 2011.)

WHAT'S AT STAKE

The now-familiar method, PEGylation, attaches polymer filaments of PEG on therapeutic molecules to slow their elimination from the body, avoid immunogenicity, and eliminate receptor binding in certain parts of the body (e.g. brain). With some exceptions — enough to make room for a next-generation improvement — the technology has worked ideally for proteins, and there are 12 products in the market today that are PEGylated drugs. But its use has been limited largely to proteins. That is the cue for Serina's entrance.

Serina's POZ platform adds the advantages of low viscosity, high drug loading, and active targeting of drugs to the disease site. The precise targeting ability and large drug-carrying capacity of the POZ molecule is meant to optimize dosing and reduce side effects, especially with the famously toxic class of oncolytics. But POZ's first application will likely be in an entirely different area where drug delivery is critical: Parkinson's disease.

That points to one of Serina's more unique and interesting characteristics: It is not waiting for other companies to license and use the POZ platform. Instead, it is pushing its own pipeline while it looks for partners. Its lead candidate, SER-214, went through IND (investigational new drug)-enabling toxicology studies in fourth quarter 2012, and results of a rat study in Parkinson's disease will be published in early 2013. Serina will initiate a monkey efficacy study in late 2012, with results in mid-2013, "to confirm that repeat-dose administrations of SER-214 once a week for up to three months fully rescue Parkinsonism in the most relevant model available and will provide compelling evidence of being able to do the same in humans," says its president and CEO Randall Moreadith, M.D., Ph.D. After formal GLP (good laboratory practices) toxicology is completed in mid-2013, a pre-IND meeting is planned for the third quarter of 2013, perhaps leading to the first human dosing in late 2013 or early 2014. "This is particularly exciting as this drug candidate may be advanced for several very important unmet medical needs — Parkinson's disease, restless leg syndrome, levo-dopa induced dyskinesias, and impulse control disorder," Moreadith says. The drug will be administered once a week with a standard insulin syringe and provide continuous dopaminergic stimulation (CDS). "A long-sought clinical strategy for these patients," Moreadith adds.

The company may also be contributing to innovation in another area — financing. Moreadith recommends that more companies look at Serina's $9.5 million "direct public offering," completed in June 2011. "While the usual vehicle for this type of financing is VC funding, we elected to try something new. We approached several local business people in the Huntsville community and were elated at their enthusiasm for funding our programs at such an early stage. We brought in an additional two dozen new shareholders and closed the $9.5 million round within a few months."

Moreadith says the company has sufficient capital to carry it through the next two years. After winning key patents for POZ earlier in 2012, it has been reaching out to potential partners for nondilutive capital to sustain company growth for another few years. Despite VC interest, "We don't foresee a VC round in the near future," he says. "Many of our existing shareholders have indicated they recognize the needs of a small company like ours and can step in with additional resources if the need arises." Patient shareholders with an understanding of the challenges a small company faces in drug development? What a concept.

VITAL STATISTICS

- Employees: 9
- Headquarters: Huntsville, AL
- Finances/Funding: June 2011: $9.5 Million "direct public offering"

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Benchmark 48 | 74

BY PHASE OF DEVELOPMENT
Phase I
54 | 75
49 | 73

BY THERAPEUTIC AREA
Cardiovascular Diseases
51 | 74
47 | 73

BY SERVICE CATEGORIES
Fill & Finish
57 | 75
51 | 72

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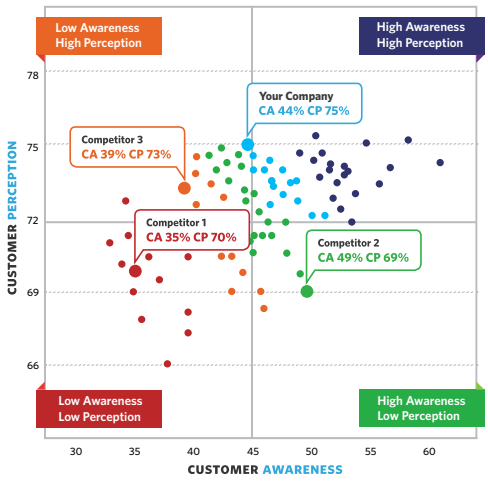
COMPETITIVE LANDSCAPE

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



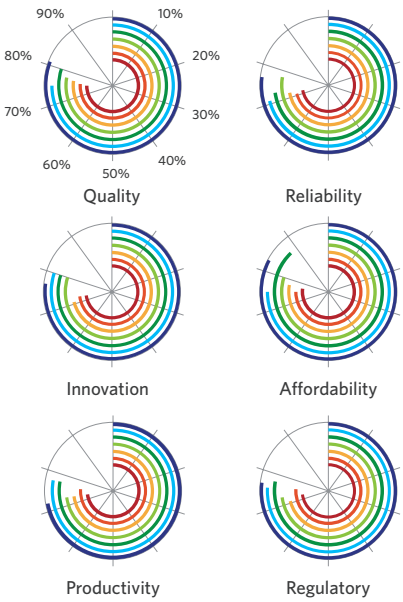
7 therapeutic categories

25 outsourced service categories tracked

6 phases of drug development

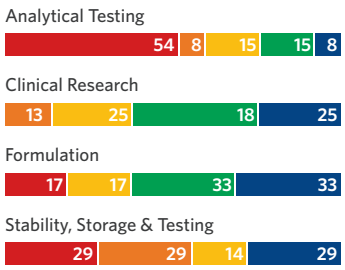
CUSTOMER PERCEPTION OUTSOURCING DRIVERS BY THERAPEUTIC CATEGORY

Cardiovascular Diseases · CNS Disorders · Endocrine Diseases · Infectious Diseases · Metabolic Disorders · Oncology Diseases · Respiratory Diseases



CUSTOMER AWARENESS BREAKDOWN

Never heard of them · Recognize logo/name · Know little about · Know them, haven't collaborated · Worked with them



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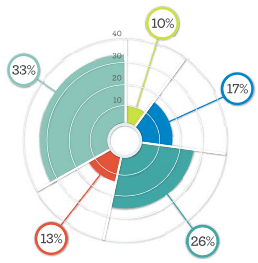
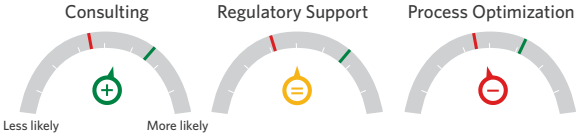
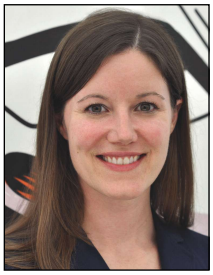


6 key departments are represented

LIKELIHOOD OF WINNING A PROJECT BY SERVICE



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



OUTSOURCING INSIGHTS

CROs and CMOs: Continuing Drug Delivery Innovation

By Kate Hammeke, director of marketing intelligence, Nice Insight

Drug delivery has been an avenue for innovation in the drug development industry for decades. Initial improvements focused around delivering medicine with the maximum efficacy and safety in a form accepted by patients, leading to greater patient compliance. At the time, the potential financial impact of drug delivery technology wasn't appreciated and therefore couldn't sway Big Pharma's focus from finding the next blockbuster. As a result, specialty pharmaceutical companies took up the mantle and began to offer the service while Big Pharma retained its focus. This resulted in partnerships with benefits for both parties when it became clear that improved drug delivery boosted therapeutic potential and that experimentation with delivery forms could lead to additional therapeutic indications, providing a different facet of innovation. As the need for drug delivery innovations specific to biologics unfolds, we can anticipate a new type of relationship emerging.

Over the past ten years, a number of contract research and contract manufacturing organizations have added drug delivery technologies to their service offering. It makes sense for manufacturers to be concerned with improved delivery as it helps to reduce wastage of valuable therapeutics. Whether in the form of overfill, disintegration, or lack of absorption, a reduction in the required dosage increases profit margins for manufacturers. In addition to the benefits inherent to manufacturing, proprietary delivery technology can cement customers into long-term relationships.

Looking to 2013, there is a steady demand among buyers of outsourced services for drug delivery support. Results from the Nice Insight Pharmaceutical and Biotechnology Outsourcing survey show that one in five plan to outsource a drug delivery project in the coming year. Big Pharma comprises the largest segment of drug delivery outsourcers at 42%, followed by Biotech (23%), Specialty Pharma (16%), Emerging Pharma (12%), and Emerging Biotech (7%).

Considering the challenges inherent to delivering biologics-based therapeutics, it isn't surprising that four out of five who outsource drug delivery are engaged in the development of biologic-based therapeutics. The development of biologics-based therapeutics drives the need to consider drug delivery technology earlier in the development cycle, which was reflected in research results in several ways. These outsourcers supported a growing trend among biopharma companies, which is to engage outsourcing partners earlier in the development life cycle. More than half (55%) of drug delivery outsourcers agree it would be valuable to use the same delivery form from early phases through the development cycle. Also, when respondents were asked specifically which companies they would consider when outsourcing a project, CROs held two of the top three positions.

Respondents selected Boehringer Ingelheim, Covance, ICON, and Baxter BioPharma as their top four choices when outsourcing drug delivery. There was a three-way tie for fifth between AAI Pharma, Alkermes, and Catalent. The top CMOs mentioned by respondents — Boehringer Ingelheim and Baxter BioPharma — received "excellent" scores for quality and reliability, which are the two most important outsourcing drivers according to this group. However, these two companies were perceived as less affordable compared to CROs Covance and ICON. Among CROs that offer drug delivery services, Covance and ICON received the highest quality and reliability scores of the group. Yet, interestingly, the CRO companies received their highest scores in productivity and regulatory compliance. This suggests that different criteria are driving drug delivery business to CMOs (quality and reliability) and CROs (productivity and regulatory history).

As the outsourcing model evolves towards more strategic partnerships, where biopharmaceutical companies are looking to CROs and CMOs in order to access specialty skills as well as improving quality, it makes sense for these contract providers to expand their service offering to include drug delivery. The results will likely be mutually beneficial to the drug developer and contract organization, helping each of them to maximize their resources.

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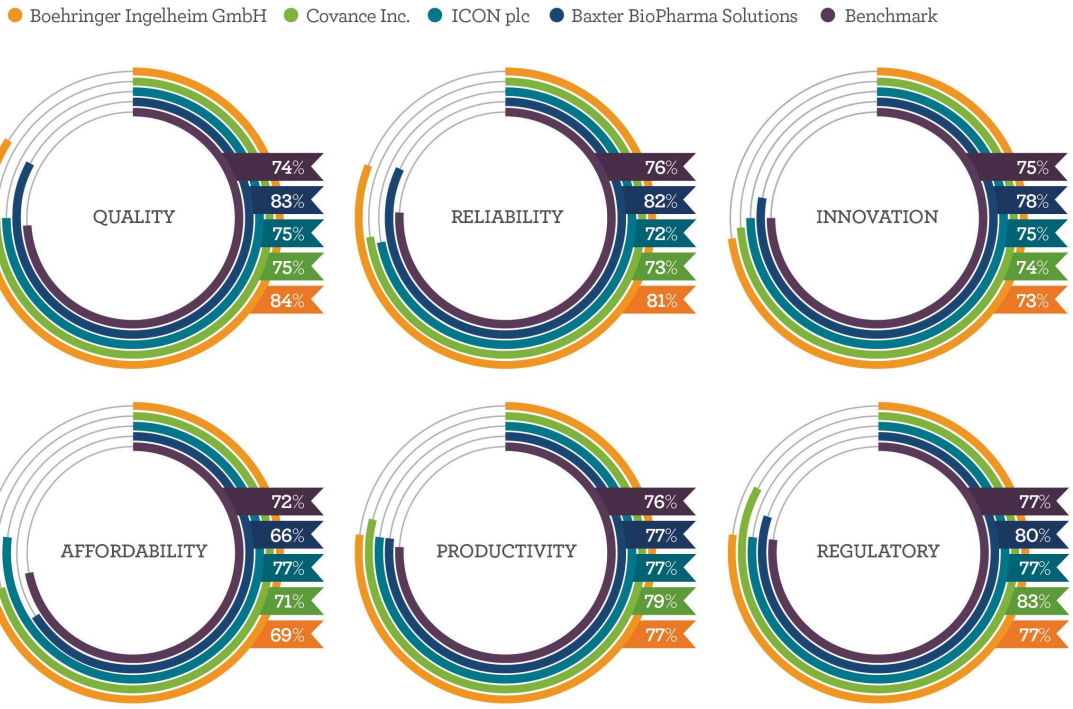
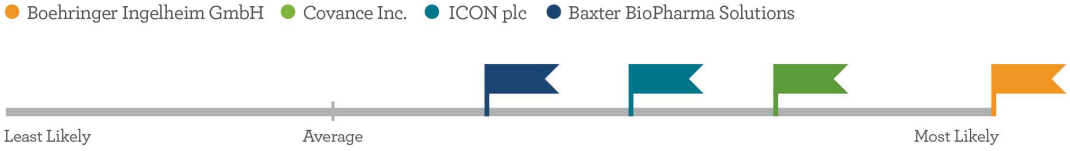
NI Customer Perception Scores Among Top Drug Delivery Providers



NI Top Drug Delivery Companies Based on Project Likelihood

The 'Project Likelihood' graphic indicates a company's probability of being selected for a project relative to competing businesses that also offer the service.



Survey Methodology: The Nice Insight Pharmaceutical and Biotechnology Survey is deployed to outsourcing-facing pharmaceutical and biotechnology executives. The 2012-2013 report includes responses from 10,036 participants. The survey comprises 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 the top 100+ CMOs and top 50+ CROs servicing the drug development cycle. Over 900 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 how to participate, please contact Nigel Walker, managing director, or Salvatore Fazzolari, director of client services, at Nice Insight by sending an email to niceinsight.survey@thatsnice.com.

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BIO DATA POINTS

Biomanufacturers Look To 2013 For Continued Process Improvements

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

According to our annual evaluation of biopharmaceutical trends, in 2013 the biomanufacturing industry plans to address common challenges through process improvements — especially in areas of downstream process improvements and single-use implementations. In addition, analytical methods to evaluate and monitor bioprocessing continue to be hot buttons.

Of respondents who identified process improvements as their hottest trend going into 2013, 24% specifically named downstream process improvements. It is no surprise that biomanufacturers are focused on downstream process optimization, given that, as yet, the incremental improvements in downstream purification technology have not matched the improvements in upstream and cell expression technologies.

Process improvements come into play specifically because the industry requires continual, incremental performance improvements in biomanufacturing to remain competitive and to manufacture at higher quality and lower costs. In our 9th Annual Report and Survey of Biopharmaceutical Manufacturers, we asked more than 300 biomanufacturers around the world to identify the factors in biomanufacturing that create performance improvements. We identified 15 key areas. The largest portion, 72% (the same as last year), cited overall better control of processes. This relatively general response indicates that a large majority of the industry is implementing some activities associated with process control. Also high on the list: better process development, indicated to contribute to "significant" or "some" improvements in performance by 64% of respondents.

A large majority of the industry is implementing some activities associated with process control.

Because process improvements and performance are becoming increasingly critical to competitiveness, the industry has been very resistant to cutting back on funding for these improvements. Indeed, this year funding and budgets for upstream and downstream process improvements have accelerated their lead in terms of budget allocation compared to all bioprocess operations. In addition, when we asked respondents the top operational changes they have made due to recent global economic conditions, just 1.1% of biomanufacturers had cut funding significantly for manufacturing process improvements.

PROCESS IMPROVEMENTS COMBAT BOTTLENECKS

Process improvements prove particularly important in downstream operations and to address bottlenecks. This year, when we measured implementation of different activities to combat bottlenecks, we found that general process-driven improvements were just as popular as consideration of new technologies. That is, the way facilities are tackling their downstream purification operations is to optimize their running conditions (43.4%), rather than introducing new technologies. This involves developing downstream processes with fewer steps (42.1%), reducing the number of process steps (39.5%), and investing in downstream process development (31.6%).

PROCESS IMPROVEMENTS FOR BIOSIMILARS

Players in the biosimilars/biobetters market will have to compete against the original reference product and multiple other biosimilar/biobetter versions. Cost to the consumer will likely be the number one factor affecting market share for most products. Thus, the cost of goods or cost of manufacture is a critical factor. Many biosimilar/biobetter developers are adopting the newest and improved bioprocessing methods, expecting to achieve process improvements lowering the cost of manufacture. These companies simply have to minimize the costs of manufacture to be competitive.

To minimize manufacturing costs, biosimilar manufacturers are pursuing high yields and efficiencies in product manufacture. For some, this involves having a CMO plug their product into that CMO's well-established in-house manufacturing platform, such as the CMO adapting its current preferred CHO (Chinese hamster ovary) expression system to the manufacture of the biosimilars/biobetter. In other cases, the in-house or CMO manufacturer will adapt bioprocessing methods, including novel expressions systems and equipment to attain needed process efficiencies. While biosimilars manufacturers are focusing closely on process improvements, all biomanufacturers are evaluating and funding both incremental and disruptive approaches to better processes.

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Figure 1: Summary Of Biomanufacturers' Expected Top Trends For 2013

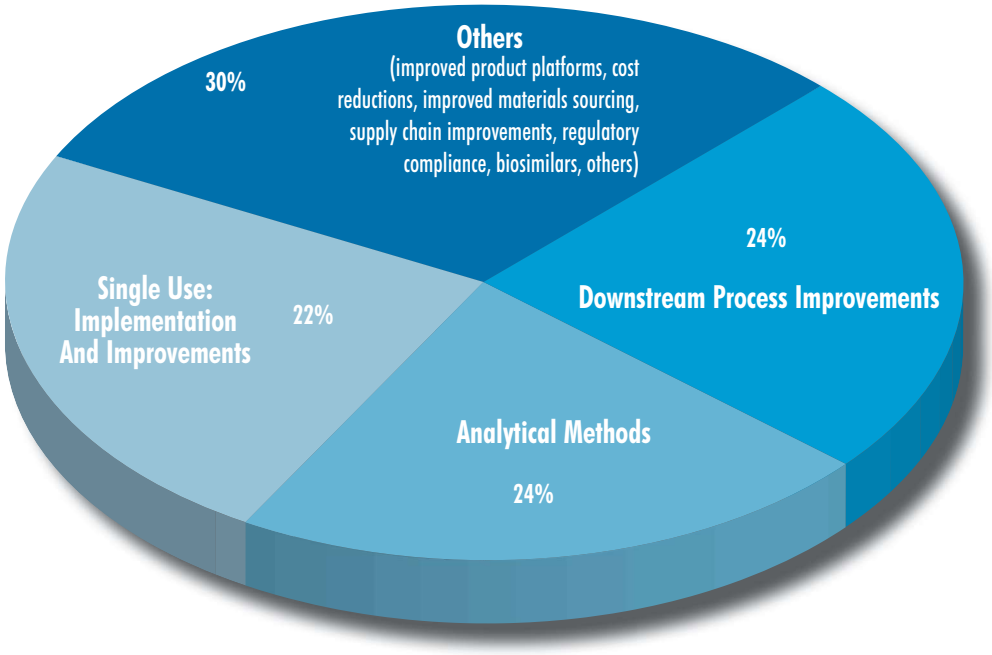
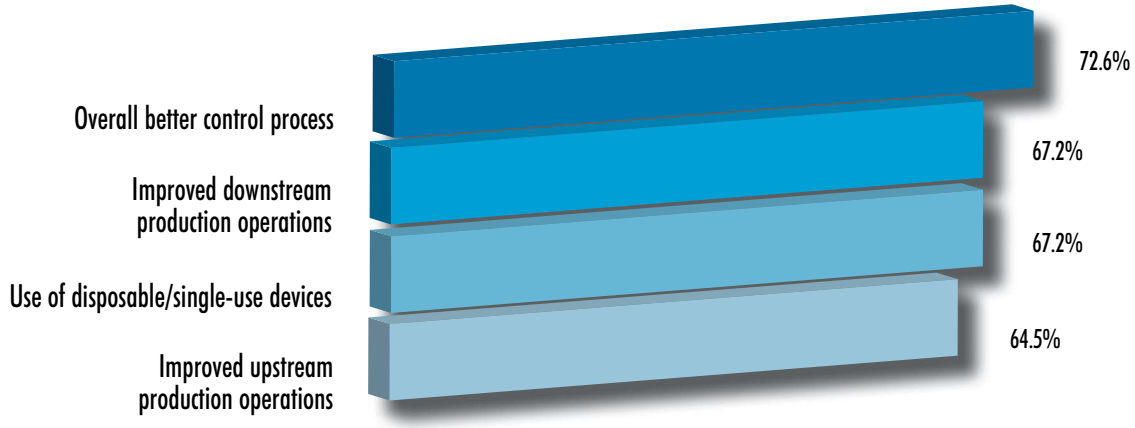


Figure 2: Selected Factors Improving Biomanufacturing Performance

"How much have each of the following improved biomanufacturing performance at your facility over the past 12 months?"



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

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

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How To Take Charge Of Your Manufacturing Process

By Rob Wright

JIM ROBINSON GREW UP JUST 20 MILES AWAY FROM MERCK'S MASSIVE, 397-ACRE, WEST POINT, PA, CAMPUS. His brother, a proud union member, has spent the past 37 years working on the Merck manufacturing line. During the course of his 29 years in the pharmaceutical industry, Jim tried to join his brother as a Merck employee, applying for a job six times. "They never responded to me," he admits. "It was quite demoralizing." He theorized that he must not meet the typical Merck hire profile. That all changed when one of his former Sanofi Pasteur colleagues, Jacks Lee, who joined Merck in 2007, recommended Robinson to fill a position in early 2010. Merck had just completed a merger with Schering-Plough and was in the process of a major restructuring, including considerable layoffs. Some might view this as a rather precarious time to come on board, especially if you don't fit the typical hiring profile. For Robinson, however, the timing to become one of Merck's approximately 86,000 employees couldn't have been better. As the VP of vaccine product & technical operations, he explains the lessons learned throughout his career which he feels can help improve vaccine manufacturing.

Jim Robinson, VP of vaccine product & technical operations, Merck

LESSON 1: GETTING YOUR STAFF TO BE ADVOCATES

Having worked 20+ years at both large and small pharmaceutical companies, he has experienced the contrast of complex versus simplified manufacturing operations. One of the most important things he has been exposed to is the potential benefits and simplicity of single-use manufacturing systems. "You can see the flow which helps you to understand better what's happening," explains Robinson. "When you have stainless steel pipe network and automation panel, you're told what should be happening, but you can't see it. You can't confirm it, and you're relying on the technology to tell you that it's right." His experiences have forced him to think differently and to consider other ways to be innovative and creative in the manufacturing process. He feels that if you want to bring these ideas to your vaccine manufacturing process, you must first obtain a critical mass of advocates, and the best place to start is with your own team. But before you can convince them that there might be a better way, you must first change their mindset.

For example, during his first six months at Merck, he asked the question of his team "Why are you here?", and he gave them one sentence to answer the question. Answers typically included "Merck is a great company", and "we create products which save lives." These weren't what he was looking for. He wanted to get his team to think much differently about their work, a technique he learned from one of his first mentors. Robinson defines a leader as "someone who takes you to a place you wouldn't otherwise go." In order to accomplish this, one must get people anchored around the concept of showing up to work on purpose and truly understanding why they went to work every day.

In order to change the way people think about and how they approach work, a leader needs to help their team self-discover how they can bring more value to the company. People must understand that just because you are smart enough to create truly complex systems doesn't mean you should, especially when a simpler, more pragmatic approach can be just as effective and less costly.

LESSON 2: CHALLENGE YOUR TEAM TO SIMPLIFY YOUR MANUFACTURING PROCESSES

As companies look to expand outside of the developed world, affordability becomes more important and difficult to achieve when you have high fixed costs and high complexity. Robinson recalls reviewing a manufacturing skid for a stainless steel system that contained more than 240 valves, several thousand feet of stainless steel pipe, about a dozen sterile vessels, connected over four different floors in the building. "Some of the piping was running through noncontrolled mechanical space," he describes. "This whole system was designed to be maintained sterile, and so, hypothetically, if a valve happened to leak, and it leaked in an area where it was noncontrolled, the question would become, 'what is the impact on the disposition of those batches?'" Robinson saw the process of managing deviations within this type of system to be a huge time sink, so he decided to have his team think about the process differently, asking them to design a system that had half the number of valves and pipes. The team came back to him with a design which was about 1/3 the size of the original system. Robinson asked them to cut their new design in half. "And then I asked them to halve it again," he states. When this was done, the team had created a simple system, with ~40 valves, 3 tanks, and a very small sterile boundary, which fit within one room. "You can

Deep System Understanding Prevents Negative Consequences

During his career, Jim Robinson (currently VP of vaccine product & technical operations at Merck) always looked for opportunities to deepen his staff's technical competency via the implementation of his process intimacy program. "Over the years, I've spent a lot of time with complex manufacturing systems, walking them with staff members from end to end, with the valve sequencing tables, and the P&IDs (piping and instrumentation diagrams)," he states. One of the things one team found during a walk-through was that a system had a water, air, and steam system, all connected to the same header.

Water was used to wash the line, sterile air to remove excess water, steam to sterilize; and then to cool it down, sterile air would be blown through the line again. "This is something you don't really think of, until you get into the detail of exactly how it works," Robinson explains. "Water pressure is 60 pounds, air pressure, 20, and steam, 15. So, if you use water to rinse out the line, the line is sitting at 60 pounds. If you close that valve and open the air valve at the same time to blow the line down, that water will back up into the air system. You no longer have a sterile air system. You steam sterilize the line, and then you blow it out with sterile air, which now has contaminated water in it."

Robinson advises to make the time to really understand the way a process works via process intimacy to avoid negative consequences. In the above example, if you didn't make sure that people using the system understood the importance of having a lag time between turning the water off and turning the air on, to prevent backflow, you would end up running a contaminated system, which would result in loss of batches, potential recalls, and lost productivity spent investigating the system to determine when the contamination occurred and if it could have negatively impacted the quality of previous batches.

Lack Of Standards Leads To The Creation Of The Single-Use Network

Jim Robinson, VP of vaccine product & technical operations at Merck, believes a lack of single-use standards is one of the reasons many companies have been slow to adopt the technology, including Merck. When he initially started talking about utilizing single-use systems at Merck, he found there were many Merck advocates for single-use manufacturing systems. "When we started to share our positive experiences we created some of that critical mass of advocates and in time, the Single-Use Network was born," he relates.

The Single-Use Network (SUN) is an internal program created to facilitate the adoption of single-use systems within Merck. SUN is in the process of creating a book of standards for single-use components. Robinson is careful to point out that he wasn't the inventor of the Single-Use Network (SUN), but notes that it evolved from this early group of advocates who shared a common interest and passion for change. He realizes that for single-use manufacturing companies, differentiation represents a competitive advantage. However, differentiation does not serve to facilitate rapid adoption of single-use by Merck. The more different the product, the more difficult it is to duplicate (or substitute). According to Robinson, in the vaccine business, reliable supply is paramount. "We like to have interchangeable parts, so that if a vendor has a problem," he explains, "we don't have to live with or stop production for that problem." Standards created by SUN could not only help accelerate Merck's adoption of single-use technologies, but perhaps push companies which manufacture single-use systems to more quickly create and adopt standards for certain single-use components. "If we build connectivity and interchangeability, there will be greater use of single-use systems," states Robinson. "Even if there is more competition, vendors will compete in a bigger business. It's a win-win."

actually see the sterile boundary," he describes.

According to Robinson, the exercise demonstrated to the team the benefits of simplification and reminded the team that they only need a level of complexity necessary to achieve the desired outcome with good management controls. "When a system is incredibly complex, very few people understand the system, and those who designed it have usually moved on to other projects,"

he states. "This inhibits your ability to transfer knowledge of how the system works to those who operate the manufacturing process every day, which doesn't help the company operate efficiently." By simplifying the manufacturing process, the system can be run with fewer people, resulting in manufacturing throughput efficiency, as measured by the number of vaccine doses produced per number of manufacturing line employees. Robinson points out another benefit to simplification. "When there are fewer things that can go wrong, you reduce batch deviations and potential investigations," he states. The team took this new design and applied the same concepts to simplifying two similarly complex systems in the network.

LESSON 3: KNOW YOUR MANUFACTURING PROCESS — INTIMATELY

The exercise of system simplification helped Robinson to facilitate his next objective — creating process intimacy. According to Robinson, process intimacy is a term he formed and which he feels can help any team to conceptualize how they could truly bring value to their company. Robinson believes that if you don't really know your process, your system, and what can go wrong — much like a failure-mode analysis approach — you won't be able to predict problems and proactively prevent them, and you will end up spending most of your time looking at what went wrong, rather than at continuous improvement and risk reduction. "When you start talking about process intimacy, it seems self-explanatory," he relates. "But process intimacy is much more than knowing the process technically. When you're on the shop floor of an industrial operation, it has a rhythm, a feel, sound, and smell." According to Robinson, when you have that sense of rhythm, the result is such a deep and knowledgeable understanding of the process, it creates a relationship between you and the process. "For example, I could tell when a fermentation wasn't going well by the smell of the off-gases outside when I was on my way to lunch," he explains. This cannot be achieved by simply looking at a P&ID (piping and instrumentation diagram). According to Robinson, this "organic connection," rather than technical understanding, can only be achieved by frequently walking the shop floor, perhaps three times a day. The other benefit of being on the floor is that you really get to connect with the group leaders there, who will be critical in helping you to understand when something goes wrong.

Robinson's process intimacy program requires engineers to get on the shop floor, watch the process, talk to operators, and understand their issues. "If we can't first help them fix their issues, we can't earn their trust, and as a result, we aren't really going to know what the true issues are," he affirms. Process intimacy involves

assigning people to a single product, and then asking them to look end-to-end for that product to develop a deeper understanding of how the manufacturing steps throughout the process relate to each other. "Before this," Robinson explains, "people would go from product to product, issue to issue, and not own the process or the performance on an ongoing basis." People-to-product alignment strongly contributes to the ability to develop process intimacy. "Seeing various operators with slightly different techniques and developing the standard work for all employees is only possible if you are there on the shop floor for deep observation," he says.

> "But process intimacy is much more than knowing the process technically. When you're on the shop floor of an industrial operation, it has a rhythm, a feel, sound, and smell."
>
> Jim Robinson, VP of vaccine product & technical operations, Merck

Prior to Robinson implementing process intimacy, some staff rarely left their offices when tasked with solving a problem on the shop floor. The problem with this approach became evident when, for example, a team had an issue with a really complex manufacturing system. To gain process intimacy, the mindset had to change from being a technical organization full of really smart people, to that of a service organization — incredibly engaged with the shop floor, manufacturing leadership, as well as the manufacturing process. In so doing, you will not only understand how a system works, but learn the difference between the way a system is designed to be used and the way people who actually operate the equipment decide to use it (see sidebar on page 22).

"We serve by making manufacturing better," he affirms. "We don't serve by creating technology. Merck doesn't sell technology. We sell product, and if our technology doesn't make product better, then it's not good technology." Want to make your product better? Try Robinson's approach of gaining advocates, challenging your team to simplify manufacturing processes, and then strive to have manufacturing process intimacy.

PFIZER PERSEVERES IN PIONEERING VIRTUAL TRIALS

BY WAYNE KOBERSTEIN, CONTRIBUTING EDITOR

Craig Lipset, worldwide head of clinical innovation at Pfizer

Success is sometimes measured more by what you tried than how high you scored. In science, the maxim is self-evident: Falling short of expectations can prove more valuable than attaining them — once you look at the evidence and learn from it. How else to explain the excitement that surrounded Pfizer's REMOTE (Research on Electronic Monitoring of OAB [overactive bladder] Treatment Experience) trial, the first randomized virtual clinical trial conducted under an IND (investigational new drug) application, even after the trial ended in mid-2012 with less than stellar patient response.

REMOTE recruited and qualified patients online for a Phase 4 study of the approved OAB medicine Detrol LA (tolterodine). It attracted candidates with a cartoon video explaining the trial and how to apply and participate. During the trial, applicants went through an extensive online process of education, qualification, and enrollment, followed by self-reporting of their responses. The study was to operate essentially as a giant central trial site, with investigators overseeing data collection and analysis and primary care physicians helping screen and steer patients along the way. Investigators would ship all study drugs to the patients' homes, rather than dispensing it at a clinic. But REMOTE fell far short of its goal of recruiting 600 total patients from 10 states in the U.S. What went wrong? Therein lie some of the lessons Pfizer learned from the experiment, lessons it plans to apply while developing future studies for consideration in Europe in 2013 — and lessons that can help other companies follow Pfizer's pioneering push into virtual trials territory.

Craig Lipset, worldwide head of clinical innovation at Pfizer, discusses those lessons in the following conversation, putting them in the context of what REMOTE was intended to accomplish and what it did accomplish in the form of attained knowledge, despite or even because of its poor recruitment results. His colleague and the team leader for the trial, Clinical Development Senior Director Miguel Orri, M.D., adds details to the context and explains how the internal hurdles his team faced influenced results and steepened the company's learning curve. (See the sidebar "Virtual Trials Trailblazer.")

THE NAME OF THE REMOTE VIRTUAL TRIAL, "RESEARCH ON ELECTRONIC MONITORING OF OAB TREATMENT EXPERIENCE," SUGGESTS IT WAS A SCIENTIFIC EXPERIMENT. SO YOU INTENDED TO LEARN FROM IT FROM THE START — EVEN THOUGH IT MIGHT NOT HAVE GONE THE WAY YOU EXPECTED?

LIPSET: Well, in any research project, if you know how it's going to end, there's probably no point in doing the project, right? We were attempting to model a new approach. We chose to use the medicine Detrol for overactive bladder as the vehicle for testing this model, because Detrol has a well-characterized efficacy and safety profile. We constructed the experiment as a series of modules to make sure that we could take advantage of what works and continue trying to refine what didn't. It's also important that REMOTE fits within a much larger set of experiments, developments, and efforts we have under way to reform medical product development.

WHAT ARE SOME EXAMPLES OF HOW REMOTE HELPED YOU IN THAT CONTEXT?

When we develop new medicines, we have to understand their efficacy and safety before and after they're approved and gather continuous data on their value for payers, and that is a challenging proposition today. We need to continue to take advantage of new tools that are available to us to help us develop that data. REMOTE was an attempt to leverage many of those new tools. Clinical research is disruptive to healthcare. It requires the physician or patient to stop what they're doing and change roles — from physician to investigator or from patient to research subject. We want to make participation in research easier for the patient and the provider.

WHEN THE REMOTE INITIATIVE ORIGINATED IN THE COMPANY, WAS IT SOMETHING THAT BUBBLED UP FROM CLINICAL DEVELOPMENT, OR DID IT COME DOWN FROM TOP MANAGEMENT?

There was probably a convergence of three different efforts. One, some folks at Pfizer were internally exploring new data-capture tools and platforms. Two, in parallel, my team began to develop a discrete concept of a virtual trial that could take advantage of some prior work by Lilly and a virtual-trials start-up, then called 1747, Inc. Three, Dr. Steven Cummings at UCSF, one of the founders of 1747, began to open a dialogue with us at Pfizer. So all of those efforts came together with creative leadership at Pfizer that was willing to embrace the innovative new approaches. It was work proposed upward, but certainly it was critical that we got top management to embrace and support it.

TOP MANAGEMENT MUST HAVE HAD A MATCHING AGENDA AT THAT POINT, AT LEAST IN THE SENSE OF IMPROVING THE COST AND EFFECTIVENESS OF CLINICAL TRIALS.

Absolutely. There is general recognition that current clinical development models are largely unsustainable. There are challenges in recruitment and challenges in making clinical research viable for healthcare providers to participate — key challenges that really jeopardize the ability to continue developing medicine. Everyone knows major improvements are needed, but it's still challenging for companies to step forward and take that risk, especially in an environment that's increasingly resource-constrained.

WHAT WERE SOME INTERNAL AND EXTERNAL HURDLES OR ROADBLOCKS YOU FACED, ONCE YOU BEGAN MOVING TOWARD THE REMOTE TRIAL?

Pfizer made a decision early on that the project was going to be run within the R&D organization. There are certain innovative initiatives that it makes sense to isolate or protect from the rest of the organization, and there are theories that you need to protect very delicate new innovations or a large organization can crush it. But Pfizer decided to conduct this project within the organization rather than doing it in a small protective group or by simply writing a grant to an academic researcher and walking away. On one hand, it made things a little more difficult. We had to bring on board very pragmatic and experienced clinical research professionals and convince all of them that this was worth their commitment. On the other hand, it created a sense of ownership in the whole organization. It was not something that was just thrust upon them by senior leaders and supervisors. The clinical operations and regulatory colleagues owned it, and that created an upward wave that helped support the culture of innovation that we were trying to encourage within Pfizer. It showed that people can work on out-of-the-box new projects in parallel to their other work and help contribute to corporate change.

HOW DID THE TRIAL FIT INTO THE LARGER PICTURE OF THE FDA'S CLINICAL TRIALS TRANSFORMATION INITIATIVE (CTTI), AND HOW WAS THE AGENCY HELPFUL?

CTTI is an important initiative that relates specifically to quality and efficiency in clinical trials. And though we believed early on that REMOTE was very compatible with the CTTI, we did not see it necessarily as a CTTI project. Yet it was consistent with the spirit of collaboration and transformation that the FDA and other stakeholders want to achieve. We deliberately structured this project under the IND application for Detrol to ensure that we could have a group discussion and engagement with the FDA. This forum created opportunities to discuss key matters such as complying with requirements around drug distribution.

WHAT ASPECTS OF THE STUDY WORKED, AND WHAT FAILED?

We saw tens of thousands of patients who responded to the call, though we might have made some improvements in outreach. Thousands created accounts, thereby expressing interest not only in general, but in going to the next step of demonstrating interest in participating. We saw that our process could ensure patient consent was properly acquired without ever actually seeing the patient

live and in person. We demonstrated our ability to distribute blinded investigational drugs directly to the patients in their homes and then to use creative tools and platforms, mobile and Web-based, to capture data from those patients. We showed that you could use a centralized investigator, just as we've used centralized IRBs and centralized labs for monitoring patient safety. Now what we failed to do was to find enough eligible patients. But we were looking for patients with severe disease, as in the earlier trials with Detrol, and it was hard to find a sizable number of women purely online who had very severe OAB to qualify for the study. We also learned that for certain diseases and severity level, offline conventional channels work better than the online channels. That is not a claim of success or a claim of failure; it's a claim of learning.

DOES THAT SUGGEST THAT VIRTUAL TRIALS MIGHT BE MORE SUCCESSFUL IN LESS SEVERE CONDITIONS?

That may be one of the conclusions as we continue to dig through the data and talk to patients who expressed their interest in participating. But there may still be other areas in the near term where virtual trials make sense, say with rare diseases where patients may be very widely distributed and you can't set up a single investigator site and expect lots of patients in geographic proximity. We also want to continue to explore hybrid approaches; for instance, if healthcare providers and treating physicians are the right channel to help me find patients with severe disease, how do I make this trial model fit with that knowledge? Rather than relying completely on the Internet and social media to find patients, can we reach them through the treating physicians?

SO YOU ARE ENGAGING THE TRADITIONAL HEALTHCARE SYSTEM TO COMPLEMENT THE VIRTUAL DIRECT-TO-PATIENT APPROACH?

Every healthcare interaction is an opportunity to inform research. How do we make sure the interactions of our participating patients, physicians, and investigators are informing our research process? The primary care doctor today has only two options for research participation. They can become an investigator, but eight times out of ten a novice investigator will lose money and never do another study. Or they can participate by referring patients into someone else's study. But why would a physician refer a patient given the pay-for-procedure reimbursement of healthcare in the U.S.? So the current system isn't very friendly for the treating physician to participate. But we are creating ways for physicians to participate more easily, to share data more easily.

HOW WERE YOU ABLE TO ELIMINATE INTERFERING FACTORS IN RECRUITMENT, SUCH AS THE EFFECTIVENESS OF THE WEB ANIMATION OR SIMPLY THE LACK OF HUMAN INTERACTION?

We were able to do it by looking at the patient numbers and drop-off at various steps in the process, rather than just looking at the total number of patients we reached or randomized through a social media campaign or other campaign. By seeing where patients are dropping off, we may conclude, say, that it is not the informed consent process causing the loss but disease severity or maybe it's a mix of both. We actually reacted to the analytics in real time, making adjustments in our outreach tools based on the patient feedback we were receiving. There were other elements that analytics could not answer, such as patient psychology or attitudes. In those cases, we asked the patients questions about why they did or didn't participate, just to help us toward the goal of learning.

WHAT ROLE DO YOU SEE VIRTUAL TRIALS PLAYING IN THE CONTEXT OF IMPROVING DRUG DEVELOPMENT IN GENERAL?

As an industry, we will continue to fail to recruit patients in our studies if we cannot create an ecosystem of patients already engaged and aware about research studies and research

participation. We need to plant the seed of patient engagement earlier on in the process. As we are rethinking patient engagement, we are looking at all of our touch points with the patient — from informing about research participation, informed consent, study participation, and even opportunities after the study concludes.

WHAT ABOUT A SET OF BEST PRACTICES THAT WOULD APPLY TO ANY VIRTUAL TRIAL?

We don't try to generate intellectual property for ourselves in this space. We are a medicine development company. We also believe that if we are the only one exclusively using a new method, that doesn't necessarily serve us well. We need others to adopt the new methods so that regulators, providers, patients, and payers are familiar with and support them. If it's only a Pfizer way of doing things, that process will be slower. Even so, we will be more competitive, we will have a head start, and we will know how to do it better and faster. But we are transparent about this and even prepared to work together with other companies. The recently announced TransCelerate BioPharma collaboration is indicative of the type of collaboration and sharing we are seeing across pharma sponsors to improve the drug development process.

HOW DO YOU ENVISION THE INCREASING USE OF ELECTRONIC PATIENT MEDICAL DATA AFFECTING VIRTUAL TRIALS AND DRUG DEVELOPMENT IN THE FUTURE?

In the REMOTE model, we were highly dependent on patient self-reporting. In the not too distant future, when all health data is digital, we will no longer have to rely on patients to self-report their data. Patients will have access to their electronic health records and will simply authorize and share that data. Today, we have very inconsistent access to our health data electronically, but financial incentives such as the Center for Medicare and Medicaid EHR Incentive Programs through the HITECH act are driving widespread adoption of electronic health records by providers who satisfy specified "meaningful use" criteria — including a requirement that patients have access to their own electronic health data. And when patients are empowered with such access, it changes the game because they become a truly trusted broker of health information for research.

VIRTUAL TRIALS TRAILBLAZER

On the front lines of Pfizer's trailblazing REMOTE (Research on Electronic Monitoring of OAB Treatment Experience) trial was United Kingdom-based Miguel Orri, M.D., clinical development senior director. Orri's views of the trial complement those of Craig Lipset, worldwide head of clinical innovation, by adding details of how the REMOTE team overcame internal corporate hurdles to implement the virtual trials model in a reality-based experiment. Orri was featured in Rob Wright's Editor's Blog in September 2011 for his presentation on REMOTE at The Conference Forum's Disruptive Innovation in Clinical Trials event. Ironically, the innovation he described, though disruptive to the conventional way of conducting trials, was guided by the central principle of minimizing the disruptions for physicians and patients typically caused by trial recruitment and monitoring. "Our primary aims were to get primary care physicians involved, make clinical trials more accessible to patients, and ease the burden of recruitment for investigators," Orri says. "We were trying to make clinical trials more efficient but also more attractive and inclusive for all parties."

Creating a single central recruiting site for the trial simplified patient recruitment for investigators and allowed patients to participate from their own home. Primary care physicians were able to stay engaged with their patients by helping to screen and care for them during the trial. Patients also received their own data at the end of the trial and could choose to share the data with their physician if they wished. "In many studies, it might be a bit far-fetched to go completely remote. Specifically in earlier phases of drug development, you will need initial contact and an in-person assessment to establish the diagnosis, but then all the follow-up could be done remotely."

Virtual trials may be done in a modular fashion: "Even if you only replace half of all the visits with a remote visit, it might make a big difference to the patients and still enable us to collect data in a more consistent way."

Use of patient eDiaries can improve data collection, Orri says. "Patients enter the data without this being filtered and transcribed, the entries are time-stamped, and you can verify that the data was actually filled in when they say it was filled in." He describes what the company learned about patient qualification in REMOTE:

"In the informed consent process, we asked patients to fill in a questionnaire after they had read the informed consent document and watched a video, so we could assess that the patient understands. They then went through a telephone call with the investigator, and finally they signed electronically that they wanted to participate."

Patients, physicians, and investigators may welcome such improvements over more cumbersome conventional methods, but internal players were less open to them, at least at first. "Recruitment was a challenge, and that was mainly triggered by a tendency in the team to be overly regulatory-cautious, and thus to ensure that no wrong patients got in because we made it so difficult for anyone to get into the study."

The REMOTE team got the FDA involved at an early stage, Orri says. "They were very supportive of the project, but on occasions some team members wanted to take a more conservative approach than in conventional trials, which would then typically be escalated in the company hierarchy to a governing committee. The result was general affirmation of the project and its goals but a compromise that favored a more conservative approach."

Patients had to jump through numerous hoops, including creating an account and reconfirming their email details before they knew if they were eligible for the trial. "We learned from that, and there's actually a plan at the moment to incorporate improvements into future studies. I think we might be able to run the next project with a bit more confidence. I can remember many times saying, 'This is much more vigorous than what we do in the conventional setting.' Our increased confidence should make it easier the next time around."

Orri believes virtual trials will eventually be seen as part of quality by design applied to clinical development. "We have so many options here as well to make the trial population 'cleaner.' In clinical trials, protocol violators often get into the study, and here we actually had an electronic system that wouldn't allow the investigator to enroll patients that were deemed ineligible. So part of the system selected the patients; it still had to go through the investigator, but when a patient was deemed ineligible based on predefined criteria, then the investigator couldn't override that, so the patients were automatically disqualified from the study. And that basically gave us zero protocol violations for patients entering the study."

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HIV/AIDS Vaccine Development: Are We Any Closer?

By Clifford Mintz, Ph.D., contributing editor

This year marks the 31st anniversary of the discovery of the Human Immunodeficiency Virus (HIV), the causative agent of HIV/AIDS. At present, there are approximately 34 million people worldwide living with HIV/AIDS with more than 2.5 million new cases reported each year.

Advances in HIV prevention and antiretroviral therapies have made successfully living with HIV/AIDS a reality, and some of the newer treatments can dramatically extend the life expectancies of HIV/AIDS infected persons. Although HIV/AIDS is now a "manageable disease," public health officials and HIV/AIDS researchers agree that a prophylactic or therapeutic vaccine represents the best option to prevent the worldwide spread of the virus and reduce the enormous healthcare costs associated with treating the disease.

Yet, despite billions of dollars in research spending and more than 20 years of laboratory experimentation, development of an HIV/AIDS vaccine has been elusive and marked with highly publicized failures. In fact, several years ago this prompted Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, National Institute of Health (NIH) and a leading HIV/AIDS researcher, to announce at an international HIV/AIDS meeting that he "wasn't sure conceptually whether we could actually have an HIV/AIDS vaccine." More recently, however, at the AIDS 2012 Vaccine Conference held in September in Boston, he said (based on a more thorough analysis of the results from a 2009 HIV/AIDS vaccine Phase 3 clinical trial), "We proved the concept that we can do it; now we need to do much better to create a vaccine."

A GLIMMER OF HOPE

From 2003 to 2007, four experimental AIDS subunit vaccines were tested in more than 11,000 clinical trial participants but failed to provide any protection against HIV infection. However, as mentioned above, careful analysis of results from a 2009 Thai Phase 3 clinical trial of over 16,000 participants revealed that 31.2% of participants were protected against HIV infection. While these results suggested only modest protective (nowhere near the 80% or better protective efficacy typically required for commercialization of infectious disease vaccines), it convinced many researchers that an HIV/AIDS vaccine may ultimately be possible and that co-immunization of a live viral vector plus a subunit and/or DNA vaccine would be required to develop an effective vaccine to protect against HIV infection.

This reinvigorated HIV/AIDS vaccine researchers and helped to advance several new experimental vaccine candidates (see Table 1) in Phase 2 clinical development. Currently, there are three experimental vaccines in Phase 2a clinical testing and only one that has advanced to Phase 2b trials (see Table 1). More importantly, there are 41 other experimental vaccines currently in Phase 1 testing. Curiously, unlike most other infectious diseases vaccines which are usually developed by life sciences companies, clinical development of HIV/AIDS vaccines is mainly funded by government agencies like the NIH, philanthropic organizations, and a variety of academic institutions around the world.

Of the four vaccines in Phase 2 clinical testing, only one of them — DNA MVA — was developed and is being tested by a commercial entity. DNA MVA was developed by GeoVax Laboratories, Inc., a small 11-year-old Georgia-based biotechnology company. NIH is sponsoring the GeoVax clinical trial. The remainder of the trials is being exclusively funded by various U.S. government agencies including the NIH and the Army.

WHO SHOULD PAY FOR AN HIV/AIDS VACCINE?

In 2011, roughly $841 million was spent on HIV/AIDS vaccine development with $615 million provided by the U.S. government, $103 million from philanthropic organizations, and the remainder contributed by European and other governments ($94 million) and the life sciences industry ($30

million). It is obvious that development of a vaccine is disproportionately being funded by the U.S. government and philanthropic organizations without much involvement from the pharmaceutical and biotechnology industries. Interestingly, many life sciences companies withdrew support for HIV/AIDS development vaccine programs after disappointing clinical trial results in the mid-2000s.

Bob McNally, CEO of GeoVax, feels that a lack of meaningful corporate financial and commercial involvement with HIV/AIDS vaccines has seriously impeded development. McNally said, "The U.S. government, especially the NIH, has been extremely supportive both scientifically and financially." However, he added, "While the U.S. government generously sponsors vaccine research and helps to underwrite much of clinical trial costs, it does not pay for commercial vaccine manufacturing, nor does it pay overhead and operating costs for smaller companies seeking to develop a safe and effective commercially viable HIV/AIDS vaccine."

IS AN HIV/AIDS VACCINE EVEN POSSIBLE?

The quest to develop an HIV/AIDS vaccine is one of the costliest and most labor-intensive vaccine development projects in history. This has left many scientists and public policy officials to wonder whether or not development of a prophylactic or therapeutic HIV/AIDS vaccine is scientifically feasible. And that, perhaps, a better use of the government and philanthropic funds annually spent on HIV/AIDS vaccine development ought to be used to improve global HIV/AIDS education and prevention.

Nevertheless, Vincent Racaniello, a professor of microbiology and immunology at Columbia University Medical Center and former editor of the *Journal of Virology*, is upbeat about the possible development of a vaccine. He said, "The recent identification of human antibodies that can neutralize the infectivity of nearly every known HIV strain is a huge breakthrough." Further, Racaniello added, "The ability of HIV to evade immune responses has always been a thorn in the vaccine strategy, and having such antibodies seemingly overcomes that problem. If we can figure out what kind of immunogen to use to elicit these antibodies, I believe that will constitute an effective vaccine candidate."

Steve Bende, formerly of NIAID's Division of AIDS vaccine program and once executive secretary of the NIH AIDS Vaccine Research Committee (now called the AIDS Vaccine Research Subcommittee) and now a biotechnology and vaccine consultant, also believes that development of a vaccine is a worthwhile effort. He said, "While results from the RV144 trial suggest that it is possible to develop an HIV/AIDS vaccine worthy of licensure, the best scenario has industry participating fully with government and philanthropic efforts. The emerging science hopefully can bolster, and continue to bolster, the business case for the pursuit of an AIDS vaccine by industry."

Likewise, GeoVax's McNally understands that future clinical development and commercialization of a vaccine will be difficult without participation of larger vaccine production companies. He said, "It has taken us 11 years to get to this point, and we are almost there. Companies like GlaxoSmithKline, Sanofi-Pasteur, Merck, and Novartis, which have their own vaccine development programs, are always looking to smaller companies like ours that can help to develop a potential commercializable vaccine." McNally added, "Hopefully we can find the necessary financial resources to get to that point so that we can pique their interest!"

THE SCIENCE IS STILL YEARS AWAY

A conceptual framework for development of a safe and effective HIV/AIDS vaccine is now in place. Nevertheless, NIH's Fauci is quick to point out that there is no definite timeline for development of such a vaccine. At the 2012 AIDS Conference, he offered, "This [a vaccine] is not going to happen tomorrow; the science is going to take years. And even when the science gives you a concept and product, the actual design and implementation of clinical trials is going to take years." Further, Fauci opined that perhaps the best way forward was to continue to nonvaccine modalities such as microbiocides, condoms, and education to reduce HIV infection rates and then combine those efforts with a vaccine when it becomes available. Finally, he said, "The likelihood of a vaccine has radically changed the possibility of us controlling the HIV/AIDS pandemic and eventually eradicating the disease."

Table 1. HIV/AIDS Vaccines in Later-Stage Clinical Development

Trial Name	Phase	Start Date	Vaccine	Sponsor	Status/Expected Completion
HVTN 505	Phase 2b	June-'09	DNA Ad5	DAIDS, NIAID, VRC	Ongoing/Expected 2012
ANRS 149 Light	Phase 2a	September-'12	DNA Lipopeptide	ANRS	Planned/Expected 2014
RV 305	Phase 2a	March-'12	Canarypox Gp 120	U.S. Medical Research and Material Command	Ongoing/June 2013
HVTN 205	Phase 2a	January-'09	DNA MVA	DAIDS, GeoVax Labs, Inc	Ongoing/2014
Abbreviations:	NIAID: U.S. Division of Allergy and Infectious Diseases; DAIDS: U.S. Division of AIDS ANRS: Agence Nationale de Recherches sur le Sida (France) VRC: Vaccine Research Center: WRAIR (Walter Reed Army Institute of Research)				

How Shire Leverages Mobile Health Apps For Patient Recruitment

By Cindy Dubin, contributing editor

While joining a clinical trial may not be a fitting choice for everyone, experts fear that too few patients are even aware of the option. A report issued by CenterWatch, a clinical trial specialty organization, showed that 70% of all trials nationwide have difficulty recruiting patients. For instance, less than 5% of cancer patients participate in clinical trials, and perhaps more tellingly, reported *The Prostate Net*, more than 85% of patients did not know clinical trials were even available to them. What's more, certain populations — racial and ethnic minorities, women, the elderly — are underrepresented in clinical trials, a deficit that experts say could impact treatment in those populations.

Less sophisticated ways of recruiting patients are still very much at play: patient recruitment firms, direct mail, and advertisements on television, radio, and in print. Slightly more savvy methods involve posting banner ads on Web pages and getting your study into a Google keyword search. "Pharma is doing what it can to add arrows to its quiver by taking advantage of all these strategies," says Joseph Kim, MBS, clinical operations director, Shire, a specialty biopharmaceutical company.

But Shire has added one more arrow to its quiver by being among the first companies to reach potential patients for clinical trials on mobile health (mHealth apps). According to a report from United Kingdom-based Juniper Research, the number of downloads for health-related apps in 2012 will total 44 million by the end of this year. The research firm also predicts that the number of health app downloads will jump to 142 million by 2016. "Everyone is developing mobile health apps, so it's only natural to put clinical research opportunities on the apps," says Kim.

SEEKING OUT THE PERFECT APP

Kim's strategy was to seek out a disease-related health app and work with the developer/owner of the app to list Shire's clinical research protocol. That, says Kim, would greatly improve the probability that Shire would reach the right types of patients. Shire was particularly interested in locating an app focused on Central Nervous System (CNS) diseases, which Kim did by simply researching the apps that were available on iTunes. He admits that there were not many apps dedicated to CNS. He did download all of them, though, to see what they had to offer the patient. "I was looking for an app that had a pleasing user interface, was simple to use, and what I believed would add intrinsic value to the patient," explains Kim. "User reviews were also important. I was looking for signals from patients that an app was sticky and bug-free. Yes, I read all the reviews for all the apps."

Once he found the app, Kim identified the developer and CEO on LinkedIn and contacted him. The CEO wasn't all that aware of clinical trials and how they worked from a recruitment standpoint, so there was some time spent educating him — a process made difficult

by the fact that the CEO is in Australia and Kim is located in Pennsylvania.

"I didn't want the trial invite to be an advertisement on the app; it needed to be a feature of the app," says Kim. The CEO was quite serious about his product and agreed to avoid models that looked like advertisements, such as iAds that deliver pop ups on the bottom section of mobile device screens while people use apps. Kim and the developer worked on new code to create a tab that would invite patients to learn about the clinical trial. Much like LinkedIn that has a feature allowing people to connect, Kim wanted trial listings to be a feature of this app. "This notion of being able to connect was based on the assumption that many patients consider trial participation an extension of their healthcare as it provides them with excellent care and potential access to treatment," explains Kim.

The original app had some nice features that helped the patient track treatments, symptoms, and behaviors so they could better identify patterns that might help them manage their disease better. There was also a website version of the application where users could examine their data in greater detail.

Now, when a patient downloads the CNS app for $4.99 (initially, the app was free to help grow the user base), a tab appears on the screen for the patient to click. At that point, the language about the trial appears along with a link to a recruitment website. If the patient is interested in learning more about participating in the trial, they are routed to a third-party website to see if they prequalify and are in close proximity to the study site location. Prequalified patients are then referred to the nearest study site. Once the patient is enrolled in the trial, Shire keeps them engaged through text message reminders to help them stay compliant with their visit schedules.

Thanks to special features in the new app, Shire is able to keep track of click-through rates to the trial invitation. "We are currently reaching patients with the app for specific trials, and the click-through rates are 7 to 12 times that of direct mail, and upwards of an 80% to 90% increase over Google keywords," says Kim. "Though the reach is not yet as big as these other outreach tactics, the results are encouraging and hold great promise."

MOBILE APPS ARE A DISRUPTIVE INNOVATION

mHealth as a patient recruitment tool also holds promise as a disruptive innovation. This term, coined by Harvard Business School Professor Clayton Christensen, describes a process by which a product or service takes root initially in simple applications at the bottom of a market and then relentlessly moves up-market, eventually displacing established competitors. In his book, *The Innovator's Prescription*, Christensen discusses if pharma is poised to be disrupted and that profit is no longer in the pills — it is in the services or products that surround the pills. However, he said he didn't know enough about the pharmaceutical business to identify exactly what those products or services might be.

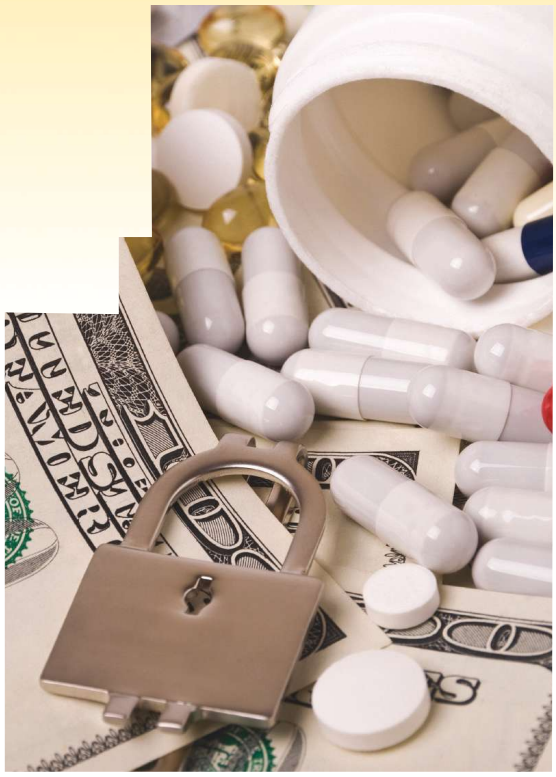
mHealth as a patient recruitment tool also holds promise as a disruptive innovation.

Kim believes that mobile technology could be that disruptive innovation. Considered the most rapidly adopted technology, mobile phones and computers are reaching unprecedented levels because they are becoming less expensive. This technology also crosses socioeconomical levels, race, and gender, making it accessible to all.

"Mobile technology, in particular mobile health apps, empowers patients today because they can become sophisticated managers of their disease," says Kim. "And there is a huge opportunity for pharma to use the technology to become more patient-centric from a research standpoint."

So, while mHealth will not obviate the need for patient recruitment firms, the apps will force a disruptive change. "Television ads still make the phone ring, but you can never expect to reach everyone though one channel," says Kim. "Pharma leaders and recruitment firms need to learn the paradigm of mobile health to adapt and stay competitive."

5-Year Survey Reveals Supply Chain Product Protection Concern



By Cathy Yarbrough, contributing editor

The security and integrity of drugs and medical devices are a growing concern to supply chain and logistics executives in the life sciences industry, according to a 2012 survey of 375 pharmaceutical, biotech, and medical device company officials. In 2008, when the annual survey began, only 13% of the life science executives who were questioned identified the protection of their products during transit, storage, distribution, delivery, and sale as a top supply chain concern.

During the past five years, the respondents who said that they were worried about product protection have more than quadrupled to 57%, according to the latest survey, which was conducted in April and May 2012. Product protection, which covers damage and spoilage as well as security, is one of the fastest growing concerns of respondents in the blind, in-depth "Pain in the (Supply) Chain" survey, which is sponsored by UPS, the international delivery and logistics company. The market research company TNS conducted the survey for UPS.

The UPS survey also revealed that a related topic, IP protection, is receiving more attention from supply chain decision makers. Over the past three years, the respondents ranking IP as a top general business issue have grown from 40% in 2010 to 48% in 2012.

"Globalization has made IP more important to biopharmaceutical companies," said Craig Audet, senior VP, operations and head of global regulatory affairs at San Diego-based Arena Pharmaceuticals, whose weight-loss drug BELVIQ was approved by the FDA in 2012. To safeguard the IP on BELVIQ, Audet said that in the years preceding the submission of the NDA for the drug, Arena "was very focused on obtaining composition-of-matter patents in 98% of the world's countries."

According to the 2012 UPS survey, supply chain leaders in Asia are the most worried about product damage and spoilage, while their counterparts in the U.S. and Western Europe are more concerned with regulatory compliance and cost containment. However, leaders in all areas said protection of their products in emerging markets was a major focus.

The rising importance of product protection, like IP, is due in large part to both globalization and the increasing sensitivity of healthcare products, said Scott Szwast, healthcare segment director at UPS. Other contributors include a larger and more diversified customer base and the increased number of controlled substances and higher value drugs and medical devices now in the supply chain. "The longer supply chains of the global market create more situations where product can be at risk, both for temperature excursion and for thieves seeking to sell healthcare products, particularly controlled substances," said Szwast. And with the growth of outpatient surgical centers and other alternate care locations, more controlled substances are in the supply chain, he added. "In the last decade, product theft and counterfeiting have increased by 34%."

According to news reports, an estimated $80 million in drugs were stolen in the largest pharmaceutical heist in U.S. history, which occurred in 2010 at an Eli Lilly and Company warehouse in Connecticut.

GLOBAL SUPPLY CHAIN CREATED HIGHER RISK FOR PRODUCT DAMAGE

In the survey, Asian and Latin American leaders ranked product damage and spoilage as one of the top three supply chain issues. For their counterparts in North America and Europe, damage and spoilage are among the top five issues. The likelihood that products will be damaged or spoiled has increased because globalization has created longer supply chains and thereby more opportunities for reducing product integrity, and the products have become more sensitive, according to UPS.

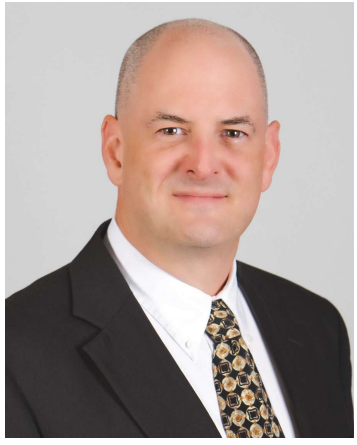
However, product protection was not the supply chain topic about which the respondents are the most worried,

according to the 2012 survey. It was ranked number three after regulatory compliance, identified as the top concern by 65% of the respondents, and managing supply chain costs, voted as the second most important concern by 60%.

According to the survey, only 41% of the supply chain leaders said they successfully managed their supply chain costs. "Concerns around regulatory compliance and cost management have been constants for healthcare supply chain decision makers over the past five years, while we've seen growth in concern around areas such as product security and product protection," said Szwast.

When the executives were asked to identify the number one barrier to global expansion, the regulatory landscape received the most votes. A total of 46% of the 2012 survey respondents ranked country regulations as the number one barrier. However, 77% of the executives reported their companies had tapped into new global markets in the past 18 months, and 83% said their companies planned to invest over the next three to five years in expanding their markets, particularly in China, Brazil, India, and the U.S.

"The longer supply chains of the global market create more situations where product can be at risk, both for temperature excursion and for thieves seeking to sell healthcare products, particularly controlled substances."



Scott Szwast, healthcare segment director, UPS

The survey also revealed that the executives planned to invest in advanced technologies to improve the management of their supply chains. A total of 83% of the respondents said that they would invest in technologies including order management, Web ordering, serialization/e-pedigree or track-and-trace, and security-specific and temperature-sensitive technologies. Such technologies have become essential to managing a supply chain because the customer base is no longer primarily hospitals and pharmacies, but also nursing homes, doctors' offices, outpatient medical and surgical clinics, and even patients' homes, Szwast noted.

"The customer base is a larger and more diversified market," he explained and added that it's also more global, with countries outside the U.S. now responsible for almost 60% of today's demand for healthcare products. That means supply chain executives are under pressure to serve customers worldwide, while complying with a growing number of regulatory requirements in the U.S. and other countries and keeping their costs down, Szwast pointed out.

SUPPLY CHAIN SHOULD BE TAILORED TO EACH "PATIENT UNIVERSE"

To cope with these pressures, supply chain decision makers should be more collaborative, adopt segment-based supply chains, and leverage new innovative models and technologies such as order management software. "They should work with suppliers as well as their customers to exchange information," Szwast said and added that the supply chain should be tailored to the "patient universe" for each product.

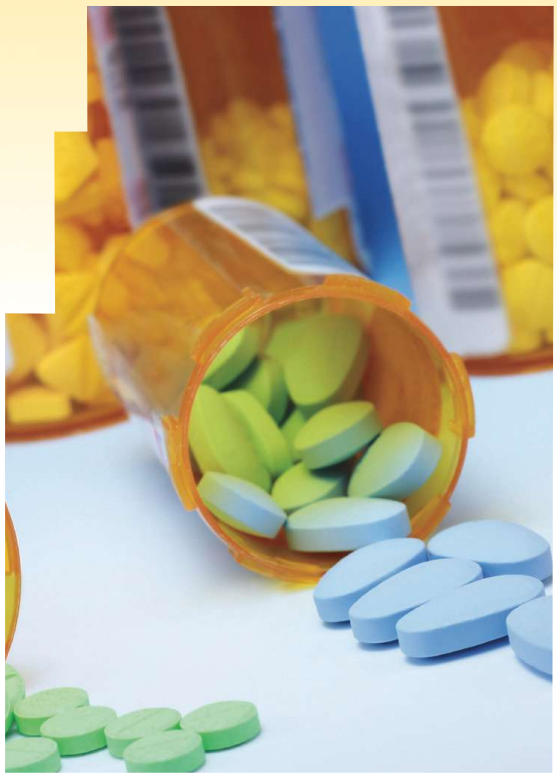
"The healthcare supply chain too often has been one-size-fits-all," said Szwast, despite "an expanding patient universe," which now ranges from senior citizens with chronic diseases treated with mass-market prescription and generic drugs to patients with cancers that depend on biologics, many of which are temperature-sensitive and thus require constant temperature control from manufacturing to administration.

Industry leaders are realizing that their supply chains can affect their companies' bottom lines. "Companies that are regarded by their industry peers as having best-in-class supply chains outperform by 7% to 26% their peer groups in terms of market capitalization," said Szwast. "And, studies have shown that supply chain management directly impacts 75% of a company's business operating costs."

Since BELVIQ is Arena's first product to receive FDA approval, the company had the opportunity to create a new supply chain from the ground up. However, Arena decided to partner with another biopharmaceutical company, Eisai Inc., with an established system and substantial experience in shipping, storage, distribution, and delivery of drugs.

Eisai will pick up the boxes of BELVIQ in containers from the dock of the Arena manufacturing plant in Switzerland. "In the future when we have more products, we may develop our own supply chain," Audet added. "But for now, we're pleased to collaborate with a pharmaceutical company with expertise in this area."

Serialization And Regulatory Compliance: Start Small To End Big



By Matt Walker

Many pharmaceutical and life sciences companies are feeling the pressure of pending state and federal regulations that take a more stringent stance on drug safety and supply chain integrity. Spurred on by consumer advocacy and a rise in drug diversion, theft, counterfeiting, and shortages, forward-thinking pharmaceutical and biomedical manufacturers are proactively assessing their readiness to adhere to new and ever-changing regulatory requirements. For most, waiting is not an option. Without firm standards currently in place, a cautious approach is sensible, but misjudging the pace of regulatory changes or the determination of competitors can put pharmaceutical, biotech, and medical device companies behind the curve, scrambling to catch up to a changing market environment.

There is no doubt that for most organizations — even those that control a majority of the manufacturing in-house — upgrading to item-level serialization and e-pedigree tracking capabilities to match anticipated regulatory changes and market shifts can be a highly daunting proposition. In analyzing the various challenges of serialization, pharmaceutical and life sciences companies must first evaluate the processes, partners, and technologies within and outside the organization.

Harnessing the enormous complexity of increasingly global and diverse pharmaceutical supply chains is a formidable task. As a result, many organizations embark on an iterative process, starting small to end big. For most organizations, it starts with an evaluation of internal manufacturing, packaging, and shipping processes. A medium-tier biopharma firm, for example, recently completed a pilot project related to item-level serialization that involved the integration of an electronic product code information services (EPCIS)-compliant event repository (ER). The ER receives data from shop floor tracking and serialization software, which is also fed to the ERP (enterprise resource planning) system. Both systems receive the data they need for reporting, analytics, and decision making. The next step for this company will be to expand its evaluation to supply-side trading partners, transportation, and buy-side trading partners to develop a closed-loop serialization and traceability solution.

ASSESSING THE CURRENT STATE OF READINESS

The first and crucial step is an assessment of processes and systems, where organizations look internally, to assess risks, gaps, and opportunities. Organizations must ask a series of questions. It's best to begin with key top-level areas of focus. Who owns the issue? Who else is impacted? (Many times the impact can go all the way to pharmacovigilance and regulatory affairs.) What level of visibility and decision making is required? Will there be a need to support regulations from other countries or regions of the world? Is there executive sponsorship? Is this viewed as a cost center, or is it viewed as a way to reduce leakage from chargebacks? More tactical questions are also required. What are the capabilities of current systems? What will it take to convert to item-level serialization? Is there technology in place to allow the necessary level of data communication with all trading partners downstream, even when the pallet and case parent/child relationship is disrupted? Solutions must go beyond packaging to encompass process alignment with manufacturing, trading, and distribution partners for coordinated quality and compliance, and smart technology (that collects and analyzes data in near real time) integration.

Engaging early and often in conversation with supply chain

partners, like contract manufacturers, third-party logistics (3PL) providers, and distributors can be a good proactive next step, especially as regulatory issues become more certain. Understanding the serialization capabilities of partner organizations (i.e. the capability to serialize and trace at the item level) and filling in any gaps by freeing up the flow of data across the supply network are critical requirements. Aligning internal resources to share best practices and data across the extended supply chain is crucial in ultimately ensuring closed-loop serialization and traceability compliance. Another forward-thinking biopharma company is leveraging collaboration technology to create small-batch serialization and traceability on their APIs. In the event of a quality issue or recall, the raw materials data is readily available and allows for faster and more accurate pinpointing at the batch level, reducing cost, time, and potential brand risk.

ENSURING DATA TRANSPARENCY AND SMART DECISION MAKING

As with many business problems today, technology can be a key facilitator to aligning people and processes. Next-generation serialization and traceability solutions are evolving into a network of integrated systems that include a number of components, including item-level serialization and traceability at multiple levels (i.e. before, during, and postpackaging line), regulatory monitoring, EPCIS-compliant event repositories, and B2B/EDI (electronic data interchange) communications that allow data flow across all parties. Some organizations have components of these systems already in place, but need to work on assessing their role in an integrated, technology-driven solution. Serialization and traceability as well as business communication and collaboration technology is required. The good news is that as technology continues to mature and become more heterogeneous, the requirement to rip and replace current systems is rapidly fading. In many cases, a good part of a company's existing technology can be leveraged in one way or another as a part of a forward-thinking serialization and traceability solution. Supply chain executives must work with IT to assess the value of existing systems and applications and assess technology gaps. This also adds value to solution partner selection and pilot program development.

THE "LEGO" APPROACH

Not surprisingly, biopharma as a whole lags behind other industries, such as aerospace, defense, and high tech, in supporting item-level serialization and traceability across the value chain. There are a number of causal factors; however, part could be attributed to the historical regulatory ceiling, and part could be attributed to the increased role wholesalers and distributors have taken on in the area of information services. However, as manufacturers become more responsible for item-level e-pedigree, this will most likely change.

Today, more companies are taking the first steps toward proactively assessing existing systems and processes and determining the serialization and traceability requirements of the upcoming changes in California law. The goal is to create a seamless system of technology and processes that not only collect information on items, cases, and pallets at various stages of movement through the value chain, but also free up the movement of that collected data in a way that it is available in real time to key stakeholders for faster decision making.

Developing and implementing a scalable serialization and traceability system can be a time- and resource-intensive process.

Developing and implementing a scalable serialization and traceability system can be a time- and resource-intensive process. That is unless a "LEGO" approach is employed and organizations create and stack the technology, resources, and process-building blocks toward true item-level serialization and traceability capabilities. From accessing the current state and ensuring item-level data collection to creating a layer of data flow across disparate internal and external systems, the smart approach, in an increasingly more restrictive regulatory environment, is to seize the opportunity today and start down the road toward broad implementation.

About the Author

Matt Walker serves as TAKE Solutions' EVP for supply chain. He has more than 20 years of leadership experience in supply chain solutions, life sciences, and consulting.

The Rise Of Precompetitive Collaboration

By Gail Dutton, contributing editor

With funding tight and innovation often outsourced, biopharmaceutical firms are turning to precompetitive agreements to exercise economies of scale in areas that are common challenges to the industry and that, in the early stage, confer no competitive advantage. According to Baruch Harris, Ph.D., chief business officer, Enlight Biosciences, "Vertical integration is breaking down as companies focus upon their core competencies." Resultant precompetitive collaborations range from public/private partnerships such as the NIH-Industry Target Validation Consortium to syndicates like Enlight Biosciences, which was formed expressly for precompetitive collaboration. "There's a lot of experimentation with partnering structures now," Harris says.

DRUG COMPANIES OPEN UP

Traditionally, precompetitive agreements were formed to develop the technology needed to advance the science. At Janssen, "We used to collaborate in safe haven areas like new technology platforms for screening or biophysical methods for measuring binding of molecules to drug targets. Target identification and validation, however, remained confidential," says Barry Springer, Ph.D., senior director, Biotechnology Center of Excellence, Janssen Research & Development, LLC, of the Janssen Pharmaceutical Companies of Johnson & Johnson. "Now the industry is more open to sharing data around target molecules in a specific class and competing much further downstream in the drug development process where we can add significantly more value."

Companies often participate in multiple precompetitive collaborations simultaneously. Janssen, for example, is a partner in Enlight Biosciences, TransCelerate BioPharma, the Alzheimer's Disease Neuroimaging Initiative, and, in Europe, the Innovative Medicines Initiative. As Springer, the Janssen lead for the technology-focused Enlight syndicate, says, "Right now, the capital is flowing behind molecules with shorter-term ROI, so we feel the R&D technology critical for drug development is underfunded."

Enlight Biosciences, for example, was founded by Pure Tech Ventures upon the principle that a better understanding of the fundamental biology can lead to designing better drugs. "It's become clear that many things have gone into clinical trials without an understanding of the underlying biology or mechanism of action. It's not surprising there have been a lot of expensive, high-profile failures," Harris emphasizes. Consequently, this syndicate considers the research not just in terms of science, but of scale-up, standardization, costs of goods, market barriers, and the types of experiments necessary to increase value and decrease risk. Abbott, AstraZeneca/MedImmune, Johnson & Johnson, NovoNordisk, Lilly, Merck, and Pfizer are Enlight's member companies.

TransCelerate BioPharma was formed August 2012 by Apple Tree Partners with 10 participating companies (Abbott, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Johnson & Johnson, Pfizer, Genentech, and Sanofi). To reduce R&D bottlenecks, the TransCelerate syndicate is operating five projects in parallel. Members are developing a shared user interface for an investigator site portal, standards for study site qualifications and training, a risk-based site monitoring approach, clinical data standards, and a comparator drug supply model. "These were selected from a list of 30 projects. We expect each to meet significant milestones and produce deliverables in 2013," says Garry Neil, interim CEO, TransCelerate BioPharma.

CONCERNS WITH PRECOMPETITIVE AGREEMENTS

There is very little downside to precompetitive agreements except for the inability to own the technology outright. Increasingly, however, there is little value in owning a technology at such an early stage, Harris counters.

TransCelerate concentrates upon developing standards and processes rather than on projects that could involve conflicts of interest or IP issues. Nonetheless, "We could develop IP someday," Neil says. "We are very cognizant of antitrust issues and have strong antitrust counsel working with us. Therefore, we try to centralize and formalize things more than a company working alone."

"Antitrust issues are a particular concern with precompetitive collaborations," agrees Chad Landmon, cochair of IP practice and chair of the FDA Practice Group, Axinn, Veltrop & Harkrider LLP. "There are ways to engage in precompetitive agreements without antitrust coming into play, but be

very careful who your collaborators are and how data is shared. You don't want to be accused of either sharing or stealing trade secrets." Therefore, when possible, Landmon suggests separating the team actively collaborating from the rest of the corporation to minimize the opportunity for inadvertent release of sensitive information. For example, the individuals actively engaged in a collaborative agreement on, say, Alzheimer's Disease therapies, shouldn't be actively working on the company's own in-house Alzheimer's therapeutics.

In contrast, "Antitrust issues usually don't exist with academic partnerships, but IP concerns are the same," Landmon continues. The IP developed in academia often forms the basis of precompetitive syndicates, which are geared toward commercialization. When working with academic partnerships, the financial structure of the deal also differs. "University partnerships expect funding in exchange for participating in the project," whereas industry collaborations share the costs.

ADVANTAGES OF PRECOMPETITIVE AGREEMENTS

"Precompetitive agreements are a creative way to share risks," Springer says. Financially, the funds required to participate typically are low. The Massachusetts Neuroscience Consortium, for example, is funded by seven companies contributing $250,000 each. The low contribution is possible because much of the work is done in academic labs.

Entry costs vary with the organization. As Neil says, "The amount of funding precollaborative syndicates need is in the millions of dollars." TransCelerate's financials aren't public, but Neil says it has established a combination of financial support and contributions in kind, such as personnel or access to equipment or facilities. In this consortium, the scientists and operations personnel actively collaborating are working directly on those collaborative projects at partner companies. "We aren't working in isolation," he adds. "We work with the regulatory, advocacy, academic, and industrial communities."

Economies of scale also extend to due diligence for interesting technology. For example, Harris says, "Enlight looked at more than 100 technologies before forming this company." Individual companies could have done that, but collaborating is more cost-effective.

The ability to shape the direction of research is another significant advantage. "Academic collaborations often lack this ability or have goals that are not aligned with commercial interests," Harris says. Precompetitive collaborations, in contrast, tend to use a research plan aimed at commercialization. For example, "We identify the reasons a project won't work and then determine the critical experiments needed to make it work. If those experiments are successful, we have something special."

"Precompetitive agreements bring together experts throughout the industry, so participants can have detailed, deep discussions to shape the direction of projects," Janssen's Springer adds. They provide a sort of "best practices" approach to a given challenge and are structured to encourage free flow of information among participants. For example, when Enlight's academic researchers debated the best animal model for a particular project, the syndicate was able to pick the brains of industry experts and return a synthesized answer.

Academic research agreements, in contrast, tend to involve one or two experts. "The difference between academic research agreements and precollaborative agreements is that academic projects tend to be narrowly focused around a key question, while precollaborative projects typically are broader because of their ultimately commercial focus.

THERE ARE NO "IDEAL" PROJECTS

There's no agreement on the type of project best suited for precompetitive agreements. Harris advocates high-risk projects that, if successful, offer potentially large payoffs. The Alzheimer's Disease Neuroimaging Initiative (ADNI) is one example. This groundbreaking study seeks to identify presymptomatic brain alterations in people who eventually develop Alzheimer's disease. Additionally, Springer says, "There are opportunities in well-tested and validated technical platforms that may be better developed in a shared environment. For example, high-throughput screening or compound library development could be developed precompetitively. A database of preclinical toxicology data could be of high value, but not high risk."

Regardless of the type of precompetitive agreement, calculating payback is a real challenge. Springer says, "The development timeline is long, and you would have to back-calculate." Therefore, the determination to participate in any particular precompetitive agreement is a calculated decision based upon alignment with the company's strategic priorities. Each company makes that decision differently. "When looking for platforms, we want to align with areas where we have the ability to compete scientifically and commercially," Springer continues. "At Janssen, the decision starts with our strategic priorities, but opportunity also plays a role." Projects that have the potential to be transformational would be enticing, for instance, and based upon the likelihood of technical and regulatory success.

STRUCTURE

To minimize patent squabbles, Landmon recommends listing the collaborative entity as the patent holder. Members then license the IP from that entity just as they would any other company. Having such a formal structure for sharing IP is important when there are many collaborators, because it minimizes any confusion regarding IP ownership, Landmon says. That said, a clear understanding of exactly what is contained in the resulting patent pool is necessary to avoid disputes.

Enlight Biosciences uses a similar approach. In it, members work directly through Enlight rather than collaborating directly with each other. That helps create a degree of separation among collaborators that protects members' own trade secrets. "We have a lot of flexibility regarding the level and extent of each collaboration, so we can accommodate varying levels of trust," Harris says.

Precompetitive agreements are becoming more popular as companies understand the relative advantages of collaborating early on the spadework that must be done to prepare the field for advances later. At this stage, before competitive advantages are possible, while economies of scale can be leveraged, collaboration makes sense.

Crowdfunding: A New Route To Finance

By Suzanne Elvidge, Contributing Editor

It's currently hard to get funding, especially for those companies that are too small or too early stage to interest the large-scale investors. As Marc Lemonnier, CEO, ANTABIO (a French drug discovery company focusing on novel drugs to treat and prevent antibiotic-resistant bacterial infections) explains, at the early stage of development, venture capital companies can be reluctant to invest money, but as the research advances, the founders' money may not be enough. So, the company is too young for venture funding, but too mature to be funded by founders, their friends, or families.

So, if you can't get large amounts of money from a few investors, what do you do? You could get much smaller amounts of money from a much larger group of investors. This is crowdfunding, and it can provide funding on a project-by-project basis or equity investment in a company. There are two main forms of crowdfunding, donation-based or securities-based.

In donation-based crowdfunding, people may simply make donations, or they may get rewards or perks or have the opportunity to buy products preproduction. "Nonprofits and charities in the life sciences have a long history in crowdfunding in the form of large numbers of small donations, such as through sponsored events," says Lee Barken, CPA, energy and cleantech practice leader at Haskell & White (business advisors for a range of companies including hi-tech; Barken speaks and writes on crowdfunding).

ACCESSING CROWDFUNDING

Investors access crowdfunding opportunities through portals, where they can search for projects of interest, such as a specific disease, or in their local area and then invest online, even as little as a few dollars. Some portals operate on an "all-or-nothing" basis — the project must reach its funding goal, otherwise no funding is provided, and no fees are taken.

There are crowdfunding portals designed for the sciences, allowing people to donate money to companies and individuals in return for rewards or simply for the knowledge that they have supported research and development. Examples include MedStartr, which focuses on medical innovation; and Microryza, iAMscientist, Flintwave, Open Genius, SciFlies, and TechMoola, which all offer access to projects across the sciences.

Securities-based crowdfunding, whether lending money or buying equity, is a newer move for crowdfunding and is a more complex undertaking. In order to protect both companies and investors, regulations are necessary. There is a regulatory framework in place in Europe that allows securities-based crowdfunding, and according to Nesta (the United Kingdom innovation foundation), in 2011 companies and individuals raised €1.5 billion (approximately $1.9 billion) through crowdfunding for projects and businesses.

Examples of European equity-based platforms include:

- Anaxago (France)
- BankToTheFuture (U.K.)
- CrowdMission (U.K.)
- Crowdcube (U.K.)
- FundedByMe Equity (Sweden)
- Innovestment (Germany)
- MyMicroInvest (Belgium)
- seedmatch (Germany)
- Seedrs (U.K.)
- Symbid (Netherlands)
- WiSEED (France)

Securities-based crowdfunding is not yet available in the United States. However, the JOBS (Jumpstart Our Business Startups) Act should ease some securities regulations, including allowing companies to source money from a wider pool of smaller investors, controlled by fewer restrictions. President Barack Obama signed the JOBS Act into law in April 2012, and the Securities and Exchange Commission (SEC) has about 270 days to create rules and guidelines. Both David Palella, founder of BioScience Ventures, a biopharmaceutical consulting firm, and Barken predict that the guidelines could be in place during 2013, but raise concerns that the SEC could make it very easy or very difficult for companies to use this funding route. "If the SEC guidelines are delayed, this could create obstacles for equity-based crowdfunding in the United States," says Palella.

ANTABIO AND WISEED

ANTABIO has used crowdfunding to get a

seed-round of financing through WiSEED, a crowdfunding platform based in France. WiSEED is dedicated to innovative and technology start-ups, and investors can invest directly online, with as little as €100 (approximately $130).

"At ANTABIO, we are a pure drug discovery company with no fee-for-service arm, so we rely on fundraising. We needed €300,000 (approximately $389,000) to validate our technology and molecules, to get enough data to attract a business angel. WiSEED's innovative crowdfunding process allowed us to complete ANTABIO's seed financing in a record time," says Lemonnier. ANTABIO used the money to fund a proof-of-concept trial of its technology, and the data attracted a second investment from a business angel, which in turn led to an undisclosed drug discovery player acquiring the crowdfunding holding. This allowed WiSEED and the more than 200 small investors to exit with a profit. According to Nicolas Seres and Thierry Merquiol, founders of WiSEED, this is the first complete "virtuous circle" for crowdfunding applied to biotech start-ups.

MAKING THE MOST OF THE OPPORTUNITY

Raising money through crowdfunding is not quite the same as raising money through traditional routes — while you need to present a business case, members of the public will need different information and different levels of detail. "To make the most of a crowdfunding opportunity, you need to have an exciting technology, a solid business plan, and a good team. You also need to be able to communicate your science with a passion," says Lemonnier. Palella adds, "I think crowdfunding could be most effective for those companies that have a human interest story, such as a drug for a childhood disease. The technology has to create a buzz, and the management team has to be good at marketing," says Palella.

Companies seeking crowdfunding will also benefit from having a fan base — a group of "consumer cheerleaders" that will use their social media networks to spread the word. "People want a return on investment, obviously, but they also want to be part of something that is socially important, so the crowdfunding approach is best fitted to companies that are addressing major unmet needs," says Lemonnier.

SURELY, THERE'S A CATCH …

So, crowdfunding has potential to support the development of products for unmet needs, rescue companies that are falling into the funding gulf between founders' money and VC, and provide the golden glow of a job well done and a return on investment for investors. It sounds like a win-win. However, is it all too good to be true? It is important to remember that securities-based crowdfunding is still a very new model, even in Europe where there's a legal framework, and there is no legal basis for this as a fundraising route in the U.S.

"Using WiSEED was a novel idea and a very new concept, but the timing was right, and it met our needs," says Lemonnier. "I don't know whether I can generalize, but it certainly worked for us."

Crowdfunding platforms are open to fraud, especially where patients, parents, and carers are involved and where projects are allied with a celebrity name (whether or not with the permission of the celebrity)."There is always the risk of 'snake oil salesmen' in open platforms like these," says Barken. "Vulnerable people, such as those who have incurable diseases and are desperate for a cure, could be enticed to invest in dubious or ineffective treatments in return for an opportunity to get first access to a 'treatment'."

Other risks include companies that are well-intentioned but are incapable of coming up with the product, service, or rewards and scammers and opportunists who post up requests for funding but have no intention of completing the project. Crowdfunding in biopharma and the life sciences needs to develop safeguards as it expands and grows.

"There will always be risks in investing, even with high levels of regulation," says Barken. "However, relying on social networks does build in some protection — defrauding your social network is high risk because it follows you."

People can also reduce the risk of fraud by investing in individuals and organizations that they know and trust. Crowdfunding could be a huge opportunity for groups such as charities and universities to act as "curators" for research opportunities. There are other obstacles to crowdfunding beyond fraud, as Palella explains. "Biotech R&D tends to have a long timeline and requires large investments, so this would make attracting crowdfunding less likely. Crowdfunding also could run the risk of disenfranchising business angels who may believe that the process will bypass them." For crowdfunding to work, turnaround does have to be fast, as Nicolas Seres, managing director of WiSEED, explains, "It is important to quickly reward small investors and keep them focused on this seed phase so that they can reinvest in another project, to reinitiate a novel entrepreneurial adventure."

THE FUTURE OF FUNDING?

Despite these concerns, there is a lot of enthusiasm about crowdfunding in the life sciences and biopharma. The UK BioIndustry Association (BIA) is calling for Citizens' Innovation Funds, which would allow individuals to invest in innovative companies. These are based on the Fonds Communs de Placements dans l'Innovation (FCPI), which raised more than €6 billion (approximately $7.8 billion) between 1997 and 2011, investing in more than a thousand companies.

"I'm very excited about the future of crowdfunding — it could provide greater access to capital. The sweet spot will be for small companies, but there could also be potential for established companies that are looking for real-time market validation for consumer-facing products," says Barken. "For companies, crowdfunding is a cheaper way to raise relatively small amounts of money, and it also provides an early validation of the marketplace. When raising funds from VCs, companies get the money to develop the products and then sell them, hoping that there is a market. Crowdfunding works the other way around — companies prove the market by effectively selling products in advance, and then develop them."

Crowdfunding will only ever provide an additional pathway to funding, however, and won't be a replacement for VC money. It could open up possibilities of hybrid funding models, such as Angelcrowds, which is currently in beta launch. This will provide a portal where investors and entrepreneurs can meet.

Particles & Aggregation — Out, Damn Spot!

By Wayne Koberstein, contributing editor

In markets with little regulation, litigation soars. As regulation rises, litigation falls. Unless consumers are bound by so-called tort reform, their only recourse when harmed by an unregulated product is to sue its maker. That is the basic logic behind my assumption that legal standards, such as those established by the U.S. Pharmacopeia (USP), protect companies that manufacture and supply prescription drugs — either as the primary drug sponsor or as a contractor.

You might have expected me to mention the FDA or its international counterparts in speaking about regulation. And, yes, it's a bit of a semantic stretch to depict the USP's role as regulatory. But in a real sense, drug standards and regulation are intertwined. The United States, Europe, and other regions with central regulatory authorities also have similar and related standard-setting bodies. Regulators view every step of drug development and manufacturing by how it affects the character and consistency of the compound. Standards, both physical and written, are the touchstones for measuring any changes in the compound as it moves from one step to another, from characterization, through process development and validation, production scale up, and periodic process refinement.

PURITY PREDICTS RISK

Besides monitoring changes to the molecule itself, the major role of standards is to mark a baseline for assessing its purity and potency — interrelated qualities that can change greatly as the scale of production increases. Particles of unwanted substances may form and aggregate at any stage depending on multiple factors such as batch viscosity, concentration, and molecular charge interactions. Commonly, there is a trade-off between potency and purity — the more potent the compound, the more concentrated and thus subject to aggregation it is likely to be.

In turn, the same qualities affect product stability and delivery, and thus affect fill/finish, storage, transportation, administration, and other portals along the supply chain. The burden is on the producer, the company responsible for the compound's development and manufacturing, to ensure that those qualities, once established and approved, remain constant at every point. In outsourcing arrangements, contractors share a variety of risks with sponsors (e.g. product defects, recalls) to varying degrees defined (or not) in their contracts. The "or not" refers to the wild card of litigation. When actual harm occurs, no shelter may shield the supplier from liability.

In some irony, the degree of CMOs' responsibility has increased generally in parallel to that of the sponsors, rather than shifting from one to the other with greater regulatory and litigatory pressures. When a sponsor feels more exposed, whether by current regulation, legal action, or pending legislation, it will naturally find ways to share the exposure with its suppliers.

Contractual liability is one obvious way to share the risk; continuous involvement with and monitoring of outsourced manufacturing is another. Some small companies are leading the charge by insisting that their CMOs institute advanced systems, such as quality by design (QbD), new batch purification and characterization tools, and process analytical technology (PAT). But large companies, feeling the sting of product recalls, plant closures, and supply shortages, are now imposing similar demands on their suppliers.

TOWARD GLOBAL BASELINES

All such approaches depend on standards — "vertical" standards that uniquely define the "critical quality attributes" (CQAs) of each product, and "horizontal" standards that apply to broad product classes and types. Without them, each producer would be on its own, internally assuring itself that all will be right in the end and thereby taking the full risk of liability when something goes wrong. Oh, wait…that's the way it was, and, thanks to large loopholes currently making the news (such as "compounding pharmacies" operating as factories without effective FDA oversight), and the practical limits of regulatory inspection, still *is* to some degree.

Quality assurance means nothing if quality control is like a hidden hand of cards, self-dealt by every player. That is why the USP and similar groups formed early in pharma's history, even in the gilded age of 19th century free enterprise. Shared standards offer shared protection.

The difference these days is the extent of standard setting and verification evolving worldwide, now gaining considerable momentum despite lagging behind the accelerating globalization of outsourced pharma production. Even the USP has become global, not just in collaboration with its international peers, but also in its physical presence around the globe, as well as its ongoing role as a template for emerging standard-bearers in other nations.

RISK-REDUCING INVESTMENT

A serious impediment in today's standards environment is the woeful inadequacy of pharma companies, suppliers, and regulators to keep pace with the changes needed to meet standards reliably, consistently, and predictably. Fragmentation of regulatory responsibilities — either between international authorities or within them — explains some of the lag. But the industry bears much of the blame for clinging to legacy systems, treating manufacturing as a low priority, and generally failing to practice progressive, GMP-based QA/QC throughout the supply chain.

All these factors relate to particles — their size and degree of aggregation — as a strategic concern for the suppliers and sponsors of any compound in development. When the CMO lacks the ability to create the optimum formulation, conforming to the highest standards of purity and potency, the investment in specialized formulation expertise will be justified by a concomitant reduction in risk, including the risk of quality-related liability. The same expertise will be cost-effective at the other key stages of process development, scale up, and production changes.

Yet, as I expound upon in my related report on recent industry events ("From Industrial to Investment Strategies in the Life Sciences"), general resistance to major manufacturing reform in large companies remains as powerful as the need for it is obvious. Where such change is afoot, it is typically isolated to single-facility initiatives inside a company's fragmented collection of factories and limited in its effects on outside suppliers.

Only outside forces can keep the industry moving in the right direction, taking everyone, from the engineer to the CEO, out of the old comfortable sphere of traditional manufacturing into an age of greater efficiency and purpose. Customers, regulators, and litigators will exert much of the pressure. But only high standards, starting with product purity and potency, will positively protect companies and their suppliers by reducing the risk of liability.

Answering The FDA Guidance For Prospective Assessment Of Suicidal Ideation And Behavior In Clinical Trials

Michael Federico

Michael Federico is VP of ePRO solutions at ERT and is responsible for managing all aspects of the ePRO Solutions suite at ERT, including product development, operations, and sales.

Prospective assessment of suicidal ideation and behavior (SIB) in clinical trials has been strongly recommended by the FDA for more than two years. Many sponsors have benefited from technologies to assess possible treatment-emergent suicidal ideation in their trials. In particular, this assessment is required for psychiatric indications. It is also common for trials in therapy areas such as depression, smoking cessation, and weight loss to require this assessment due to long-standing concerns with SIB in these study populations. Per the FDA's revised guidance, "Prospective assessment of SIB might reasonably be used more broadly, perhaps with any drug that appears to have a CNS effect." The application is as broad as the goals, the first of which is to ensure that patients in clinical trials who are experiencing suicidal ideation and behavior are properly recognized and adequately treated. The second goal is to ensure the collection of more timely (i.e. closer to the event) and complete data.

REGULATORY OUTLOOK

First released in September 2010, the FDA's draft guidance, "Suicidality: Prospective Assessment of Occurrence in Clinical Trials," cited the agency's current thinking on the assessment of treatment-emergent suicidality. Revised in August 2012, it reinforces the application principles of the guidance. The newly revised guidance clarifies the expectations of when, where, and how to assess SIB, suggesting that although it is mandatory in only psychiatric clinical trials, it should also be included in clinical trials involving at least selected drugs for nonpsychiatric indications, with already recognized indications of suicidal ideation and behavior. It also cites data showing that this assessment is a low burden and that the lifetime evaluation is a good risk assessment for the patient.

In addition, coding is clarified in the document. Findings must map to 11 Columbia Classification Algorithm for Suicide Assessment (C-CASA) codes specifically noted and defined in the appendix. As the prospective counterpart to C-CASA, the C-SSRS (Columbia Suicide Severity Rating Scale) is an accepted instrument used to assess the suicidal ideation of trial participants. The free-form, clinician-administered interview is designed to be conducted with subjects during trials. The C-SSRS results in findings that directly code to those noted in the guidance, without requiring further coding.

A SELF-RATED APPROACH

Procedural variances in the way this and all clinical assessments are performed by human raters are associated with a number of shortcomings negatively impacting the reliability of results. Even with extensive training, raters' skills deteriorate over time, and clinicians are often influenced by prior experiences with patients. As a result, researchers are actively looking for ways to overcome these limitations. The eC-SSRS, a self-rated electronic version of the C-SSRS, has been cited by the FDA as a way of meeting this assessment requirement. The eC-SSRS is a validated, computer-administrated version of the C-SSRS interview, accepted by the FDA and used in a number of clinical trials. Streamlining the data collection process, eC-SSRS facilitates the collection of high-quality, unbiased data directly from the patient, while at the same time eliminating processing delays. It also has been proven that due to the confidential nature of suicidality assessments, patients are more likely to give true answers to an electronic instrument than to a person, further improving the quality of data. This approach is expected to ensure patient safety and provide more consistent and reliable data.

To meet the requirements of the FDA guidance, it is essential that drug development programs consider using progressive, yet efficient, approaches to incorporate the eC-SSRS into their clinical trials. Not only will doing so ensure patient safety, but it will also protect their compound from false-positive findings. Although not mandatory in most trials, the use of suicidal ideation and behavior assessments is now recommended by regulatory bodies and industry leaders. The recent release of the FDA's newly revised guidance for industry, "Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials," strongly suggests, but currently does not mandate, that these types of assessments be conducted in drug development programs with CNS involvement.

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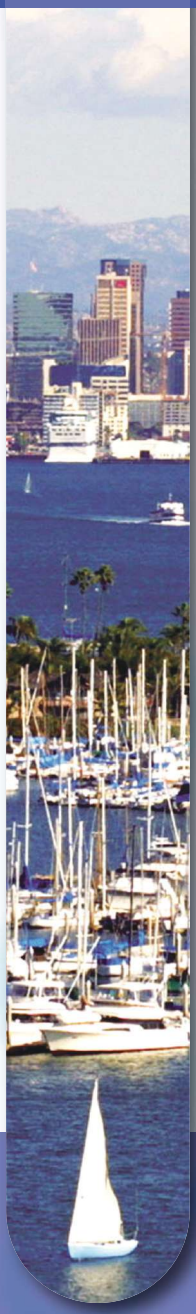

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How Registries Can Close Peri-Approval Info Gaps

Clinical trials conducted for regulatory approval of new pharma, biotech, device, and diagnostic products frequently do not provide the market intelligence required for successful product launch, in-market brand management, and long-term product growth. Queries about the proper use of a new product, expectations of treatment response, key drivers of market uptake, and performance against competitors often begin before market approval. The answers to these questions require real-world data over a broad spectrum of patients and physician-prescribing patterns — data that well-controlled or randomized clinical trials cannot deliver. The information gaps that remain at the conclusion of a clinical trial handicap decision makers who must make early choices about clinical messaging based primarily on the product's approved labeling. By comparison, real-world studies — including disease registries — can provide a sponsor's medical affairs and marketing managers with an early warning system for possible threats, as well as insight into potential future research opportunities, as they map a product's life cycle. These managers are increasingly recognizing registries as a flexible and cost-effective strategy for closing the information gaps left by clinical trials to obtain the data needed to support clinical and marketing strategies. Registries, when designed effectively and integrated with a sponsor's market research activities, can provide a steady stream of new information suitable for external communication to physicians and other healthcare providers, private and public payers, and regulatory authorities. At the same time, registries, along with market research findings, can provide early and ongoing feedback on the effectiveness of clinical messaging and brand management strategies for a sponsor's internal audience.

BECOME RECOGNIZED AS A LEADING RESEARCHER

The activities surrounding the launch of a new registry, as well as descriptive statistics of early registry data, can help establish the sponsor as a leading researcher in a new disease indication. Initial demographic and disease status data collected as patients enroll in a registry can better define the broader, real-world patient population beyond that studied in the controlled clinical trial. This increased understanding of affected patients, with their wider range of demographic characteristics, disease severities, and comorbidities, helps enhance mapping of the natural course of the disease, as well as develop evidence-based guidelines for patient diagnosis and monitoring. Early data from the registry also can be effectively combined with market research findings to position a new product in a new or crowded market. Effective positioning tells physicians and patients how a sponsor's product is unique and the value it offers the target market. Even with the limited amount of information that often results from a registry's first year of operation, registry data and market research findings in the peri-approval time frame can help build a solid foundation for future clinical research and brand management.

A REGISTRY CAN EVOLVE TO KEEP DATA RELEVANT

As the sponsor's needs change, or as the needs of the medical and patient communities adjust to new clinical advances over time, a registry can also evolve to address these new challenges. Clear strategic direction and appropriate planning can ensure that the registry will keep pace with the clinical and commercial information required for successful in-market brand management, providing early warnings for the medical affairs and marketing management teams, and monitoring effective strategy adjustments. During the early phases of the registry, sponsors can begin defining why physicians are exhibiting certain prescribing behaviors based on analyses of the registry's clinical data, rather than tracking uptake and market share only. As a result, current (as well as future) gaps between the expected market effect of a product's labeling and clinical messaging and actual prescribing behavior can be identified and addressed sooner rather than later, thereby providing opportunities for course corrections to optimize a product's success in a complex medical marketplace. Evolving a registry to continually produce data and other important market information requires a periodic strategic reassessment of the key registry design and operational elements, continually building on the base of registry data and market research findings already gathered. The overall goal of any registry program is to continually produce reports and other communications that keep the registry output fresh and relevant to the participating physicians and patients, thereby encouraging their continued engagement in the registry program.

Neal Mantick

Neal Mantick is senior director in PAREXEL's Observational Research franchise. He has more than 25 years of experience in pharmaceutical product development.

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Preparing For The New Workforce

By Kenneth Gronbach

Generation Y, born 1985 to 2004, will prove to be an exciting management challenge. Generation Y is actually bigger than the baby boomer generation born 1945 to 1964 by over one million. It will easily rival the boomer generation in consumption and influence.

Generation Y is a huge population (79.5 million) that follows a small Generation X (69.5 million). This means that the job footprint left behind by Generation X as it advances past entry level into mid-career is too small to accommodate Generation Y as it enters the labor force. Couple this with a downturned economy and baby boomers who can't afford to retire and you have dismal job prospects for millions of Generation Y young people. This creates an employer's market. It would logically follow that the best and the brightest Generation Y applicants will accept skinnier offers, work harder, and just be grateful just to get the job.

Employers can now hire the best and brightest labor in twenty years. Will this create management issues? Yes. We will have three distinct generations in the workplace, and they are from different planets. The obvious difference of course is age. Cultural issues will also come into play. Some examples:

Boomers are immigrants in the cyber world, speak with a thick accent, and know just enough to get by. Generation X is bilingual. Generation Y is native born and moves about the cyber world naturally. They will be able to hack weak employer IT systems routinely, so make sure your systems have the appropriate safeguards. They will shock their boomer coworkers as they text each other during meetings. Email and telephone are embraced by Generation X and baby boomers, but they are foreign to Generation Y. Generation Y will be stunned by a handwritten thank-you note, especially if it is written in cursive, which they cannot read. Hold a meeting at a quarter of nine and Generation Y probably won't show because they don't know what that or even the phrase "clockwise" means. Appearances will be a real issue. Yes, Generation Y does believe that piercings make them more attractive, and they are not concerned with the long-term consequences of covering their bodies with vivid tattoos. Clearly it is time to address appearance issues in management's sensitivity training and HR manuals!

Generation Y does not see a difference in race, color, or ethnic origin. They will demand transparency from their employers regarding humanitarian and environmental issues. A Generation Y worker will probably not stay with a company that he or she considers disingenuous. Clearly, the new mandate is transparency. If this requires cultural change, make the change.

Get ready for boomers to begin to retire by the millions as the housing crisis eases and they can sell their homes. Generation X, currently 28 to 47 years old, does not have the critical mass to satisfy the labor demand created by retiring boomers. Employers will be forced to hire more Generation Y and accelerate their career advancement into mid-level. Young people will manage older people and in some cases much older people, creating a world of new conflicts.

Remember when baby boomers used to be hippies? Were they embraced by upper-level management? We need to get past the appearances and foibles of Generation Y and build a workforce that is ready to take on the challenges and leadership of the next 20 years. Invest in your future now by beginning the process to create a culture of tolerance to attract the best-of-the-best Gen Y employees. You might even want to get a tattoo.

Kenneth Gronbach is an internationally recognized expert in the field of demography and generational marketing. He regularly provides counsel to Fortune 500 companies, as well as large and small U.S. businesses.

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

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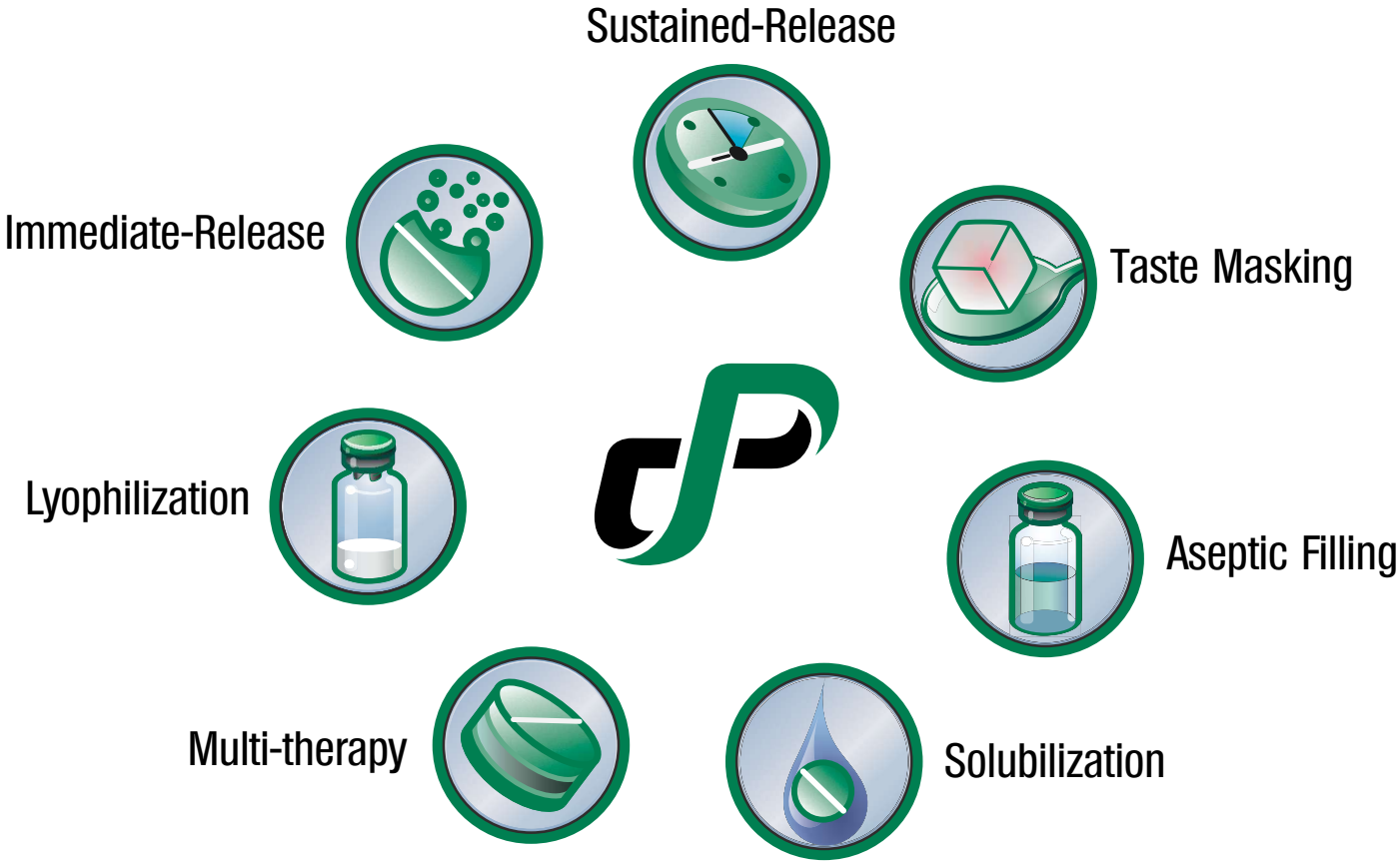

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