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JULY 2014

Millennium: The Takeda Oncology Company's Shift In Strategic Direction

Michael Vasconcelles, M.D., global head, the Oncology Therapeutic Area Unit, puts the company's past, present, and future into context. **p. 20**

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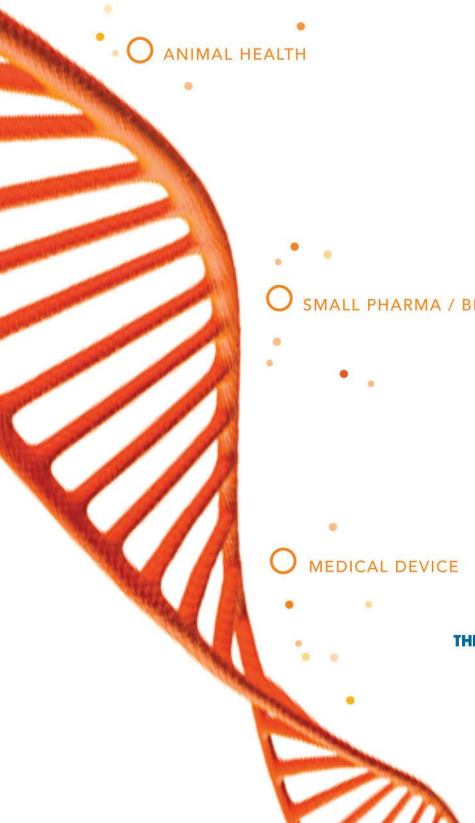

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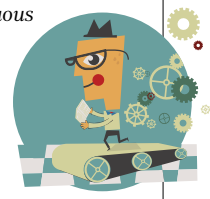

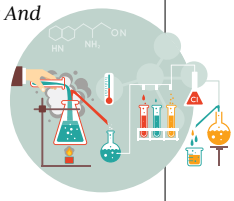

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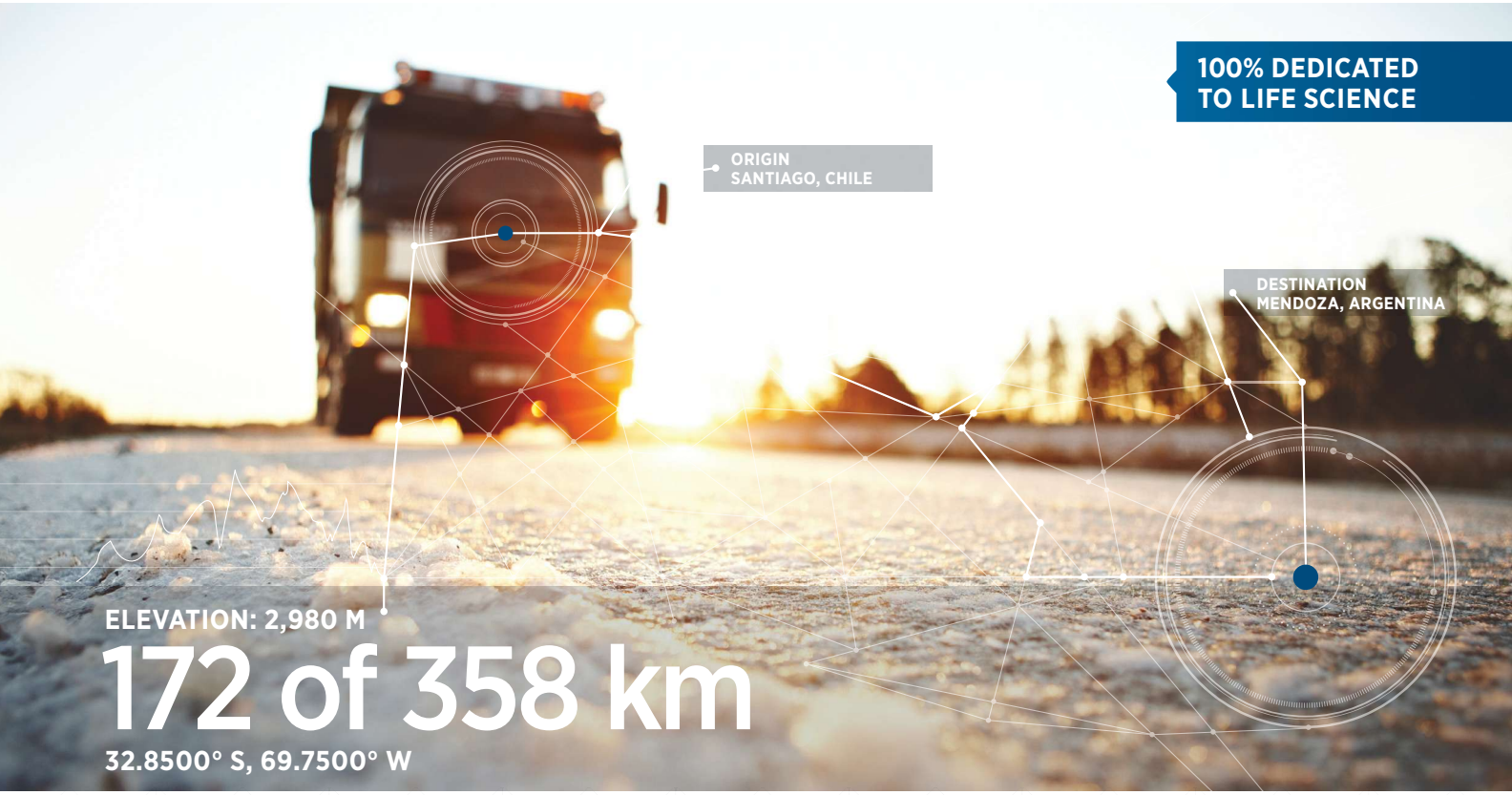

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Want To Find Some Disruptive Innovators?

ROB WRIGHT Chief Editor

One of the most productive conferences for me in terms of getting innovative ideas, as well as meeting people of a disruptive nature, is The Conference Forum's Disruptive Innovations To Advance Clinical Trials event. For example, this is where I first met Pfizer's head of clinical innovation, Craig Lipset; Lilly's VP of clinical innovation and implementation, Jeff Kasher, Ph.D.; as well as VP of clinical trial innovation and external alliances, Andreas Koester, M.D., Ph.D. — the subject of this month's feature article on page 26. In fact, at *Life Science Leader* we are hoping to create a similarly disruptive conference, Outsourced Pharma West (www.outsourcedpharmawest.com), geared toward pharmaceutical and biopharmaceutical executives who form and manage partnerships for development and manufacturing. In my discussions with executives, many have shared their insights regarding the battle being waged around acquiring top talent. If this involves securing disruptive innovators, I have some information to consider.

According to Malcolm Gladwell, bestselling author of numerous groundbreaking business books (e.g., *Outliers: The Story of Success* [2008], and *The Tipping Point: How Little Things Can Make a Big Difference* [2000]), truly disruptive innovators share a combination of traits, including that of being disagreeable. Thus, if companies want to court disruptive innovators, they need to learn how to cultivate people who may not fit their usual employee profile. According to Gladwell, this is part of the role of senior management — to create an atmosphere of innovation that allows for people to be disagreeable. Gladwell stresses not to confuse disagreeable with allowing people to be obnoxious. Rather, disruptive innovators will have what many perceive as a strong sense of self-esteem that comes across as being indifferent to the ways others see them. Gladwell believes the characteristic of being disagreeable is what lets innovators pursue breakthrough ideas, even in the face of objection and derision. Unfortunately, this same characteristic can make for a challenging work environment for fellow employees.

According to Gladwell, for disruptive innovators to be truly successful, the disagreeable trait must also be paired with the ability to be receptive to new ideas, a solid work ethic, and a strong sense of urgency. All of these traits can be tested for during the hiring process. Though people may often exhibit one or two of these characteristics, it is rare to find all of them in one person. Therefore, not possessing all three should not be used as the sole reason to not hire someone. You also can test for self-esteem and self-confidence, but don't waste your time. Instead, seek to create an environment where you can build employee *self-efficacy*, which influences the tasks employees choose to learn and the goals they set for themselves. It also affects an employee's level of effort and persistence when learning difficult tasks. You can test and hire for this as well. But if you put such a person in a nonchallenging, micromanaging environment, why bother? A great short article, *Self-Efficacy In The Workplace: Implications For Motivation And Performance*, by Fred Lunenburg (Sam Houston State University), can quickly get you up to speed on the subject. I read a motivational expert's insights on self-esteem and self-confidence, and I think your time would be better spent understanding the implications of self-efficacy if you want better motivation, performance, and perhaps, a little disruptive innovation.

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Q What book has had the greatest impact on you personally/professionally and why?

A THREE CENTURIES OF MICROBIOLOGY by Hubert Lechevalier and Morris Solotorovsky. Both authors were professors at Rutgers University. They taught a class called The History of Microbiology. You had to read the book and take an oral exam at the end of the course. They told me that if I got an "A" in the class they would accept me in their lab as a Ph.D. student. They also told me that no one ever got an "A" in their class. That "A" changed my life! The first change involves attitude. I learned to accept, even embrace, challenges with a realistic but consistently positive attitude. The second change confirmed the importance of persistence. Keeping the goal in mind, it is important to persevere and stay the course. Sometimes, the only difference between you and your colleagues is your perseverance and commitment to achieving the goal.

MITCH KATZ
In his position at Purdue Pharma L.P., Dr. Mitchell Katz is the executive director of medical research operations responsible for leading activities across all clinical programs. He has 26 years' experience in the pharmaceutical and biotech industries.

Q What would you describe as being the biggest game-changing technology in clinical trials and why?

A ELECTRONIC MEDICAL RECORDS (EMRs). I recently attended the MAGI Clinical Research Conference in Philadelphia. I was stunned to learn the issues with implementing EMR systems and equally shocked at the number of systems in use. When I Googled EMR (according to one website www.capterra.com), I found there are 329 EMR systems on the market. Sites indicated that they struggle to get study-specific information into the EMR systems and have issues about output of information from the systems regarding management of protected health information (PHI). A requirement to train clinical research associates (CRAs) on systems is rarely factored into study setup. On the sponsor and CRO sides, I am concerned that we are woefully unprepared to achieve potential efficiencies of data capture through EMR and question if we are doing enough to ensure alignment with the various EMR system procedures.

MARY ROSE KELLER
As a former VP of Clinical, Mary Rose Keller has proven success in planning, management, and delivery of global Phase 1 to 4 clinical trials for drug, biologic, and diagnostic products.

Q What is the best leadership advice you ever received?

A THE BEST LEADERSHIP ADVICE I EVER RECEIVED WAS GIVEN TO ME BY MORT COLLINS, CHAIRMAN OF THE VENTAIRA PHARMACEUTICS BOARD. I rapidly rose through the ranks at Ventaira and became president & CEO. During this time Mort advised me to "trust my gut." He was an incredible mentor who empowered me at a pivotal point in my career. His belief in my capabilities, even when I was unsure, allowed me to grow. I began to rely on my intuition to gauge the appropriate timing of decisions and the course of action for the company. Of course, when and how to act is driven by the collection and interpretation of hard and soft data. As I look back, I do share this advice with others, but I also add the importance of having a good mentor.

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

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New Medicare Data And Litigation Provide Fresh Reasons For Congress To Reform 340B

JOHN McMANUS The McManus Group

Medicare continues to release unfiltered information on provider utilization, which gives some illuminating information, particularly when that data is cross-walked to other sources. A case in point is the publication of the top Medicare hospital billers in the country: 21 of the top 25 are 340B hospitals and therefore access the substantial pharmaceutical discounts under that program. (See Figure 2.)

All of the top 10 hospitals are 340B hospitals, and many have far-flung subdivisions and contract pharmacies that enjoy access to the program. New York-Presbyterian Hospital, the number one Medicare biller, has 96 subdivisions; Cedars-Sinai Medical Hospital has 31 subdivisions; and Norton Hospitals in Kentucky has 109 subdivisions and 53 contract pharmacies.

Under the statute, these hospitals are entitled to discounts ranging from 23 percent of the average manufacturer's price to 50 percent and often more for *every outpatient drug* provided to *every patient*, regardless of whether they have insurance or Medicare coverage. Nothing requires 340B hospitals to pass these discounts on to the patients — they are simply a vast revenue source, and most of these hospitals continue to charge market rates to Medicare, commercially insured patients, and even the uninsured.

The Affordable Care Act (ACA) expanded the 340B program in several important ways:

1. It increased the size of the minimum discount from 15 percent to 23 percent because it is tied to the identical higher Medicaid rebate that PhRMA negotiated with then-Finance Committee Chairman Max Baucus.
2. It increased the number of hospitals eligible for the program by substantially expanding the Medicaid program, a key component in the formula for determining 340B eligibility.
3. It explicitly increased the number of 340B hospitals by designating certain rural hospitals and other entities as eligible.

Just as important as these statutory expansions is the growing trend of hospital acquisition of physician practices, which studies now show to have substantial distortionary effects on the market. A June study published by the Berkeley Research Group found that at least 120 340B hospitals had acquired physician-based oncology practices between 2008 and 2012, which resulted in a shift of 11.6 percent of the overall chemotherapy claims volume from physician offices to hospital outpatient departments. For 86 of the hospitals, the acquisition led to a 20 percent or greater increase in the volume of chemotherapy claims billed to Medicare.

How can free-standing, physician-led practices compete with 340B-eligible hospital-based systems that are acquiring oncology practices at such a rapid rate when a major cost component is the acquisition of chemotherapy drugs? The Berkeley study notes that, "By acquiring physician-based oncology practices, 340B hospitals are able to increase volume of oncology claims that use chemotherapy drugs and thereby increase the margins realized on the reimbursement of those drugs." In Figure 1 (below) is an example of this pricing differential.

The public policy concern is that Medicare and commercial insurers pay substantially more for care delivered at hospitals than care delivered in physician offices. Berkeley estimates this cost Medicare and Medicaid nearly $200 million from 2008 to 2012.

There was some hope that the Health Resources and Services Administration (HRSA) would finally release a mega-regulation clarifying certain aspects of the 340B program and possibly address the more abusive aspects of the program that have emerged over the last several years. In the 22 years of the program, almost all policy was executed through subregulatory guidance and outside the normal transparent rulemaking process. For example, the policy change to allow 340B hospitals to contract with multiple pharmacies was executed through "subregulatory guidance" — that is, outside the transparent notice and comment rulemaking process. HRSA announced earlier this year that it would issue a regulation addressing the following areas:

1. definition of the patient
2. compliance requirements for contract

FIGURE 1

Drug A	340B Hospital	Non-340B Hospital*
Reimbursement	$2,000	$2,000
GPO Purchase Amount		($1,900)
340B Purchase Amount	($1,200)	
Margin	**$800**	**$100**

*or Physician Practice

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But litigation by PhRMA over the definition of "orphan drug" stopped that regulation in its tracks. PhRMA asserted that HRSA violated the Administrative Procedure Act because HRSA did not have the authority to issue the final rule, and even if it did have that authority, the statute exempts all uses of orphan drugs from 340B, not just the orphan indication.

The District Court ruled in favor of PhRMA on HRSA's legislative authority to issue the regulation, stating that HRSA only had authority in three narrow areas:
1. the establishment of an administrative dispute resolution process
2. the methodology for calculating the 340B ceiling price
3. the imposition of civil monetary sanctions.

Notwithstanding that District Court decision, HRSA updated its Web page on June 18, 2014, and asserted that the decision did not, in fact, invalidate the agency's interpretation that manufacturers must continue to provide 340B discounts for non-orphan conditions of orphan drugs.

This raises a fundamental question: How can HRSA continue to implement a policy that was created through a process the District Court has found to be invalid?

This may be the worst of all possible outcomes for the pharmaceutical industry: The District Court's decision hamstrings HRSA from reining in egregious aspects of the 340B program but does not prevent it from continuing to demand 340B discounts for non-orphan indications for orphan drugs.

Unless and until HRSA appeals the District Court decision on its fundamental ability to issue regulations, the pharmaceutical industry and provider community is left in limbo and will continue to operate under the current regime.

In the 22-year history of the 340B program, Congress has held exactly one oversight hearing. Perhaps this is because 340B hospitals and other qualified 340B recipients reside in every Congressional district, while pharmaceutical companies are limited to a few zip codes in several states. But real reform of the 340B program must now come from Congress.

The easiest thing for Congress to do would be to punt on substantive matters of the 340B expansion and simply empower HRSA to issue a rule that would clarify and implement all aspects of the program.

But that would be a lost opportunity to fundamentally reform a program that has spiraled out of control and bears little resemblance to its original purpose of providing discounted outpatient drugs to uninsured and indigent hospital patients. L

FIGURE 2 — The McManus Group

Top 25 Hospitals – Medicare Payments

	340B	# of Entity Subdivisions	Contract Pharmacies
New York-Presbyterian Hospital	Yes	96	0
Florida Hospital	Yes	57	36
Cleveland Clinic	Yes	0	0
Massachusetts General Hospital	Yes	1	1
Cedars-Sinai Medical Center	Yes	31	0
Barnes-Jewish Hospital	Yes	1	1
Norton Hospitals, Inc.	Yes	109	53
Methodist Hospital (Henderson, KY)	Yes	0	2
Methodist Healthcare Memphis Hospitals	Yes	8	91
Christiana Hospital	Yes	0	0
William Beaumont Hospital	No	–	–
Duke University Hospital	Yes	7	0
IU Health	No	–	–
University Of Michigan Health System	Yes	41	54
Evanston Hospital	No	–	–
The Methodist Hospital (Merriville, IN)	Yes	7	0
Aurora St. Luke's Medical Center	Yes	1	0
Scott & White Memorial Hospital	Yes	33	256
Yale-New Haven Hospital	Yes	28	18
Mount Sinai Hospital	Yes	21	54
Pitt County Memorial Hospital	Yes	3	0
Stanford Hospital	No	–	–
Vanderbilt University Hospital	Yes	22	175
Lahey Clinic Hospital	Yes	0	0
Hospital Of University Of Pennsylvania	Yes	48	0

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

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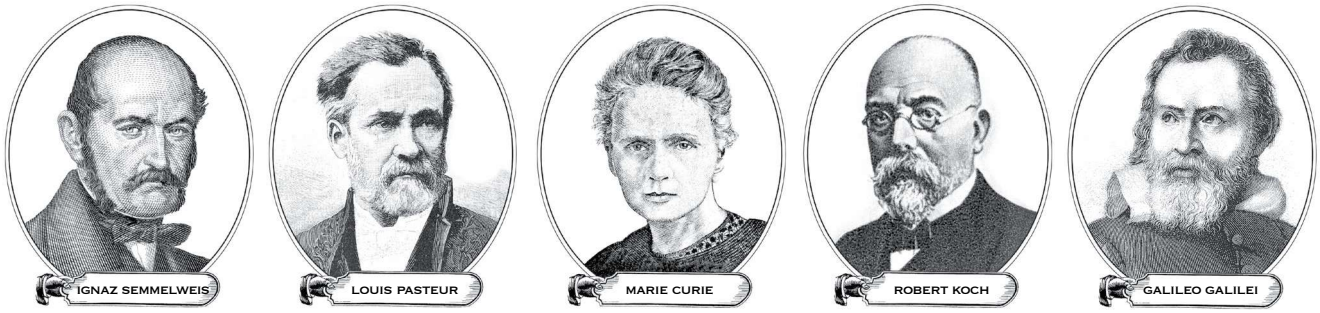

Company No. 1	*Company No. 2*	*Company No. 3*	*Company No. 4*	*Company No. 5*
Company looking for hormone business	*New depots open for sample distribution*	*Lab equipment upgrade demanded*	*European client demands specific reporting procedures*	*Biobetter presented to the EPA*
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WAYNE KOBERSTEIN Executive Editor
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SNAPSHOT

Second Genome has staked an early claim to a piece of the new microbiome space; in fact, the company may be helping create the space even as it occupies it. It has also made an equally early leap into partnerships with some of the biggest biopharma companies, reflecting the quickly growing industry awareness of "microbiomics," the study of disease-causing interactions between microbes in humans and their hosts. The company is also discovering and developing its own therapeutics and biomarkers based on its knowledge and platform.

WHAT'S AT STAKE

Human genome research once promised us the keys to defeating many diseases, if only we could tie particular genes to each condition. It turns out genes do play a leading role in morbidity, but not just human genes. Another, even vaster genome surrounds and fills us — a regular stew of bacteria, viruses, and genes — aka the microbiome. The microbiome creates the immediate environment for our genes as they play out their part in disease mechanisms.

"We now understand that biological processes such as inflammation, barrier function, metabolism, and energy homeostasis are directly linked to our microbiome," says Peter DiLaura, president and CEO of Second Genome. "As our understanding of microbiome science has moved from correlations to causal relationships, it has become a relevant area for drug discovery."

That is why, in DiLaura's view, this is the right time — scientifically, medically, and commercially — to create a new microbiome space, and his company is one of the earliest innovators in the field. "Second Genome has focused on building a platform that enables us to identify and understand relationships between the microbiome and host biology, which provides access to novel targets and therapeutic approaches."

Second Genome studies the interactions between microbes that live in humans and the host human cells in causing a disease state. Such interactions can be positive or negative, either helping to maintain a healthy condition or to disrupt one. Diabetes, colitis, and some types of infection are among the diseases caused or exacerbated by disruptions in the normal dynamics between microbes and humans. The company has aimed its platform at discovering and developing small molecule drugs, peptide biologics, probiotics, and symbiotics to intercede and modulate microbe-microbe and microbe-human interactions.

When the company was formed in 2010, it faced a steep educational slope, but nowadays many of the large pharma and biotechs have matched speeds with the microbiome concept and are actively interested in its drug discovery potential. Some of their education has come through basic, preclinical research collaborations with Second Genome. More recently, Janssen and Pfizer have upped the ante with partnerships aimed at identifying drug candidates.

The partnerships still involve the kind of basic research that normally would take place in a university lab — another case representing the current, to some troubling, trend of commercial entities taking over academic science that would otherwise be shared with the world. But DiLaura considers private-enterprise funding and organization essential to making treatments available for patients in a practical time frame. "It is our expectation that commercial involvement can push this important work further more quickly."

Meanwhile, Second Genome has plowed ahead with its own products in the pipeline. It has three preclinical programs and "additional discovery efforts" of its own, but has announced no details. "We have worked across a wide range of disease areas and have a significant amount of experience in the complexities of experimental design, execution, and analysis in the highly specialized microbiome space," says DiLaura. "This work has been highly leveraged for our own therapeutic programs."

PETER DiLAURA
President & CEO

Vital Statistics

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Research Partners

Janssen Pharmaceuticals
in ulcerative colitis

Pfizer
in metabolic disease

Latest Updates

June 2013: Announced collaboration with Janssen to apply Second Genome's platform to discover novel drug targets in ulcerative colitis, focused on understanding disease mechanisms mediated by the microbiome.

May 2014: Announced collaboration with Pfizer to apply Second Genome's platform to conduct the largest study to date in understanding the microbiome in metabolic disease.

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Outsourcing Trends In Small Molecule API Manufacturing

Lately, much of the enthusiasm in drug development is centered around large molecule API / biologics. However, the vast majority of drugs on the market, and in development, have a chemical-based, small molecule active ingredient. Considering the dominance of this type of medicine on the market, it is not surprising that one-third of the CMOs included in Nice Insight offer commercial-scale small molecule API and advanced intermediates manufacturing, as compared to 20 percent that offer biologic API manufacturing.

KATE HAMMEKE
Director of Marketing Intelligence
Nice Insight

> *"Only one in 10 respondents indicated their company was not interested in forming new strategic partnerships."*

Respondents to Nice Insight's annual survey, who will outsource commercial scale manufacturing (25 percent), reported small molecule API manufacturing at a lower frequency than large molecule API or finished dosage forms (28 percent vs. 37 percent, respectively). However, this likely speaks to the many existing outsourcing relationships that are based on small molecule API manufacturing, as the survey inquires about new projects that will be outsourced in the next twelve to eighteen months.

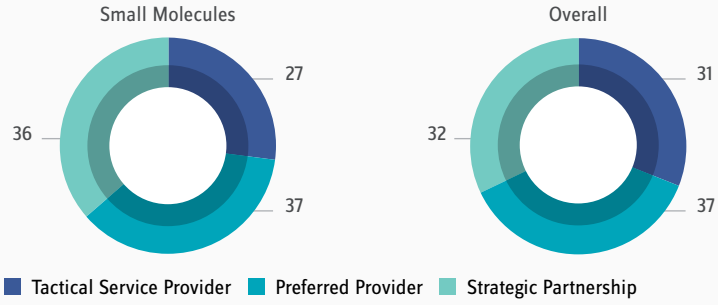
To gain greater understanding of outsourcing small molecule API and advanced intermediates, Nice Insight reviewed the buying behavior and outsourcing preferences among Big Pharma, specialty/midsize pharma, and emerging pharma companies. When looking at the buying market for outsourced small molecule API, it is not surprising to see Big Pharma comprises the majority, at 58 percent. However, when putting that figure into context, only 35 percent of Big Pharma companies that will outsource commercial-scale manufacturing projects will be engaging a CMO for a new small molecule API project, which amounts to 8 percent of all Big Pharma respondents to the survey. Emerging pharma will account for roughly one-quarter of the new small molecule API projects, and specialty pharma accounts for 18 percent of the buying market.

Companies that are looking to engage a new supplier for small molecule API are markedly more likely to consider emerging market CMOs than the overall average (86 percent vs. 66 percent). Yet when it comes to actually offshoring API production, there is much less of a divergence. In fact, more projects are currently allocated to suppliers in Western Europe (21 percent vs. 12 percent) when compared to offshored projects overall. The percentage of small molecule API projects allocated to U.S. & Canadian suppliers is on par with the overall average (27 vs. 26 percent).

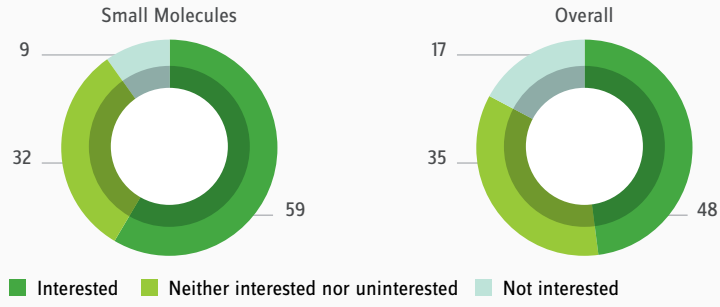
SMALL MOLECULE API OUTSOURCERS ALLOCATE MORE WORK TO STRATEGIC PARTNERS

Whether the CMO is local or overseas, buyers of outsourced small molecule API manufacturing services tend to outsource fewer projects to tactical service providers (27 percent vs. 31 percent) and a greater number to strategic partners than the average (36 percent vs. 32 percent). These buyers also tend to show greater interest in forming strategic

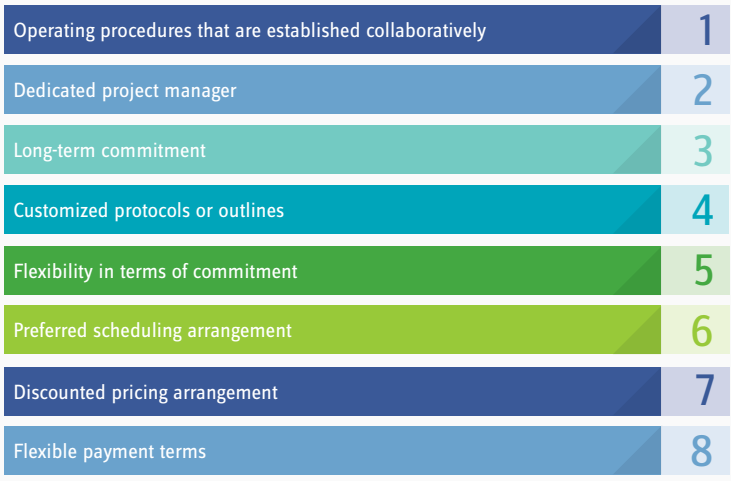
Small Molecule API and Advanced Intermediates Outsourcing



Interest Level in a Strategic Partnership with a CRO / CMO



Prioritized Attributes for Strategic Partnerships



Survey Methodology: The Nice Insight Pharmaceutical and Biotechnology Survey is deployed to outsourcing-facing pharmaceutical and biotechnology executives on an annual basis. The 2013-2014 report includes responses from 2,337 participants. The survey is comprised of 240+ questions and randomly presents ~35 questions to each respondent in order to collect baseline information with respect to customer awareness and customer perceptions of the top 100+ CMOs and top 50+ CROs servicing the drug development cycle. 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. In addition to measuring customer awareness and perception information on specific companies, the survey collects data on general outsourcing practices and preferences as well as barriers to strategic partnerships among buyers of outsourced services.

partnerships with CMOs when it comes to new outsourcing relationships (59 percent vs. 48 percent). In fact, only one in 10 respondents indicated their company was not interested in forming new strategic partnerships. The key attributes that influence strategic partner selection among this group are not the traditionally clichéd qualities. In reality, flexible payment terms and discounted pricing arrangements ranked last, while operating procedures established collaboratively, a dedicated project manager, and long-term commitment were prioritized in the top three positions.

If your business is planning to engage a new supplier for small molecule API, identifying the right CMO may take a different approach than in the past. Four out of five respondents indicated that the first place they turn to identify suppliers is industry research, followed by referrals from colleagues (71 percent) and consultants (65 percent). And a company's affordability or a discounted pricing arrangement is no longer top of mind when establishing a short list. Rather, quality and reliability — secured through collaboratively established operating procedures — lend more towards a mutually beneficial relationship between the buyer and contract manufacturer.

N. WALKER

S.FAZZOLARI

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

Best Practices In Standardizing Single-Use Device Connectivity

Even the way devices are connected raises debate

ERIC LANGER
President and Managing Partner
BioPlan Associates, Inc.

The spread of single-use devices in the biopharmaceutical manufacturing industry has been well-documented, with some devices reaching penetration rates approaching 90 percent, according to various studies conducted by BioPlan Associates. Yet there remains plenty of room for further adoption of single-use, disposable devices, particularly in commercial scale production, where they have yet to displace traditional stainless-steel systems.

But the debates over standardization continue. And even the most basic connectors create controversy. The ability to hook up and integrate various devices is an increasingly important factor as single-use applications push into mainstream biopharmaceutical manufacturing. Connectors can allow for interconnectability between various single-use components and vendor devices, allowing end users a plug and play approach that permits a greater assortment of options. From this perspective, connectors play a significant role in the expanding use of single-use equipment.

This industry segment is still in its early stages, and it is currently faced with an assortment of vendor devices, many of which present difficulties with interoperability. If connectors are to expand single-use penetration, suppliers and end users will likely need to agree on aspects of physical standardization — similar to how computer connectivity moved from various sizes and configurations to more common USB-type connectors. In fact, connector compatibility is one of the most sought after areas for standardization in the single-use arena.

In BioPlan Associates' latest annual industry study, the *11th Annual Report and Survey of Biopharmaceutical Manufacturers (see www.bioplanassociates.com /11th)*, respondents were asked which of several areas they felt were important for single-use/disposable vendors to work harder to standardize. Connector compatibility (interchangeability) was near the top of the list with 88 percent of global respondents considering standardization "important" or "very important."

A BASIC CHOICE: GENDER OR GENDERLESS CONNECTORS?

The inherent issue with standardization is that some vendors will have to change their existing product lines to meet whatever standards are set. For connectors, the most basic standardization boils down to a binary choice: gender or genderless connectors.

Genderless sterile connectors are those where both connector ends are the same (hence genderless). These tend to be uncomplicated and require fewer parts for inventory. Gendered sterile connectors, with their different ends, are slightly less straightforward to use and require more inventory, but generally are perceived to present a lower risk of incorrect connection.

Competitive aseptic options on the market include GE's ReadyMate (genderless) and Pall's KleenPak (gendered). Each can be gamma sterilized or autoclaved and come in a variety of sizes. Pall was one of the earliest entrants into the field and provided a huge boost when it shortened the connection time by introducing its half-inch connector.

INDUSTRY ATTITUDES ABOUT GENDER

To gauge industry attitudes to gendered and genderless connectors, BioPlan Associates carried out a small survey of qualified individuals with interesting results. Some 73 percent of the 26 respondents surveyed said they prefer genderless sterile connectors for their clinical-scale and larger bioprocessing, as opposed to the remaining 27 percent who favor gendered sterile connectors.

We explored the reasons why respondents made those choices. Sorting respondent comments into broad categories, the survey yielded some intriguing results: While the simplicity and inventory control afforded by genderless connectors are key considerations, risk mitigation is top of mind with the majority of those who selected risk mitigation as a reason

for their preference for *gendered* rather than *genderless* connectors. This suggests some ambiguity: While the industry wants genderless connectors, its most common reason for selecting a connector focuses around risk mitigation (over a third lean toward risk factors, vs ~71 percent focusing on reasons related to genderless connectivity).

Representative comments offered along with the survey responses are similarly illuminative:

In favor of gendered connectors:

- "Risk mitigation with regard to incorrect connections — possibility to establish workflows based on 'one-way-correct' connection [connectivity defines the process]."
- "Gender-sterile connectors [ends are different] are more reliable in my opinion."
- "Lower risk of incorrect use."
- "The biggest contributor to [problems] in single-use production is the operator. This is a small and easy way to minimize errors."

In favor of genderless connectors:

- "Genderless help with inventory control and simplify preparation."
- "Allows the flexibility to choose which attachment to make at any given point in the process."
- "You always want it to be as simple as possible."
- "Having genderless connectors allows for more flexibility when having to come up with disposable strategies."
- "Easier to set up bags and tubing with connectors that can connect to each other for multiple combinations."

VENDORS SHOULDN'T REST EASY

While study participants seem to prefer genderless sterile connectors, questions of reliability are paramount, and as one respondent noted, there are other questions surrounding cost and availability to consider. That suggests the choice may not be as clear-cut as it initially might appear.

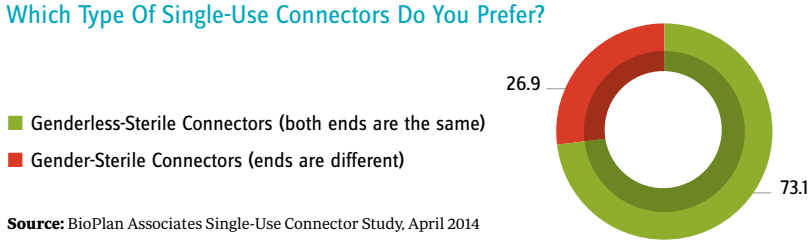
One thing seems clear from BioPlan surveys: The industry is looking for innovation in this area. According to our latest industrywide study, some 38 percent of respondents consider disposable bags and connectors to be among the top five areas they want their suppliers to focus their development efforts on. That was the fourth-highest result of the 21 innovation areas listed in the study. These devices have consistently seen hot demand for innovation over the past eight years.

Suppliers responding to the study were a little less committed to innovation in this area, though. Asked which new technologies or new product development areas they are working on today, roughly one-quarter (27.3 percent) cited disposable connection technology. As vendors look to increase their market penetration, standardization of their products — including of connectors — may be unavoidable. Currently, while three-quarters of the industry believes it important or very important that single-use vendors standardize their devices, only 28 percent are satisfied to any degree with their current vendors in terms of device standardization.

As one director of technology for a large biopharma noted, "Suppliers will only truly achieve the SUS (single-use system) value proposition they champion if they resolve these variability concerns." For manufacturers of single-use connectors, end user desire for standardization is particularly acute. Some financial pain may be inevitable in the short term, but suppliers may well win in the long term by standardizing their offerings to meet end user demand. An interesting bellwether for the industry's commitment to standardization may be in the most basic of choices: gendered — or genderless.

FIGURE 1

For Your Clinical-Scale & Larger Bioprocessing, Which Type Of Single-Use Connectors Do You Prefer?



Source: BioPlan Associates Single-Use Connector Study, April 2014

FIGURE 2

Reasons For Selecting Connectivity Gender

Source: BioPlan Associates Single-Use Connector Study, April 2014

Survey Methodology: The 2014 Eleventh Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production yields a composite view and trend analysis from 238 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations (CMOs) in 31 countries. The methodology also included over 173 direct suppliers of materials, services, and equipment to this industry. This year's study covers such issues as: new product needs, facility budget changes, current capacity, future capacity constraints, expansions, use of disposables, 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.

MILLENNIUM CARRIES ON WITH THE TAKEDA ONCOLOGY EXPANSION

WAYNE KOBERSTEIN Executive Editor

Since I've been writing about the pharma industry for many years, I often find it impossible to walk in any direction without bumping into a connection from the past. It seems like a thousand years ago that I interviewed Millennium's founder, Mark Levin, soon after the launch of its hallmark cancer drug. Certainly enough has transpired since then.

MICHAEL VASCONCELLES, M.D., Global Head, The Oncology Therapeutic Area Unit at Millennium: The Takeda Oncology Company

By W. Koberstein

MILLENNIUM CARRIES ON WITH THE TAKEDA ONCOLOGY EXPANSION

Millennium itself found success — and some frustration — with championing a new class of cancer drugs inspired by release of the first human genome maps. The prize, the company's proteasome inhibitor Velcade (bortezomib), won its initial FDA approval in 2003 for treatment of refractory multiple myeloma (MM) and was later approved elsewhere for MM and for mantle cell lymphoma. Velcade remains Millennium's sole original oncology franchise product, though it shares commercial rights with Seattle Genetics for Adcetris (brentuximab vedotin) for Hodgkin lymphoma and systemic anaplastic large cell lymphoma (ALCL).

In 2008, Millennium became "Millennium: The Takeda Oncology Company," when it was acquired by the Japan-based corporation as the keystone of an ambitious global expansion in the cancer area. Now in charge of all of oncology R&D at Millennium and Takeda is Michael Vasconcelles, M.D., as global head, the Oncology Therapeutic Area Unit (OTAU). Vasconcelles helps put the company's past, present, and future into the context of Takeda's oncology expansion.

STRUCTURAL CLUES – TAKEDA & OTAU

A continuum of integration seems to be developing among the many industry mergers, acquisitions, and business-unit swaps now transpiring. Typically, on one end, a large company will absorb the smaller one, harvesting the "synergies" and erasing all vestiges of the acquired entity. On the other end, the acquired organization becomes the dominant force in the merged company. Millennium's acquisition falls nearer the latter, continuing its former identity and contributing most of the operational support for the OTAU, which is the umbrella that covers all of Takeda's oncology R&D. Hence, Vasconcelles' remarks apply to the parent company's entire oncology program, including R&D partnerships, yet they also draw from Millennium's achievement.

"Millennium built a legacy that led to a transformation in treatment of a disease that not long ago had a very poor outcome," he says. "Velcade is a large reason the lives of patients with myeloma are looked at substantially different today. It is a foundation that still drives the way we think."

Vasconcelles could be naturally skeptical of mergers, considering he joined his current company only two years ago, in March 2012, after coming from Genzyme following its purchase by Sanofi. The Takeda/Millennium union had a four-year track record by then, however, and it offered continuity, especially in his area. "The company's commitment to the oncology space was unchanged, and that was actually one of the challenges. We were in the midst of many late-stage programs and an early pipeline that has real potential. First and foremost, we needed to continue to prosecute those efforts as flawlessly as we could. But we also made a shift in strategic direction, which was to integrate the R&D structure of legacy Millennium into the Takeda R&D organization."

In addition to realizing efficiencies from the integration, Vasconcelles says the company had the strategic goal of "a truly global footprint" for its R&D beyond what a wholly owned subsidiary such as Millennium could achieve. "Operating reasonably independently, even at the scale of Millennium, would potentially present growing challenges as our portfolio matures and our footprint in oncology strengthens and deepens."

According to Vasconcelles, another action that strengthened Takeda's global R&D footprint was its acquisition of Nycomed in September 2011. A long-time licensor and developer, Nycomed immediately increased the number of products in Takeda's product portfolio and pipeline, and it bolstered Takeda's presence in Europe and "high growth emerging markets."

"Now we have all the key organizational ingredients for delivering medicines to patients truly in a global sense. But we also need to make sure we think about our opportunities in the context of variations in disease patterns that occur in cancer globally, and our thinking was strengthened by the global integration."

Have the downside effects of large-scale corporate change intruded into this global harmony? "I've seen many similarities to the changes I went through at other times in my professional life. It is critical that leaders within the organization do everything possible to be clear in their communication and transparent in their actions — to paint a clear picture of the underlying reasons for the changes and their intended results. Because, I believe, we have done a good job in that respect, we now have a settled organization with a clear set of objectives, and we are as passionate and excited about our mission as ever."

> "We have all the ingredients here to take Takeda Oncology to even broader and deeper places than it's ever been before."
>
> **MICHAEL VASCONCELLES**, M.D.
> Global Head, The Oncology Therapeutic Area Unit, Millennium: The Takeda Oncology Company

FROM FRONTIER TO FRONTIER

Besides globalization, another challenge for Millenium and the OTAU has been moving beyond the legacy of Velcade in ways that reflect the scientific progress since the product entered the scene. The initial enthusiasm over genetic and molecular targeting has been tempered by experience — tumors quickly develop resistance to targeted drugs, and their remarkable heterogeneity defies application to broad patient populations. Though Vasconcelles might be expected to mount a rigorous defense of the targeting strategy, his response is quite nuanced.

"There are certain malignancies with identifiable disease-driving mutations that have allowed us to sufficiently understand the biology and target our discovery efforts accordingly," he says. "But there are also large areas of human cancers where the genomic complexity obligates us, not necessarily to shift from

the targeting paradigm, but to increase our biological understanding with even more sophisticated tools and methodologies so we can refine the paradigm."

He cites the collective need of targeted drug developers to use and interpret whole genome sequencing for a higher-resolution understanding of the biologics in cancer. "Understanding and targeting cancer is a struggle that all cancer-drug developers are facing right now, and we recognize we may not be able to build some of our development programs around a highly specific, genetically designed approach."

Because scientists' ability to interrogate tumors is at an "inflection point," Vasconcelles says his unit must also rely on other ways to define appropriate patient populations for its medicines. "But because of these incredible successes that we have demonstrated, whatever set of criteria we use — biomarker-driven, a constellation of biomarker and clinical factors, or simply understanding the target sufficiently — I believe we will duplicate those clinical successes more often than not. The bar has been raised by past successes, and our job has just become more challenging."

Vasconcelles also acknowledges the need to find new strategies against tumors. He likens the current battle with cancer to the historical fight against communicable diseases, with tumors quickly developing resistance to drugs the way microbes evade antibiotics or antivirals. He is particularly interested in immunotherapeutic approaches.

"My former company, Genzyme, had an early commitment to cancer immunotherapy, so I was steeped in the complex effort at the time. Now we may have the opportunity with the checkpoint inhibitors to see a real transformation in the care of patients, at least with certain cancers. So we are looking at immuno-oncology very carefully."

He explains that the company's oncology R&D now incorporates three primary areas: protein quality control, cellular infrastructure targets such as cancer metabolism, and antibody-drug conjugates, with the last two still at the discovery stage. Its immunology expertise resides mainly in the last area, antibody-drug conjugates, a focus of Takeda scientists in Cambridge and San Diego. As with targeted therapy, he believes further progress in immuno-oncology will require continued study and greater understanding of the biology involved. Combinations of immunotherapies will likely be necessary in widespread practice to obtain a sufficient immune response to arrest and kill tumors, he believes, at least initially and in clinical development.

As OTAU integrates the company's oncology programs, it is also increasing its outreach to external discovery. "We have a great internal discovery team, and their work will continue unabated, but Takeda and Millennium have long been leaders in working with external partners," says Vasconcelles. Takeda most recently established important new collaborations with major academic centers in New York and a "novel incubator effort" in Israel. Even though neither of those is cancer-specific, he says, "One of the nice benefits of being part of our integrated R&D is having a connection into those initiatives. For example, the three institutions involved in the New York effort are Rockefeller University, Memorial Sloan Kettering, and Weill Cornell Medical College, so clearly there is a potential focus on cancer or related biology. We also have some specific oncology collaborations, and we examine them on an ongoing basis to make sure they remain consistent with our own internal strategy."

ONE STEP AT A TIME

Vasconcelles expresses some concern that external forces of a different sort (e.g., unrealistic outsider expectations) will cause unwanted difficulties for cancer-drug R&D — not by impeding it, but by pushing it too hard. "In oncology, in my lifetime, we have made real headway, but the usual and customary way we make headway is in a methodical, incremental fashion, and eventually we might get all the way from A to Z. And that process will more often than not continue to be the path to success. What I hope is that those who set high expectations for innovators do not disparage the incremental path, because it has worked well for us for many years. The widespread expectation is that we can just go from A to Z or close to it every single time."

He recalls walking into Millennium's Cambridge headquarters for the first time and seeing a large sign proclaiming the company's vision of curing cancer. "I literally stopped short. I'm an oncologist, I know how hard that is to do, and I've reflected on the vision repeatedly and come to imbed it in myself. It is audacious, but if you're not audacious, you'll never succeed. I see the same passion throughout the organization and I'm doing everything I can not only to maintain it, but deepen it. We have all the ingredients here to take Takeda Oncology to even broader and deeper places than it's ever been before."

Returning to the Millennium legacy, Vasconcelles emphasizes the continued importance of the company and its operations in Cambridge. In the globalization of Takeda Oncology, Millennium's headquarters remains "the center of our universe." For all of its global commercial infrastructure, he says the company is committed to maintaining that center — and its original vision.

NEW STARS RISING

Takeda's Oncology Therapeutic Area Unit (OTAU) has 15 clinical development projects under way. The global head of OTAU, Michael Vasconcelles, M.D., sheds some special light on several outstanding candidates in the pipeline.

IXAZOMIB is a novel molecule that targets the proteasome, the "waste remover," in cancer cells. But Vasconcelles says the drug has features that differentiate it from other proteasome inhibitors, including Velcade. Ixazomib is in several late-stage programs in multiple myeloma and earlier-stage programs in other hematologic malignancies. "The profile of this agent clinically suggests it has real potential to make additional step changes in the care of patients with myeloma. It is orally bioavailable and has an emerging safety profile that would allow for protracted administration. The incidence of peripheral neuropathy and cumulative toxicities typically seen with other agents is much lower with ixazomib. Velcade-based regimens are the only ones that have demonstrated overall survival advantages in myeloma, and administering such a drug for a protracted period of time could allow for exposure of the underlying malignancy to produce more inhibition, making it a compelling candidate for us."

ADCETRIS (brentuximab vedotin), the focus of the company's development and commercialization partnership with Seattle Genetics, is an antibody drug conjugate targeting the cellular protein CD30, which is expressed on Hodgkin lymphoma and T-cell non-Hodgkin lymphomas, including anaplastic large cell lymphoma. Adcetris is already approved in the relapsed and refractory setting in both Hodgkin lymphoma and anaplastic large cell lymphoma. OTAU has a substantial development program to study the drug in combination with earlier lines of therapy in those diseases, which represent significant unmet needs in Western countries but have an especially high prevalence in Asian populations compared with Western countries. It is also studying Adcetris in a more uncommon but severe disease, cutaneous T-cell lymphoma. "Adcetris is a transformative therapy, and it has the opportunity to change the standard of care for those diseases," says Vasconcelles.

MLN4924 targets a specific enzyme called the NEDD8 Activating Enzyme, the first step in a subset of proteins that go through "ubiquitination" (attachment of the regulatory ubiquitin molecule) on their way to entering the proteasome. It is in a combination Phase 1b study with 5-azacytidine in acute myeloid leukemia as well as with standard-of-care agents in solid tumors. "Both areas of interest are based on nonclinical data showing very nice synergy between 4924 and agents already used in those diseases. We are quite intrigued with the signals emerging there, and I look forward to later-stage development with 4924. We also have another molecule, MLN7243, that is earlier in development but is even further upstream in the same pathway, targeting the ubiquitin-activating enzyme. The compound recently began testing in a Phase 1 program."

MLN0264 is an antibody drug conjugate that targets the cell surface protein, guanylate cyclase-C (GC-C), which is expressed in the luminal surface of the GI tract. It is entering Phase 2 studies in gastric cancer, pancreatic cancer, and gastro-esophageal cancer in the United States, Europe, and Asia this year. "GC-C expression is restricted to GI malignancies, and because the target expression is restricted to the luminal surface of normal epithelial cells (essentially an immuno-restricted site), we thought it would be a good target."

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J&J'S APPROACH TO CAPTURING DISRUPTIVE INNOVATION IN CLINICAL TRIALS

ROB WRIGHT Chief Editor

In the pharmaceutical industry, gaps often exist between companies and internal working groups. Consider one of the industry's largest players, Johnson & Johnson (NYSE: JNJ), which has more than 127,000 employees and operates more than 250 companies organized into several business segments in 60 countries.

J&J's pharmaceutical segment consists of six Janssen pharmaceutical companies, including Janssen R&D, which contains the Janssen Healthcare Innovation (JHI) team. And while the R&D arm is focused on discovering and developing medicines for unmet medical needs, JHI's vision is to help accelerate the transformation of J&J from a healthcare product company to simply a healthcare company.

To bridge the gap between the two, as well as facilitate external collaborative alliances with consumers and companies, J&J created Clinical Trial Innovation (CTI) — an organization integrated with JHI and Janssen R&D Operations. Headed by 20+ year R&D veteran Andreas Koester, M.D., Ph.D., CTI has some ambitious goals — develop solutions that will modernize clinical trials, improve data quality, and enhance the clinical trial process for patients and investigators. Having 13 new medicines approved in the last decade, J&J ranks at the pinnacle of the most productive pharmas, and perhaps is one of the most disruptively innovative. Koester, VP of clinical trial innovation and external alliances, shares what the CTI team is doing to keep it that way.

THE IMPETUS FOR CREATING CTI

Like most ideas, the creation of CTI was neither derived from a "Eureka, I've got it!" epiphany nor driven by just one person. In actuality, CTI was the result of a collaborative effort which first began with a project. In the spring of 2011, executives at J&J sat down to tackle a growing problem — inefficiencies in clinical trials. Everyone knew that drug development costs were spiralling out of control, primarily due to increasing amounts of clinical evidence needed to obtain regulatory approval. Furthermore, it was understood that Phase 3 clinical trials represent about 40 percent of pharmaceutical company R&D expenditures. "Essentially we wanted to have a fresh look at how we in the industry do clinical trials," recalls Koester.

The goal of the workshop was to brainstorm on what the future of clinical trials might look like in five to 10 years — given not much had changed in the previous 20. Utilizing various tools and techniques, such as gap analysis (see sidebar — *How To Get The Gap Out Of Analysis*), approximately 50 people representing internal Janssen Pharmaceutical segments (e.g., R&D operations, therapeutic areas, biostats, data management) and external organizations (e.g., CROs, IBM, Oracle) were involved in the workshop. "During this three-day meeting, we came up with a number of actionable items we thought we should do to prepare and shape Janssen for the future," Koester says. For example, the group identified a fair number of ongoing improvement projects which could benefit from an increased focus. "We realized that more follow-up and follow-through were needed to move projects more quickly from concept, to pilot, all the way through to implementation," he shares. "We also concluded that it is difficult, if not impossible, to change the way you are working on a broad scale while still executing on the highest priority — the development of your own company portfolio. We needed a different group which had the 'luxury' to focus only on innovation while not being tasked with executing on the pipeline." It was this conclusion that led to the formation of CTI in early 2012 — nearly a year after the workshop had ended.

THE KEYS TO CREATING A CLINICAL TRIAL INNOVATION ENGINE

According to Koester, at every company there are key questions to answer before undertaking such an initiative. For example, where will the head count come from? (Koester's team has seven full-time members.) What about the budget? "Those are the first two questions that need to be answered so that you can integrate the team and its expenses into the overall organization and budget." Next, who would be the right person to lead such a group? What would be the appropriate profile and background of group members? "These were the questions we were

The Investigator Databank — A CTI Success Story

"The Investigator Databank project was actually started before CTI was formed," says Andreas Koester, VP and head of CTI (clinical trial innovation) and external alliances at Janssen. The idea was to create a repository of key information (e.g., infrastructure, GCP training records, site profile forms) about investigators and clinical trial sites for multiple pharmaceutical companies. Previously, if Janssen trained an investigator on GCP, and the person wanted to serve as an investigator for another company, they would have to complete very similar GCP training for every single company. "Everybody hates it," Koester attests. "This redundancy does not improve the quality of the trial and only serves to further increase the administrative burden of investigators."

Research conducted by the Tufts group from 1999 to 2005 revealed that the average clinical trial staff work burden had increased by 67 percent. Further, studies have shown that 70 percent of investigators drop out after one or two trials. "Can we reduce the administrative burden for the investigator by not asking them the same questions at the initiation of each clinical trial?" Koester laments. Though the project was under way prior to the formation of CTI, it became the responsibility of the group to see it through to completion.

The project team members within Janssen began reaching out to other companies through informal contacts made at conferences and other forums. "Remember, this was pre-TransCelerate," he reminds. Reducing redundant trainings would benefit pharma companies by lowering trial costs. Investigators might be inclined to participate in more trials, thus further reducing pharma costs related to recruiting clinical trial investigators. But there were a number of hurdles which needed to be overcome to make the Investigator Databank a reality. For example, they needed to find a place to store the information outside the walls of one particular pharma company to avoid the perception of a competitive advantage or restricting access. Another hurdle was getting buy-in from internal legal departments that this was okay and beneficial to do, as well as to create language so the activity would not be perceived as collusion.

Privacy laws, how many companies to involve — the list of hurdles seemed endless, and the task of overcoming, daunting. Yet the creation of the Investigator Databank via collaboration between Janssen, Lilly, and Merck proved successful. In late 2013, Pfizer joined the initiative, and in May 2014, Novartis did as well. Hosted by DrugDev (www.drugdev.org), the Investigator Databank includes nearly 180,000 investigators, 50,000 sites, and 7,335 studies, making it four times the size of the dataset utilized in the 2013 Tufts analyses of clinical trial sites.

In addition to the previously mentioned benefits, it is anticipated that the Investigator Databank will also improve investigator selection, and it holds the potential to improve clinical trial execution by enabling improved matching between studies and investigators. Most recently, the website investigatordatabank.org was launched, which allows investigators to securely log in and view the composite information held on file about them and to supplement it with additional information such as their CV and GCP training certificate.

busy with during the months after the design workshop," he says.

Though Koester is not able to disclose the budget amount allocated to the creation and running of CTI on an annual basis, he is able to share how it's structured. "We set up the group to be independently funded," he says. "The budget for every one of the pilot projects we are running is contained and preallocated specifically toward clinical trial innovation." In addition, the CTI team is given the freedom (within budget) to run projects that don't have full-blown business cases. "This is a key element to success," he states. "Because we are venturing into the unknown, you can't really create a business case. If we knew it, then it would not be innovation."

According to Koester, how to get people on board without the ability to create a complete business case is one of the most frequently asked questions posed to him at conferences. "It is one of our biggest challenges," he admits. "When dealing with a lot of imponderables, taking the approach that a project will only be undertaken if it has a positive business case doesn't work because you cannot draw a line, make a linear expansion of the past, and then foretell the future." If creating an organization similar to CTI within your company, Koester suggests setting funding aside so you can create projects without having to "pluck a business plan out of thin air." Further, allow innovation teams the ability to run pilot projects so they can gather data toward the creation of a more thorough business case. "Avoiding months of discussions and negotiations before being able to start projects makes it is easier for the broader organization to see what you are doing, as well as to help you get it done," he attests.

"Looking back, the Investigator Databank project, with all its complexity and industry cooperation, was such a moon shot."

ANDREAS KOESTER, M.D., Ph.D
VP of Clinical Trial Innovation & External Alliances

According to Koester, a core element of any successful innovation engine is to *always* keep in mind that it is working within and for a larger organization. "We are a small group," he reiterates. "If we work independently, then we are merely a think tank with a bunch of smart ideas theorizing about implementation. Instead, we want to create solutions and be an implementation engine. We want to create a blueprint that can be expanded throughout all of Janssen R&D."

With an organization name that includes the words clinical, trial, and innovation, Koester says some desirable attributes for potential CTI members were fairly obvious, such as finding folks knowledgeable with actually having run clinical trials internationally. "Since CTI would be based in the United States, we did not want it to become a U.S.-centric effort," he states. One less obvious team-member attribute was negotiation experience from both the vendor and sponsor sides of the business. In addition, Koester wanted people with the ability to ask very naïve questions. "I was looking for a combination of people who were very knowledgeable and close to the space, but had not lost their ability for expansive thinking," he says. "I wanted people who had demonstrated a past willingness to collide with very streamlined rivers of thought when it comes to challenging convention and the running of clinical trials." In other words, if you want disruptive innovation, seek disruptive innovators — then turn them loose on a project. (For approaches on how to find and keep disruptive innovators, be sure to read the Editor's Note on page 6.)

PROJECT SELECTION CRITERIA

Koester says that when it comes to selecting projects for CTI, the first and foremost driver is seeking solutions that make clinical trials better for Janssen's most important stakeholders — patients and investigators. "Though individual solutions we work on may lead to future precompetitive, cross-collaborative solutions such as the shared Investigator Databank (see sidebar *The Investigator Databank – A CTI Success Story*), we are first seeking a competitive edge," he states.

Project selection is one of Koester's most difficult tasks. "In our first year, we saw the drive and enthusiasm you might expect to see with a newly created group the likes of CTI," he recalls. "But the willingness to change things can result in the tendency to bite off more than you can chew." Thus, restraint became the key to successfully selecting projects.

He applies five filters to selecting CTI projects. "First, let's try not to duplicate what someone else is doing outside *or* inside the company. We are very careful not to create any overlap. Next, does it benefit the investigators? Does it benefit the patients? Does it increase the overall efficiency of the clinical trial?" When these questions are answered positively, then he goes to those who are supposed to use the solutions and asks, "Is this something you really want?" Koester advises not getting caught in the trap of pursuing something because you think it's great from your perspective. You really need to talk to the key stakeholders that will use the solution. This is how CTI selected other projects such as eMeds (utilizes smart technologies to overcome the issues related to medication and protocol nonadherence), electronic informed consent form, eICF (utilizes an iPad app to increase patient clinical study comprehension and improve participant retention), and a patient portal (the first website designed specifically for a patient participating in clinical trials).

"We learned a lot during our first year," he admits. "Looking back, the Investigator Databank project, with all its complexity and industry cooperation, was such a moon shot. If you asked me today, I would say, let's go for ambitious, yet feasible projects. By taking this type of approach, you can show some type of tangible results within the first year. Otherwise, you risk losing even the most enthusiastic supporters," he concludes.

How To Get The Gap Out Of Analysis

There is an analysis technique which tends to be more organic and flexible than SWOT (strengths, weaknesses, opportunities, and threats) and, in my opinion, offers much more value. Gap analysis compares the gap between your organization's actual versus potential performance.

The first step in conducting a gap analysis is to identify your company's current state. This is followed by identification of your company's desired state. In a column format, start by listing the attributes you'd like to see improved. For example, qualitatively your organization might lack diversity. Quantitatively, you might list how many orders you get a day, week, or month. The key is to be specific and factual. For the desired state, list highly specific goals, such as increase diversity by 50 percent, or more generic concepts, such as creating a more inclusive culture, in an adjacent column. Try to capture all the idealized attributes as they correspond to the current state. The difference between these two states is the "gap" and thus, where the technique gets its name. Seeing the gaps, and then creating the solutions for these gaps, is the true calling card of every successful entrepreneur. Being able to successfully bridge the cap should be the successful calling card of every business as an ongoing concern.

Begin the process of bridging the gap by creating a description for every element where a gap exists in another column. This should be followed by discerning the factors responsible for the identified gaps. Be sure to be specific, objective, and relevant. The final step is to list all of the possible remedies for bridging the gap. It is suggested that remedies should be action-oriented and specific.

Though gap analysis can be very forward-looking, you may want to create phases of gap analysis, such as gaps for one, three, five, and 10 years. Not doing this can make bridging the gap feel impossible, especially if you are trying to move from where you are, such as a biotech start-up, to where you want to be in 10 years — a Fortune 500 company. Finally, I would advise applying SMART-ER (specific, measurable, achievable, realistic, timely, and easily remembered) objectives as part of the creating remedies process. I think it is important not to forget the ER part. People can focus on fixing/bridging gaps for a limited number of things (e.g., three) at any one time. If you have people focusing on too many initiatives, they might feel overwhelmed or worse yet, lose sight of current business initiatives responsible for keeping the lights on.

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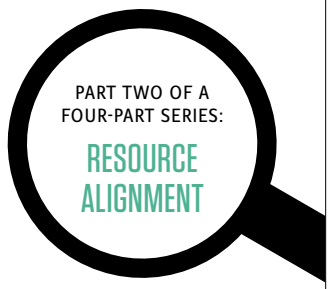
INDUSTRY PARTNERSHIPS WITH PATIENT FOUNDATIONS: THE BEST PRACTICES

Voices of BayBio's "Successful Public-Private Partnerships" Survey

WAYNE KOBERSTEIN Executive Editor



THEORY PLUS APPLICATION yields real-world lessons. When life science companies and patient-advocacy groups come together to ensure development of new treatments for unconquered diseases, they typically draw on each other's experience and inevitably learn some lessons on their own.

But this four-part series on the best practices for company-foundation partnerships, sparked by the large BayBio survey of players on both sides of such collaborations, seeks to spread some of the hard-earned knowledge over an even broader field of common interests.

In Part One of this series (June 2014), we examined what happens when two very different parties — a company and a foundation — establish their basic tenets, purpose, and goals in a common vision. In Part Two, we look at how the partners can avoid disruptive shifts and imbalances in their resources when they apply that vision to reality.

In addition to BayBio's survey — conducted in collaboration with Merrill Datasite, BIO, and FasterCures — we draw from insights voiced by key people in companies and foundations participating in the survey. The experts represent a "core sample" of industry-foundation collaborations — most focused by their common involvement in neurodegenerative diseases.

Because industry-foundation partnerships cover such a wide range — from targeted data-only exchanges, to support for proof-of-concept studies, to full-scale funding of clinical trials — they often form asymmetrical relationships in size and resources. Recognizing the resource gap is the best first step each partner, and both partners together, can take. Although each one may be left alone to work out its own solution, ideally they will work together to align their resources.

The foundations that pioneered a shift to industry funding and collaboration strongly believe that support for product development is the most efficient and effective way to deploy their resources — that is, as long as all the parties involved give due diligence to "de-risking" their relationships. Realistic assessment of each partner's assets, mapping out the development path, monitoring and measuring progress against clear milestones, and parallel adjustments to limit risk are the main best practices for ensuring resource alignment, as gleaned from the survey and its participating "voices."

COMPLEMENT & LEVERAGE PARTNERS' ASSETS

To make any rational use of resources, you must first know what you have, and in a partnership, you must also know what resources the other side can deploy. What does each party bring to the table? How and where can each partner best apply its assets to complement the other's in reaching the common goal? Aligning precious resources along the most efficient path toward the ultimate goal is critical to leveraging them — a valuable lesson employed by one of the first patient foundations to partner with industry. In this case, the first few successes generated enough leverage for the group to expand its industry partnerships many times over.

"The concept of de-risking is really central to why and how we think about placing our money and working with industry."

SOHINI CHOWDHURY
Senior VP Of Research Partnerships, The Michael J. Fox Foundation For Parkinson's Research

SOHINI CHOWDHURY, Senior VP Of Research Partnerships, The Michael J. Fox Foundation For Parkinson's Research (MJFF): We devote about $70 million toward research every year, but on the scale of industry drug development, that represents just a drop in the bucket. So we need to make sure we prioritize our funding to the most promising areas of therapeutic development, advancing a drug candidate to the point where it can be partnered with the groups that have more experience and deeper pockets to bring it to market — biotech and pharma. It took us a few years to staff up and plan how we could engage with industry and devote our resources to tackling related issues. In 2010, we launched the Parkinson's Progression Markers Initiative, a public-private partnership for an observational, longitudinal study to identify progression markers for Parkinson's disease. Though the study is in collaboration with industry, we are its sponsor and a primary funder. Sixteen pharmaceutical and biotech partners provide not only financial input, but also significant expertise and intellectual input to help us manage the study and to analyze the data coming out of it.

Although typically the size of funding from disease foundations, with notable exceptions, is relatively small in industry terms, its value in validating and attracting additional investment to small companies is evident. Less obvious, however, may be the effect of foundation support inside larger companies, as a legal expert specializing in industry-foundation partnerships points out.

DAVID LUBITZ, Partner, Schaner And Lubitz, PLLC: I have seen a number of medium to large biopharmaceutical companies come to the disease foundations for relatively small amounts of money because their programs must demonstrate internally not only that their technologies are promising, but also that they can attract seed funding to push them forward. So the disease foundations become de facto advocates for the technologies by funding them and participating in the collaboration within the companies. That is a vivid example of resource leveraging because, in a medium or a large company, which may receive at most a half-million dollars from some of the collaborations, the foundation funding may be enough to get the project off the ground, but its real value is to justify the project internally — to the folks who hold the purse strings.

In the case of the Myelin Repair Foundation (MRF), the currency of support is not money as it is with most other foundations, but knowledge. This group creates investigatory tools and produces data that guides discovery and development of drugs to repair damaged myelin, the protective sheath around nerves, primarily in multiple sclerosis. But though its native language is science, not business, the group invests many of its resources speaking to companies in terms the industry understands.

JENNIFER CHANG, Director Of Communications, The Myelin Repair Foundation: We don't view industry as a collection of quasi-CROs to bring our compounds to the market, the traditional way many nonprofits have worked with industry. We realized we needed to replicate the academic research results and formulate comprehensive data packages that would interest industry. We opened up our own lab and have created our own proprietary myelin-repair drug assays that no one else in the world has, and because we're a nonprofit, we're able to work with many pharmaceutical companies to test any of their compounds that are interesting for myelin repair, to give them further evidence and support, whether or not they ultimately go into clinical development.

Besides funding, staff, and even knowledge itself, perhaps the most valuable asset a foundation might bring to a partnership from a company perspective is its ability to attract disease experts and key opinion leaders (KOLs) – another stake the MRF can place on the table.

CHANG: Traditionally, nonprofits have used a funding model based upon peer review, giving out individual grants in academic research and hoping the published papers would reach industry. But we leverage our nonprofit status to give us the freedom to operate with many more scientists and experts. We can bring people together at a table that universities may not. We can engage with the right people at every step of the drug development process, from the bench to FDA approval, to greatly accelerate the process.

Companies may also be the catalyst for KOL-fueled collaborations. Amplimmune formed an alliance with Fast Forward, the industry-partnering subsidiary of the National Multiple Sclerosis Society (NMSS), and Northwestern University to move along the company's early development of a molecule to tame abnormal immune responses. It found that teaming the partners' hard assets with their "intangible" resources – all pushing in the same direction – brought quite tangible results.

MICHAEL RICHMAN, President And CEO, Amplimmune: Although people focus on the financial investment, the intangible value contributed by foundations is just as important, tapping into their network of professionals — exchanging and sharing ideas, obtaining access to materials such as patient blood and tissue samples that may be vital in one's research. Foundations are learning how to use KOLs (key opinion

leaders) in their network or their own in-house experts to evaluate partnering opportunities and monitor ongoing relationships. But the company can also bring in its own expertise; for example, in manufacturing, regulatory affairs, and working with the clinical operation groups such as CROs and universities. We take the partner's resources and integrate them with the company's resources, creating the alignment, and then we put all of it on a path that hopefully leads to a new product at the end. So, the resource alignment is very clear — it is focused on the specific objectives and the goals we share with the foundation.

MAP OUT THE DEVELOPMENT PATH

Best practices in industry-foundation partnerships commonly overlap; they are not always sequential or completely separate actions. For example, moving between evaluating partners' assets to planning goals and objectives is a dynamic, two-way process. Both actions – evaluating assets and setting goals – involve defining the scientific, financial, and other practical challenges. But mapping out a clear path for the collaborative project will identify key points where partners might work together to de-risk development, as in preclinical or proof-of-concept studies, patient selection, and clinical trial design. Whether the aim is lab tools or clinical trials, a clear common goal, well-defined milestones, and scientific results must guide all planning, monitoring, and decision making from the earliest point of the partnership on.

RICHMAN: There are two key value-inflection points in the critical path of developing a potential product. One is preclinical validation, based on cellular biology work or testing in animal models. The second is clinical proof-of-concept trials — controlled studies in patients for safety and efficacy. Foundations are providing preclinical proof-of-concept investments so that a company can generate the data sets needed to secure additional funding from investors and take things further into clinical trials.

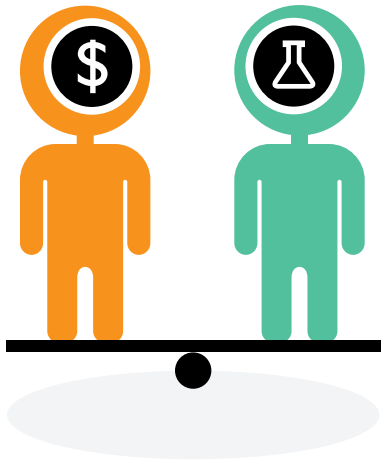
CHOWDHURY: The concept of de-risking is really central to why and how we think about placing our money and working with industry — to generate further information and more data, to either discount a particular therapeutic avenue or key it up to the point where it's been de-risked enough that another group may pick it up. And so it requires us to actually understand the industry's perception of Parkinson's disease, what they consider the critical hurdles to investing in Parkinson's, and to figure out what is their threshold for risk in obtaining the product.

MONITOR PROGRESS AND REROUTE AS NEEDED

Trust but verify – de-risking also requires diligent monitoring and steering of development projects. For Ceregene and MJFF, as for other voices in this series, continuous oversight by the foundation partner proved vital to the relationship right from the start, enabling the partners to align and leverage their resources for repeated expansions and successes.

JEFFREY M. OSTROVE, Former CEO, Ceregene: With Ceregene's Parkinson's drug, we were designing our Phase 1 clinical trial in 2004 and we wrote a grant proposal to The Michael J. Fox Foundation to fund parts of the trial because there were some really interesting endpoints — not necessarily ones that would be required by the FDA, but important scientifically. Though the group was new to funding industry research, our application was fast-tracked when the Foundation's head of research received positive feedback on the drug from outside experts, and our chief scientist was allowed to present our case directly to the Foundation's review committee. They awarded us the grant of about $750,000. Since then, Ceregene has been awarded approximately $7 million from the MJFF, but all of the grants were driven by milestones, and we worked like a family with the Foundation and our collaborators, in order to make sure we all stayed on track to achieve them.

Some of the money that we really needed from MJFF was to extend the timing of our clinical endpoint. We wanted to have up to a 24-month endpoint in one of our trials, as opposed to a 12-month or 15-month endpoint, because the experts believed it would generate a richer data set. The Foundation gave us a $2.5 million grant. It was milestone-driven: enroll the first cohort of patients, enroll the second, get some more money, and so on. Had the FDA stopped the trial for any reason, which they didn't, the Foundation wouldn't have made the next payment.



CHOWDHURY: We are clear with all of our awardees — we are not a bank. We don't just provide a check and walk away. We are very tailored in our approach to research. We view ourselves as partners in the research endeavor. All of the payments are linked to milestones accomplished, and there are frequent assessment calls or in-person meetings that happen with every awardee. Managing expectations, whether it be with industry or academia is critical to resource alignment.

Thus ends Part Two of our four-part series, "Industry Partnerships With Patient Foundations — The Best Practices." Watch for Part Three, "Partnership Structure," in next month's Life Science Leader. Many thanks to Travis Blaschek-Miller at BayBio and the BayBio team for their help with this article series. (See BayBio's white paper on the survey at http://baybio.org/?s=public-private+partnerships.)

The Falsified Medicines Directive – What Does It Really Mean?

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The trade in falsified medicines — medicines that look real but really aren't what they seem — is a huge and growing one, and it is putting patients' health and even their lives at risk. Along with regulatory authorities around the world, the European Union is putting directives into place that could begin to slow this deadly trade.

THE PROBLEMS WITH FALSIFIED MEDICINES

Falsified medicines are fakes that get into the supply chain, often via the Internet. These could be tablets or injectables that have the wrong amount of the right drug, with a dose that is too low or too high. They could include poor quality ingredients or completely different and potentially harmful active ingredients. Alternatively, they could be drugs that have been diverted from a legitimate source and repackaged, but not necessarily stored under the right conditions or with the right use-by date. The EU uses the term "falsified medicines" to differentiate these from counterfeits — copies of marketed drugs that do contain the right active ingredient but that infringe companies' patents or trademarks.

Falsified and counterfeit medicines make up around 1 percent of the volume of the global market, according to the EU, and up to 60 percent in West Africa, putting already vulnerable populations of patients at risk. The WHO believes that falsified medicines could be the reason behind around 100,000 deaths per year in Africa.

The trade in falsified medicines is a highly lucrative one, as the drugs are generally high value, such as anticancer medications, or in high demand, such as antivirals or drugs for malaria or tuberculosis. The WHO estimates the global market to be worth around $77 billion, having doubled in size between 2005 and 2010. According to Craig Stobie, global account manager, Domino Printing Sciences, speaking at the SMi Group's 8th annual conference on Parallel Trade in 2014, $1,000 investment in falsified medicines can lead to a return in $450,000, much more profitable for criminals than counterfeit currency, tobacco, and software combined. This money provides a source of income for organized groups that are hampering peaceful development, Andris Piebalgs, European Commissioner for Development, said in a statement.

THE EU FALSIFIED MEDICINES DIRECTIVE

Using legislation, countries around the world are working to combat the influx of falsified medicines into the supply chain. The approaches include track-and-trace and mass serialization, which use unique codes tied to central databases and allow genuine packs of drugs to be traced back to the license holders, manufacturers, and distributors. The addition of tamperproof technologies on the packs confirms that the product hasn't been repackaged or tampered with in any other way. In combination, these make sure that users (doctors, pharmacists, and patients) can verify the packs are authentic and contain the correct drug at the correct dose.

There are rulings coming in or already in place worldwide to stop the trade in falsified medicines:

- EU – Falsified Medicines Directive
- United States – Drug Quality + Security Act (HR3204)
- Brazil – ANVISA (Agência Nacional de Vigilância Sanitária)
- Saudi Arabia – SDC (Saudi Drug Code)
- China – CFDA (China Food and Drug Administration; previously SFDA)
- India – DGFT (Directorate General of Foreign Trade)

Around 80 percent of the requirements are common globally and tend to focus on item-level serialization and aggregation as measures for securing the pharmaceutical supply chain.

The EU Falsified Medicines Directive, adopted in July 2011 and put into place from January 2013, is the core of the EU's legal framework for the licensing,

manufacturing, and distribution of medicines. It is designed to include pan-European, harmonized safety-and-control measures to stop illegal drugs entering the supply chain. These measures begin with two key safety features — bar codes and tamperproof technologies. Under the directive, all legitimate product packs must include a unique 2D bar code that identifies the pack and that carries the manufacturer code, serialization number, national reimbursement number (if available), batch number, and expiry date. This needs to link with a repository system that stores and validates the bar codes end to end, from manufacturer to the point that the drug is dispensed to patients. The pack also needs to include a tamper-verification feature.

The directive also includes responsibilities for wholesalers and brokers, written confirmations for APIs manufactured outside the EU, and logos for legally operating online pharmacies.

In April 2014, the EU launched a three-year, approximately $5.3 million project targeted at developing strategies and legal frameworks and raising awareness of falsified medicines in developing countries.

IMPACTS AND OPPORTUNITIES

To comply with the directive, companies need to put a number of processes and protocols in place. They need to buy and install hardware and software that can generate and print unique bar codes or 2D codes. Then they need to be able to scan the codes and store and track the data. And all of this hardware and software will need to integrate with any existing enterprise resource planning (ERP) software.

Packaging designs may need to be rethought because they will have to include space for the bar codes. Furthermore, those bar codes need to be clear enough and contrast well enough against the background for easy scanning. That means companies will need to have quality control in place, and they will need to ensure the codes remain stable and legible in storage throughout the product's lifetime. As Stobie explains, this is the biggest change in the pharma industry in the last 40 years, and any system is only ever going to be as good as its worst part.

Of course, compliance with the directive will come with a price tag. According to Maarten Van Baelen, medical affairs manager at the European Generics Association (EGA), he estimated the costs as:

- printing and serialization — around $331,000 to $397,000 per packaging line
- antitampering —around $199,000 to $265,000 per packaging line
- verification with repository systems — around $53 million/year.

The EGA believes this will make medicines, particularly generics, unaffordable by increasing the production costs. Van Baelen also suggested that the verification system could limit the ability of pharmacists to dispense medicines. His organization would like to see an optional application of the safety features, a waiver for the tamper-verification feature, and a phased-in approach of the implementation.

Another area where the Falsified Medicines Directive will have an impact is parallel trade, where traders import drugs from lower-value markets into higher-value markets in the EU (see "An Introduction to Pharmaceutical Parallel Trade in Europe" in *Life Science Leader,* May 2014). Traders may replace the packaging completely, which could involve the loss of the unique codes and damage to the tamperproof seals. To comply with the Falsified Medicines Directive, parallel traders will have to put more of a packaging and IT infrastructure in place. "This raises the bar for the parallel traders, as they will also need to invest in data and artwork management," says Stobie.

Implementation also will take time. As Stobie warns, "Compliance is likely to take longer and be much harder than people think. As the directive will be enforced in 2018, companies that have not yet begun the process may not have enough time, and it could have a knock-on effect on the drug supply."

However, there is a positive side to the process, too. As well as the protection for consumers, there could be advantages for both manufacturers and consumers. The system allows manufacturers to treat each individual pack as a "batch of one,"

> *"Compliance is likely to take longer and be much harder than people think."*
>
> **CRAIG STOBIE**
> Global Account Manager,
> Domino Printing Sciences

meaning they can access precise real-time data on the production process at every stage. And for consumers, the machine-printed codes could help those with vision, language, or cognition issues.

People with a visual impairment or cognitive problems could scan the code with a smartphone and hear spoken instructions, the product name and dose, a reminder to take the drug, or instructions to replace the pack because it is near the use-by date. This also could be a way to access instructions on-screen in simplified language or as a translation. "Including information for the patients via the codes could be a way to increase patient engagement and adherence," says Stobie.

The Falsified Medicines Directive also could provide opportunities for contract packaging companies. These are amongst some of the earliest adopters of the directive, and many are already seeing the benefits of early compliance.

HOW WILL THIS AFFECT COUNTRIES OUTSIDE THE EU?

Under the terms of the directive, every batch of APIs imported into the EU from outside will have to be accompanied by a written statement issued by the regulatory authorities that confirms compliance to GMP standards equivalent to those in the EU. Alternatively, the manufacturing country will have to be "whitelisted" by the EU as a country that has GMP inspections equivalent to those in the EU.

Merck's Continuous Process Improvement

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Continuous improvement doesn't just depend upon Lean principles and/or zero-based budgeting. It depends upon people inspired by a culture that values learning, promotes problem-solving skills, and strives toward big goals by making small improvements every day.

"Every outcome can be obtained through a process and, hence, improved," says Craig Kennedy, senior VP of supply chain management at Merck. "And once it starts, it never stops."

Unlike episodic initiatives, continuous improvement is grounded in a broad vision guided by concrete goals through a series of incremental steps. Consequently, these small, sequential challenges lead to long-term improvement. Merck embraced a process of continuous improvement after years of implementing Lean initiatives that yielded periodic improvements.

With Lean, Six Sigma, Kaizen, Agile, total quality management, and other process improvement approaches, after an initial surge, results sometimes slipped backwards to baseline levels. That's because, like most companies, Merck focused on costs, outcomes, and big goals. Once the desired results were achieved, the company turned to other projects. "That approach was not focused on the human capability to make continuous improvement part of the culture," Kennedy says. "Unless you do this, methods ultimately will fail and even slip backwards."

One part of the problem, Kennedy elaborates, was that "we tried to improve unstable processes. We focused on Lean as a promise to gain efficiency and achieve results significantly different than we had at the time." The steps to ensure continuous improvement — scientific problem solving, coaching, leader involvement, and daily application — weren't fully addressed.

START WITH A CHALLENGE

One of Merck's continuous improvement challenges was to improve its line-item fill rate for its top products. As Kennedy says, "We set a very high standard for line-item fill rate. To be considered a success, each line item must be filled exactly with the quantity the customer requested and be delivered exactly when the customer requested, and this must be verified by the customer. We were filling tens of thousands of items that were shipped to 200 markets each month with high schedule adherence, but it wasn't translating to high service in the eyes of the customer. Therefore, with stability as a first goal, we focused on deliberate improvements. We worked through one variable at a time, adjusting through experiments and learning along the way. Each effort was guided by a clear sense of purpose and challenge," Kennedy says.

For example, in his previous role as a plant manager, "Our overall goal, which we achieved, was to produce 1.4 million vials per week, 95 percent of the time." Initially, Kennedy recalls, fill rates fluctuated from about 700 vials to 1.2 million vials per week on any given line. He slowed the lines until each produced a consistent number of vials each week and could maintain that consistency for about a month. Once the first goal was achieved and maintained, the goal increased, and any issues that could prevent reaching that goal were addressed. By the end of the year, each line had met the goal of filling 1.4 million vials per week, and the issues that had prevented filling so many vials consistently in the past had been resolved.

Continuous improvements can be made in other areas, too. For example, Merck has a high level of customer service because it addressed its ability to fill orders on time and in full. "A systematic program of continuous improvement addressed issues and improved our customer service scores by more than 10 percent in one year. For the past nine months, 95 percent of orders, globally, are filled on time and in full, as verified by the customer," Kennedy says. At the same time, costs were reduced.

This approach works throughout organizations because, regardless of the area

targeted for improvement, the basic questions are the same: "What are you trying to achieve? Where are you now? What's preventing you from getting the results you want? What did you try last, and what did you learn? What are you trying next, and what do you expect to happen? When can we see results?"

Importantly, Kennedy cautions that not every experiment will work. "Success requires a strong focus on scientific methods. People are expected to hypothesize, design a test, and run the experiment. Continuous improvement occurs in an environment in which people practice, fail, learn from their mistakes, and try again. It occurs by making incremental, small steps in a routine, regular fashion."

LEADER-DRIVEN

Lasting improvements must be driven by leaders. At Merck, senior leadership sets a challenging, but ultimately reachable, long-term vision. To achieve it, the company develops smaller goals with clearly identified steps that connect to that vision. Because these goals are smaller and nearer-term, the vision becomes achievable. The primary goals are not only to make an improvement but also to obtain the learning that accompanies the efforts, thereby building from previous attempts.

The situation can be compared to the space program in the 1960s. The program that began with the launch of a small satellite spurred the nation's leaders to envision the landing of a man on the moon by the end of the decade. NASA approached the challenge scientifically, one step at a time. First, launching a man into space, extending human time spent in space, and learning to maneuver the space capsule, before leaving Earth's orbit and, in 1969, landing men on the moon.

In the pharmaceutical industry, the vision may be a bit more earth-bound but nonetheless challenging. One goal, for example, may be to achieve single-piece flow on customer demand. As Kennedy explains it, "Patients and customers don't buy batches at one time; they buy doses or courses of treatment." Sometimes their personal situations or economics require that they buy single courses of treatment or even a few doses at once, excluding them from purchasing the larger quantities the industry more often provides.

In addition to better serving small markets, enabling single-piece flow helps expose problems in the process flow. Supply chains that are capable of providing single units tend to be more efficient than those that can only supply larger quantities, he says. The benefits, which include limited inventory, fresher ingredients, and longer effective shelf life at the end-user level, are comparable to those of just-in-time delivery.

The connecting challenge in this scenario is to scale down batch size to a one-month supply, and then a one-week supply, and eventually a single dose.

SCIENTIFIC PROBLEM-SOLVING SKILLS

To achieve continuous improvement, leaders must do more than provide a vision and issue a connecting challenge. They also must actively implement the needed changes and ensure those changes actually are made. "They can't merely announce a change, confirm that their people are trained, and assume the change will happen," Kennedy says. "They must not delegate their authority."

Ideally, "leaders will set challenges so people stretch, learn, and improve. A challenge too far above current capabilities may be demotivating, but I have found that people are extremely motivated when they have a good purpose and a definite challenge."

THE LEARNING IS AS IMPORTANT AS THE OUTCOME

Developing problem-solving skills and a continuous improvement mindset requires coaching. Management throughout the organization is responsible for coaching.

"Skills are different from knowledge," Kennedy points out. Training can provide skills, but it needs to be augmented by practice for it to become most valuable. Training also must be directed toward the company's goals. Aligning learning with organizational goals is key, because improvements don't arise from learning for learning's sake.

To help ensure alignment between training and organization objectives, "We record the learning and coaching sessions and measure subsequent activities." For example, rather than merely recording that a manager and employee met for a coaching session, Merck measures whether their learning is progressing, using a skills matrix divided into novice, intermediate, and expert categories. The goal is for employees to progress to the point they can teach each skill within their matrix.

Plateaus in progress are normal, Kennedy points out. "Managers need to recognize when learning has stopped and set a different challenge to help employees learn in a different direction. The manager's job is to send them back when necessary to relearn elements. Learning occurs by doing.

"People, in general, like to learn and to solve problems. Continuous improvement really means investing in people."

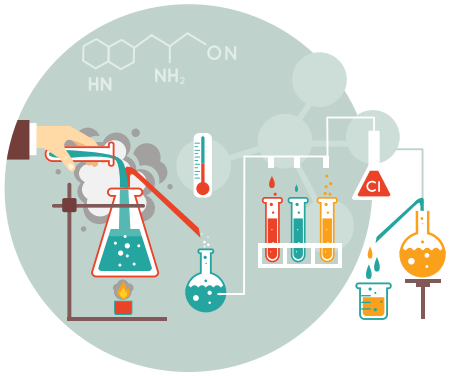
By directing the energy of people in ways that make continual, incremental improvements, companies can increase productivity and build more engaging environments. "I've never seen a piece of equipment improve itself," he points out.

Since Merck's commitment to continuous improvement some four years ago, the benefits have rippled throughout the company. The line-item fill rate has increased from 82 to 97.5 percent. Inventory has been reduced 10 percent by shortening lead times for business, financial, and physical processes. Merck's product flow and velocity have increased in four key supply chains, which led to double-digit growth in emerging markets each year. Even employee engagement has improved 15 percent. "Most importantly," Kennedy says, "we've built a measurable skills base in scientific problem solving that is being deployed and improved daily."

Achieving continuous improvement doesn't happen overnight, Kennedy stresses. Committing to a process of continuous improvement requires a mindset that is focused on excellence and efficiency and that refuses to accept the status quo. To gain the benefits, organizations and individuals must actively try to improve. As Kennedy says, "Companies build cultures over a long time, formed by rigorous adherence to the same thing, again and again."

The Evolving Role Of Drug Mechanism Of Action In Drug Discovery And Development

SETH LEDERMAN, M.D.



Discovering a new drug can reduce pain and suffering, preserve and extend life, and facilitate procedures like surgery and recovery through anesthesia and pain management. Collectively, effective drugs and their appropriate use can support the creative and cultural activities of societies.

While important, these uses and achievements reflect only a narrow view of the utility of drugs. Drugs are not only therapeutic or prophylactic, but also tools that can define the disorders they treat and unlock the mysteries of disease processes. The explosive evolution of drugs that affect the CNS illustrates these roles of drugs and also reveals distinct roles of fundamental discoveries and incremental advances. For CNS conditions, fundamental discoveries have been primarily driven by clinical observations of unexpected benefits. The incremental advances have been facilitated by understanding how drugs work, or their mechanism of action. For example, understanding the history of drug discovery may facilitate the discovery of drugs that improve sleep quality and treat sleep disorders. Such a drug may also be a tool to unlock the mysteries of sleep physiology, sleep disorders, and the roles of disturbed sleep in the chronicity of pain and the reexperiencing of painful memories.

Drug discovery can be viewed as an evolutionary process with rare fundamental discoveries interspersed within the more numerous incremental advances. The fundamental discoveries lead to branch points, while the incremental improvements march forward in a steady and relatively linear progression. When little was known about biology, drugs were discovered only by a directed but shotgun approach of human investigation that is sometimes mistaken for serendipity. Typically, natural products were tested on a variety of disorders. We can surmise that occasionally the trained eye of a physician or pharmacist noticed a benefit and then pursued a tinkering approach of adjusting the dose and treatment regimen to improve on it. Gradually, the active substances were extracted to varying degrees of purification. Together, improved dose regimens and purer ingredients led to progress in treating many conditions. Some important CNS drugs (e.g., Aspirin, Oxycodone) were improved through chemical modifications that were revolutionary in their time.

The 1950s represented a huge leap in the development of psychotropic drugs. Thorazine, Miltown, Tofranil, and Valium were all developed during this time. The rapid invention and development of these drugs gave birth to what is now called biological psychiatry, because these drugs revealed biological mechanisms underlying conditions that had previously been described only clinically.

THE POWER OF REPURPOSING

This explosion of drugs that revolutionized psychiatry also reveals a theme. Almost all of these drugs had been developed or used for a different purpose than the one for which they ultimately were found effective. Thorazine was developed as an antihistamine before it became the first antipsychotic. The parent of Miltown was a preservative for antibiotics before it became the first anxiolytic. Tofranil was designed to be a follow-on antipsychotic before it became the first tricyclic antidepressant. The revolution in biological psychiatry reveals the theme that fundamental discovery can be driven by clinical insights from unexpected drug effects. When clinical observations of unexpected effects lead to new drug approvals, it is called "repurposing." This power of repurposing to drive fundamental discovery is particularly powerful for conditions with no known animal model and insufficient knowledge on which to construct a biological basis.

The CNS drugs that revolutionized psychiatry also came to play a role in defining the illnesses they treat. The psychosis of schizophrenia became that condition that responded to chlorpromazine. Anxiety became that condition that responded to Miltown, or later, Valium. Endogenous depression became that condition that responded to Tofranil. Before biological psychiatry was born in the 1950s, psychiatrists focused on the content of a patient's

thoughts and words. After the introduction of effective medicines, psychiatrists focused on treating the biological processes underlying patients' symptoms and diseases in the realms of mood, anxiety, and thought disorders.

Beyond their role in treating disease, drugs have helped scientists understand the biology underlying patients' symptoms and diseases. A drug's mechanism of action ultimately involves interactions between the drug and its targets. Drug targets are molecules in humans or pathogens. Sometimes the term "target" is applied to the biological processes that are altered when the drug interacts with its molecular target. Sometimes the term "target" is applied to a disease state.

Understanding a drug's mechanism of action typically takes many years. Often, innovative drugs have been adopted into clinical use for many years before their mechanism is understood. In fact, the effectiveness of an innovative drug typically has provided scientists with the insight that a target molecule, biological process, or pathological condition exists. Moreover, the drug itself typically has provided scientists the tool to decode its own mechanism. In this way, drug discovery provides not only therapeutics to alleviate human suffering, but also provides profound insights into biology and disease processes.

After the explosion of new psychiatric drugs in the 1950s, research into their structure and mechanism fueled incremental discoveries that led to numerous follow-on drugs, which extended and improved the therapeutic effects of their ancestors. Many antipsychotics followed chlorpromazine and these "typical" antipsychotic drugs were ultimately supplanted largely by "atypical" antipsychotics, particularly Clozaril.

The history of CNS drug discovery and evolution supports the contention that the tremendous therapeutic impact of drug discovery is complemented by the use of drugs as tools to define the disorders they treat and to unlock mysteries of disease processes. Fundamental discoveries and incremental evolution play distinct roles in the evolution of increasingly effective and more tolerable drugs. Fundamental discoveries help decode mechanisms which facilitate the incremental advances of medicinal chemistry. Without animal models for many of the important human psychiatric and pain conditions, fundamental discoveries have been driven by clinical observations of unexpected benefits. L

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eTMFs: Moving From Electronic Filing Cabinet To Strategic Asset

JENNIFER GOLDSMITH & LISA MULCAHY

In 2010, McKinsey & Company published a report on the need to reinvent drug development through technologies designed to streamline the clinical trials process. The report recommends implementing technologies that represent a "clean-sheet" or redesigned traditional clinical trial methodology.

McKinsey identified having a single document repository with workflow management and the ability to track cost, quality, and speed as a core factor for business transformation. Turns out, McKinsey was onto something.

The growing functionality in electronic trial master file (eTMF) applications enables life sciences companies to streamline many inefficient processes that can slow clinical trials. Moreover, today's eTMFs enable sponsors and CROs to better track a study's progress by tracking the status and completion of critical documents. Doing so enables both types of organizations to proactively identify operational challenges and avoid costly delays. In fact, advanced eTMF applications can become a crucial source of trial information and performance insights to help improve and speed clinical development.

The eTMF — the electronic compilation of documents and other content that chronicle the conduct of a clinical trial — is gaining traction. According to the 2012 TMF Reference Model survey, 27 percent of respondents claim to be actively building or evaluating an eTMF, up from 17 percent in 2010. TMF management has evolved, too, from paper-based files to electronic "filing cabinets" of scanned documents and, today, to purpose-built applications, some of which have even moved to the cloud. Unlike their predecessors, modern eTMF applications provide visibility into trial operations and help ensure that the TMF is always inspection-ready. The wealth of information these applications collect about a study's start-up, ongoing operations, and close-out allows the eTMF to function as a business planning tool.

Widespread industry research highlights how document-centric processes directly impact major benchmarks, such as study start-up and close-out. Paper-intensive processes, such as contract negotiations and ethics committee approvals, are top causes of study delay, suggests data from a 2011 global CenterWatch study. Furthermore, a collaborative study on trial start-up conducted by the Tufts Center for the Study of Drug Development reveals that, on average, a Phase 2/3 study takes 16.7 months from protocol approval to 100 percent approved sites initiated. Within this time frame, high volumes of paperwork tied to pre-study visits, site selection, contract negotiations, site initiation, and first-patient visits are generated. And, according to Veeva Systems' 2014 survey of TMF owners (n = 260), 63 percent of respondents say paperless study and site start-up processes would significantly shorten clinical development times.

Recognizing the efficiencies that an eTMF application offers an organization is one thing. Transforming an eTMF into a truly strategic asset capable of improving the bottom line is another matter. To extract the full potential of an eTMF, life sciences organizations must take a few important steps with the partner, the application itself, and their own organization. These include:

- **Step 1** – Define the collaborative process among internal and external partners.
- **Step 2** – Build a repeatable framework, outlining what documents are expected, what they are called, and who is responsible.
- **Step 3** – Leverage performance metrics involving study-related documents to provide visibility and early problem resolution.

DEFINING A COLLABORATIVE PROCESS

The growing number of trial stakeholders (CROs, trial sites, agencies, committees, patients) has dramatically increased the complexity of assembling the numerous

pieces of the TMF into a coherent package. During the past decade, sponsors have been attempting to improve overall trial efficiency by concentrating operational efforts on fewer but more strategic CRO partners. In fact, 65 percent of sponsors are now using fewer than five CROs, according to Vantage Partners' Sponsor-CRO Collaborative Study. CenterWatch research from 2013 shows that 87 percent of the top 30 pharmaceutical companies have at least one strategic functional service provider (FSP) or multi-FSP alliance — collaboration that will clearly play a pivotal role in their success or failure.

With fewer partners, it is easier to specify which one is responsible for which elements of the information and which SOPs will be used. When partners run multiple trials together, both benefit from using a single process to manage their collaboration. A shared system for collaboration results in efficiencies in trial execution, which once defined, can be reused from study to study.

In many cases today, however, the sponsor and/or CRO maintain an eTMF on their own network, blocking access to outsiders. In this scenario, stakeholders send documents via paper shipments or email and maintain separate copies of TMF documents that need to be reconciled at the conclusion of the trial. Alternately, a cloud-based eTMF is by its very nature easily and securely accessible by all parties. Sponsors can define new processes that are more efficient up front, maintain visibility throughout the trial, and help ensure the TMF remains inspection-ready at all times. This type of collaborative and open process begins by uploading a document into a cloud eTMF. Because all parties have direct access, physical distribution of content becomes obsolete, eliminating the need for emailing copies of documents as attachments. Renee Fate, senior manager of document management at Kythera Biopharmaceuticals, describes one process the company is redefining in an initiative to take full advantage of its new cloud TMF system. "We partnered with a CRO for both regulatory and clinical support, and their SOPs had both teams sending us the same document. Next time, we'll define one process that has their clinical team uploading documents into our cloud TMF where I can review them before sending the approved documents to both of our regulatory teams."

Managing collaborative processes within the eTMF combines information exchange and tracking into a single system. Not only does collecting TMF documents become more efficient, but also all parties gain visibility into status and outstanding tasks.

"We are shaving at least 40 percent off the amount of time needed to reconcile the TMF at the conclusion of a trial with our cloud system," added Fate. "Now, we

have full visibility and can track the status of the TMF in real time for the duration of the study so we can identify bottlenecks or missing documents along the way. We don't have to wait until the end when 'surprises' can force us to backtrack, which wastes so much time. We can now manage workflow much better and close studies sooner, which will translate into cost savings."

BUILDING A REPEATABLE FRAMEWORK

Building a repeatable TMF framework involves defining expectations upfront to ensure all TMF participants are aligned and in agreement on what the TMF artifacts are called, when they are due, and who is responsible for filing them. In order to know what content is missing or late, all contributors must first understand what is expected. A repeatable framework sets expectations at the outset, reinforces the collaborative process, and improves overall efficiency.

Standardizing a common nomenclature drives better communication by harmonizing the filing efforts of diverse stakeholders. When multiple parties refer to items by different names (Figure 2), filing and tracking become confusing, increasing the chance for error. The nomenclature defined by the Drug Information Association's (DIA's) TMF Reference Model represents input from hundreds of pharmaceutical companies, CROs, regulatory agencies, and vendors from across the globe. In addition to standardized naming, the TMF Reference Model introduces standards for content, structure, and metadata. For these reasons, more and more clinical trial sponsors, including Kythera, are leveraging this model to build their own repeatable framework.

When setting the framework, it is essential to establish time frames for completing management milestones, as well as roles and responsibilities for execution. In many cases, the responsibility for filing TMF documents and other content will shift from a records management function to the author/owner in the TMF. Managing a successful process change is critical for gaining many of the benefits associated with using an eTMF. Because of this, establishing a repeatable framework is an important part of the change management process. Defining each stakeholder's role is also critical to successful outsourcing, finds an Avoca Group survey of 237 respondents. Collaborative relationships "require absolute clarity in roles and responsibilities and up-front planning assumptions," Avoca states. Typical clinical collaborations have lacked this clarity, sometimes resulting in difficulties and disappointment in the relationship.

"The biggest issue when it comes to transitioning to a new type of system – from paper to electronic, for example – is the fear of losing control. But, when employees and partners see the increase in efficiency that comes from a more streamlined, repeatable process, then they are more likely to embrace the system and accept a new 'digital' mindset," said Fate.

Additional elements of the repeatable framework include operationalizing SOPs by configuring them within the eTMF application, essentially codifying them into system workflows. The eTMF application orchestrates task completion across companies and stakeholders, in keeping with company SOPs. A common workflow automates many manual steps, improving productivity and trial efficiency. By comparison, a paper-based TMF or eArchive relies on people remembering and following written SOPs and then documenting them.

When collaborative processes are coupled with a repeatable framework, the foundation is in place to begin defining and leveraging performance metrics.

DEFINING AND TRACKING PERFORMANCE METRICS

The eTMF can track operational metrics for a specific study by which documents have been completed or remain unfinished and which need follow-up. These simple daily metrics are a good place to start, according to Linda Sullivan, COO of Metrics Champion Consortium, an association dedicated to standardized performance metrics.

A 2014 survey by NextDocs supports the notion that operational metrics are important but remain a challenge. In fact, the survey indicates that the second largest challenge in managing a TMF is the lack of visibility into the status of clinical trial documentation. eTMF reports such as study site document status, site acknowledgement of investigator brochure, and document expiry can all help inspection readiness by providing greater visibility

FIGURE 1

Methods Used To Exchange TMF Documents Between Sponsors And CRO

Email	68%
Paper Shipments (FedEx, UPS)	57%
Portal	43%
Cloud File Share (FTP, Box)	29%
CMS (SharePoint, Documentum)	29%
Fax	25%
eTMF application (Veeva, NextDocs)	15%

FIGURE 2

Multiple Names For Same Document

Common Name	Various Names
Specification	Requirement
Signoff	Summary Report Validation Report
Computer System Validation Packet	Validation Package Validation Documentation Release Documentation
Trial Master File Plan	Records Management Plan File Plan Filing Instructions

***Source:** Veeva Systems, The Paperless TMF, An Industry Benchmark 2014 – (Percent of respondents, n=260)

into what's approved and what's missing.

These common, trial-specific performance metrics — efficiency and completeness — establish a baseline for improvement, allowing managers to look at metrics in an organized way as opposed to extrapolating from paper-based processes. However, as more data is collected over time and across multiple trials, it also becomes possible to identify trends. "What about improving cycle time? Time to database lock? Are things getting better? Worse? Which sites are the best performers? When you start to ask those questions and get answers, users are ready to move toward a more mature phase in the process," says Sullivan. "Eventually, the eTMF expands in value when organizations can determine whether problems are unique to one study or if there is a common problem across multiple trials. For example, if the contracting process is too lengthy for numerous trials, what steps can be taken to shorten this activity and improve cycle time?"

This is the point at which the eTMF builds to a greater level of sophistication. The eTMF can help with business decisions by gathering an array of quality, performance, and operational metrics that are both internal and external and across multiple sites and studies.

eTMF: AN ESSENTIAL TOOL

With increasing pressure to meet clinical trial timelines and rein in costs, sponsors and CROs are looking to the eTMF as an essential tool for completing and collecting the array of documents involved in clinical trials — and for using the resulting data to identify process improvements. The urgent need for greater visibility into study conduct and quality benchmarks for trial operations is driving the industry's growing use of new technology. This evolution toward a single source of shared electronic documents is helping stakeholders modify processes that improve collaboration and gain business insights.

"We recognized from the outset that going electronic with our TMF would be critical to improving efficiency and enabling seamless collaboration with trial stakeholders around the world. Now, in order to maximize the system's value, we are reengineering our SOPs to reflect the advantages of a cloud-based eTMF and to move forward with study success — ultimately delivering much-needed drug therapies to patients faster," concluded Fate.

Jennifer Goldsmith is VP of Veeva Vault at Veeva Systems.

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Global Drug Discovery Outsourcing Market Gaining Momentum

JIM ZHANG, PH.D.

There is no doubt that global pharmaceutical companies have a desperate need to develop better drugs with high success rates. Consequently, more drug companies are utilizing external resources, while still constantly streamlining their internal R&D systems.

Today, externalization has become a core strategy among pharmaceutical and biotechnology companies for all types of activity, including R&D and manufacturing. In fact, the original concept of outsourcing has now been expanded to include all types of collaboration, including partnership and technology licensing.

Drug discovery has been one of the core sectors of the long value chain of drug R&D. However, in recent years, almost all major pharma and biopharma companies have focused on developing late-stage drug candidates due largely to the global financial crisis and the pressure of patent expirations of blockbuster drugs. Drug discovery research has been less focused, with many companies primarily relying on external resources, including R&D-focused biotech companies and professional discovery research service providers (e.g., CROs).

This focus on late-stage development is now making many large pharma and biopharma companies realize that their early-stage pipelines have become thin. Drug discovery research has, thus, recently regained focus among these companies. However, their research strategy in this field has changed significantly.

NEW STRATEGIES FOR DRUG DISCOVERY RESEARCH

New R&D strategies are constantly evolving in global pharmaceutical and biopharmaceutical industries. The virtual drug discovery model for small molecules that is popular with R&D-focused small biotech companies is now becoming accepted by the large players in the industry. Some of them are currently practicing this model in various therapeutic areas.

Meanwhile, all drug companies have now recognized that early-stage drug discovery is not just for identifying a new medical (either chemical or biological) entity for a target. Rather, it is about validating the identified therapeutic target and better understanding the disease biology, pathology, and interactions between the compound and the target (as well as those off-targets). Thus, biology-guided drug discovery has become a new trend in today's pharmaceutical industry. Consequently, major pharma and biopharma companies are more focused than ever on understanding disease biology in order to have more accurate therapeutic targets and to employ new technologies to truly improve R&D success rates.

Besides traditional tasks such as lead discovery and optimization, pharmacological property study and optimization, the disease biology-incorporated drug discovery now also includes the discovery and validation of biomarkers and proof of the therapeutic concept in *in vitro* conditions. This integrated, cross-functional discovery research methodology is now widely practiced.

NEW DRUG DISCOVERY OUTSOURCING STRATEGIES

Along with the change of their discovery research strategy and practice, major pharma and biopharma companies have been shifting their outsourcing strategy from a risk-sharing emphasized model to a more technology-concentrated partnership. Discovering new therapeutic targets and thoroughly validating them have become the new priorities of drug discovery research. The integrated drug discovery outsourcing model has become the prevailing trend.

To this end, drug companies need the involvement of academia in early drug discovery more than ever. Almost all global major pharma and biopharma companies have forged close partnerships with a number of academic research institutions in recent years. Moreover, they are increasingly integrating human genetics research into their discovery and development programs. Genomics and proteomics have been widely employed not only in drug development, such as for the development of companion diagnostics and patient stratification, but also in drug discovery, such as for target identification and validation, safety biomarker development and application, and development of novel antibody drugs. In all these R&D activities, academia is playing increasingly important roles.

The new outsourcing strategy also is creating broader collaborations, not only with peer competitors, technology-bearing biotech companies, and professional outsourcing service providers, but also with academics, for both drug discovery research and new therapeutic target identification and validation. The latter includes not only pure research on disease biology but also discovery and validation of new biomarkers and their applications.

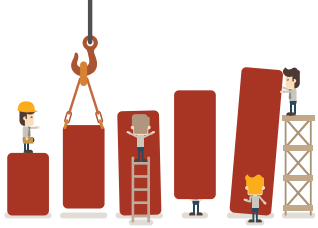
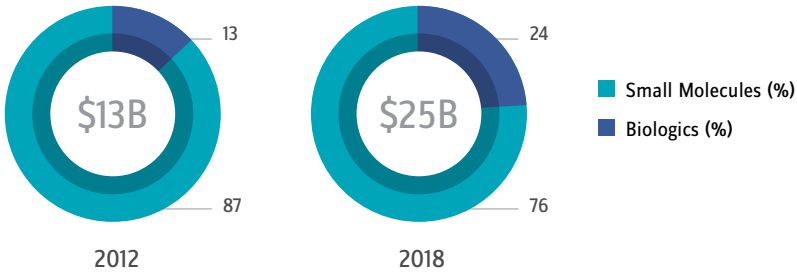


FIGURE 1

Forecasted future growth trend of global drug discovery outsourcing market



Indeed, academia has become the third key element of many companies' R&D efforts.

BIOLOGIC DRUG DISCOVERY BECOMING NEW FOCUS

Biologic drugs, especially novel antibodies, have become as important a class of therapeutics as traditional small molecule drugs. That's why they have been steadily gaining share in the pipelines of major pharma companies. This has caused many companies to create dual-track drug discovery programs for both small molecules and biologics. To do so often requires two separate R&D systems, each focusing on one field.

Methodologically, biologic drug discovery research is operated just like that for small molecules. Compound libraries of antibodies, proteins, and peptides are in high demand. Similarly, antibody fragments that are smaller in size, but still antibodies by nature, are also being employed in biologic drug discovery research. However, in this area, the most advanced technologies are developed by specialty biotech companies. To a large extent, major pharma and biopharma companies currently rely on these companies for the new technologies or for filling their pipelines.

EMERGING COUNTRIES PLAY INCREASINGLY IMPORTANT ROLES, ESPECIALLY FOR SMALL MOLECULE DRUG DISCOVERY

Until now, the most desirable technology in drug discovery research has been compound libraries with diverse structures. A fragment-based lead discovery platform or high throughput screening of thousands of compounds against the selected therapeutic targets has still been the main approach. However, this type of R&D work, especially the construction of small molecule compound libraries, has now been considered to be approaching maturity. Few drug companies large or small are now willing to assemble a large, internal team of synthetic organic chemists to do it. The majority has, instead, been outsourced, including to low-cost emerging countries. In recent years, emerging countries, in particular China and India, have been the main places for global drug companies to look for focused compound libraries of small molecules that possess diverse structural features.

On the other hand, a number of service companies in emerging countries are now also able to offer integrated drug discovery research services. Multinational drug companies are thus expanding their discovery research outsourcing scope in these countries while strengthening their current relationships with local partners.

FUTURE GROWTH POTENTIALS

According to our research, in the past few years, the global drug discovery outsourcing market has been growing at a CAGR of about 10.5 percent. Its current market size is estimated at $13B, accounting for close to 10 percent of the current total global drug R&D spending. Of the total market value, the small molecule drug discovery outsourcing service market accounts for about 87 percent, reaching about $11.25B. Between 2009 and 2012, its CAGR was around 11 percent. The current biologic drug discovery outsourcing market is estimated at only about $1.75 B, accounting for about 13 percent of the current total global market. However, its CAGR from 2009 to 2012 was about 37 percent.

The current average outsourcing penetration of small molecule drug discovery research among major companies is estimated at 40 percent. The current average outsourcing penetration of biologic drug discovery research is, however, only about 15 percent. The overall average drug discovery research outsourcing penetration is about 30 percent at present.

Driven by the strong desire of all drug companies to improve efficiencies and productivity in their R&D efforts, the global drug discovery outsourcing market is expected to grow at a decent pace in the foreseeable future. We forecast that the global drug discovery outsourcing market will likely experience a CAGR of about 11.5 percent between 2013 and 2018, and its market value will likely reach close to $25B by 2018. By then, the overall industry-wide average outsourcing penetration of drug discovery research will likely reach close to 49 percent. In other words, nearly half of the global drug discovery research will be performed by third parties by 2018.

Of the total global market, the small molecule drug discovery outsourcing will likely account for about 3/4, reaching close to $19B by 2018. Whereas the biologic drug discovery outsourcing will likely account for about 1/4, reaching more than $6B by 2018 (Figure 1).

Jim Zhang is president of JZMed, Inc., a market research firm specializing in pharmaceutical outsourcing. This article is partially based on the firm's latest research report "The New Trends of Global Drug Discovery Outsourcing."

Best Practices For Designing Cell-Based cGMP Facilities

MICHAEL FISKE

Michael Fiske, M.S., is the director of the Upstate Stem Cell cGMP Facility (USCGF), a new state-of-the-art, cell-based cGMP facility commissioned and constructed by the University of Rochester Medical Center (URMC) with support from the New York State Stem Cell Science program (NYSTEM).

CGMP regulations incorporate the concept of quality by design (QbD). This concept is used in conjunction with a quality management system (QMS) aimed at controlling the collection, processing, storage, and release of human medicinal products. "Control" is the most important concept underlying all aspects of a cGMP. A well-managed facility must have systems for each aspect of cGMP and for the documentation of that control. Good documentation practices include:

- procedures written and approved for all programs and policies
- SOPs for the operation and maintenance of all equipment, processes, and test methods
- production and testing records documenting the complete history of each production batch
- deviation documentation and investigation records.

All the factors, systems, and methods relevant to cGMP need to be considered and evaluated when the physical space is being designed. Control must be the foundation of every aspect of cGMP facilities. For example, if instruments and equipment are well-controlled (calibrated, validated, maintained, and monitored), then the processes they support, and in turn the products of those processes, are more likely to be uniform and of high quality. Critical utilities and equipment, as well as processes and test methods, all need to be validated and controlled appropriately.

DESIGN CHARACTERISTICS OF CELL-BASED CGMP FACILITIES

The design of a cell-based cGMP facility must support the manufacturing of cell-based medicinal products (CBMPs) that are safe, pure, and effective, while eliminating the risk of contamination, errors, or cross-contamination during production. The design must also ensure biosafety, minimizing the risk of employee contact with infectious agents and prevention of the release of infectious agents into the environment. Important aspects of designing a cGMP-compliant production facility include:

- design features that reduce the risk of microbial contamination as well as the risk of product cross contamination (e.g., segregated air handling systems for adjacent production areas as well as control of appropriate room pressure differentials to ensure maintenance of specific room classification)
- access control to the facility, restricted access to critical areas
- mandatory unidirectional traffic flow (for personnel, raw materials and supplies, equipment, CMBP, and waste)
- design features for ease of cleaning: seamless floors, walls and ceilings, minimal ledges, easy-to-clean materials (gelcoat polymers, epoxy paint, stainless steel), use of receptacle and light switch covers, and movable equipment and tables.

ENVIRONMENTAL MONITORING PROGRAM

Cell-based cGMP facilities are required to have a comprehensive environmental control program. Key components include systems for ongoing continuous environmental monitoring. Environmental monitoring ensures that controlled-environment manufacturing areas, as well as critical process and storage equipment, continuously comply with design intent and user requirements. These systems provide information about the performance of the equipment and the heating, ventilation and air-conditioning systems, as well as data on the effectiveness of aseptic practices and cleaning procedures.

QUALITY MANAGEMENT SYSTEM

Some basic but essential elements of the quality system for a cell-based cGMP facility include document-control and change-control systems, validation support, supplier qualification, inventory management of raw materials and CBMP, and preventive maintenance and calibration programs for all equipment. Oversight of routine quality control testing, CBMP release, and environmental monitoring are also included, in addition to personnel training programs and auditing.

VALIDATION PROGRAM

Before any batch of CBMP is distributed, a high degree of assurance in the facility's performance and the manufacturing and testing of CBMP must be attained. All aspects of the facility's environmental control are validated as well as all manufacturing and analytical testing equipment. In addition, many of the analytical test methods used to characterize the final product are validated.

The validation program must address all the elements of the facility and operations, including:

- facilities/utilities
- production equipment
- analytical testing equipment
- temperature-controlled chambers
- computer systems (equipment control, data acquisition, and monitoring systems)
- cleaning and sterilization procedures
- production processes
- analytical test methods
- shipping protocols. L

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Defining Presence As A Leadership Behavior

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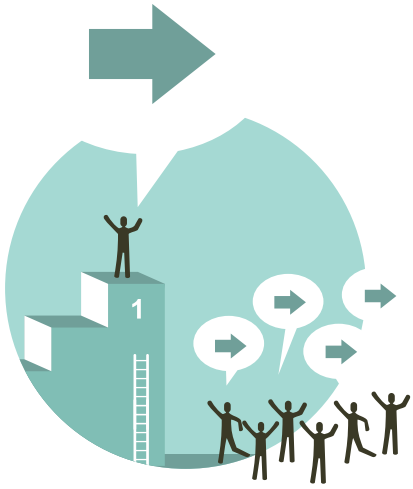

In my writings, I define leadership presence as the "right stuff of leadership," and, by doing so, I embrace a holistic concept. For me, presence is more surface appeal — as the term executive presence connotes; it denotes a leader's approach to getting the most out of themselves as well as their team. By that definition of presence encompasses conviction, authority, power, and the application of them through a leader's actions and words.

You might consider presence as defined by three verbs: be, do, review. Let's take them one at a time.

1 **Be.** Authenticity is a reflection of the leader's inner self, how they comport themselves as well as how they relate to others. Central to being is character, which is basically your sense of accountability and taking responsibility for who you are and what you do. Without such accountability, presence is negligible. That is, you may look good in a suit, but if there is nothing inside the suit, well, there is only emptiness.

2 **Do.** Leaders are defined by what they do. Most often a leader's prime responsibility is that of engaging others, guiding them with a sense of purpose and pointing them in the right direction. It's critical that you accept the consequences of your actions. Those who make excuses are not worthy of our followership. Conversely, those who stand up for what they believe and, most importantly, put people into positions where they can succeed, are worth their weight in gold.

3 **Review.** Before you can move forward, you need to know where you have been. And in today's 24/7 global framework, looking back is not a prized attribute. That leads many individuals and organizations to keep repeating the same mistakes. First, you need to reflect; set aside time to go over what you have done. Then, remember to review. I recall a pharma executive telling me that he had a boss who said the job was never over until you had a briefing with your boss about what went right or wrong, as well as what you learned.

John Baldoni is chair of the leadership development practice of N2growth, a global leadership consultancy. He is the author of more than a dozen books, including the forthcoming *MOXIE: The Secret to Bold and Gutsy Leadership*, coming this October.

While presence is composed of being, doing, and reviewing, it would be simplistic to consider it a process. It is more about an approach to life. This is a point that David Brooks made in a recent *New York Times* column where he wrote in regards to a family that had persevered through tragedy by grieving personally as well as doing what they can for others. As Brooks writes, "The art of presence [is] to perform tasks without trying to control or alter the elemental situation." In other words, change what you can change, and endure through grace what you cannot.

Leadership embraces activism; it is the outcome of a purposeful pursuit of goals. Yet every one of us has experienced adversity in the form of loss, failure, or mistakes. How leaders respond to such crises is what defines them. And here is where presence takes hold. Presence gives the leader the wherewithal — authority and resilience — to battle the odds and endure through being, doing, and reflecting. L

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