Life Science Leader
March 2013
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Balancing Science And Business At Pfizer

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Kevin Lee, Ph.D.,
VP and CSO,
Pfizer Rare Disease Research Unit

Andrew Callos,
VP of commercial development,
Pfizer Specialty Care Business Unit

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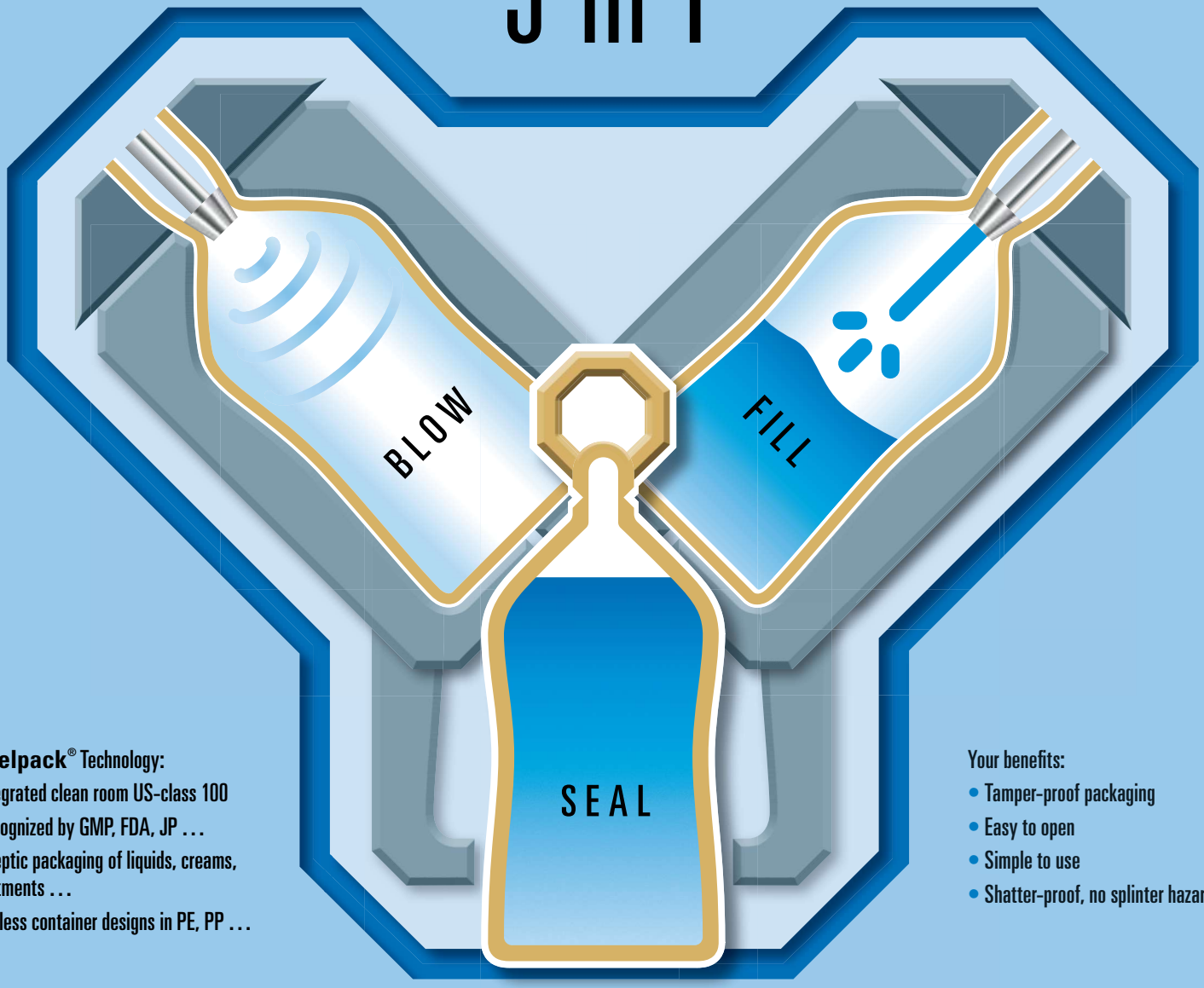

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20 FEATURE: PFIZER

Andrew Callos, VP of commercial development for Pfizer's Specialty Care Business Unit (R), and Kevin Lee, Ph.D., VP and CSO for Pfizer's Rare Disease Research Unit, discuss Pfizer's approach to developing a sustainable business in rare disease R&D.

March 2013

DEPARTMENTS

Welcome to *Life Science Leader*

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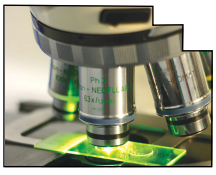

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EDITOR'S NOTE

A March Full Of Madness

Last year, during the month of March, I placed a call to a member of *Life Science Leader's* editorial advisory board. I was quickly informed that I was interrupting church. "Call me back at halftime," I was politely informed. In case you have been living under a rock, March, and the madness it creates, is the result of the annual occurrence of the NCAA Division I Men's Basketball Championship Tournament, where people fill out a tournament bracket and secretly cheer for a #16 seed to finally upset a #1 seed, even though on their bracket they most likely have three of the four #1 seeds in the final four. What I have found interesting is the number of researchers who have told me that the process of drug discovery is "the ultimate team sport." The process requires a collaborative effort across teams — from discovery all the way through to the folks on the commercialization side of the business. If you want to read an example of this, check out the article on page 20.

Another interesting similarity between drug discovery and the NCAA tournament is the focus on lost productivity. It is estimated that people filling out their brackets and using their computers to watch games and check scores average about one and a half hours a day. More than 40% of IT professionals said that the spike in Internet use affects office computer operations and in some cases, causes systems to crash. The resulting lost business productivity ranges between $175 million and $1+ billion, which on the high side, is close to the cost of developing a new drug all the way to successful commercialization.

I had my own form of March Madness last year, jetting between Orlando (twice), New York, San Francisco, and Washington, D.C. in an effort to attend a number of important events, such as DCAT Week, Partnerships in Clinical Trials, SOT, the R&D Leadership Summit, and the WIB Annual Gala Dinner. This year however, I am taking a different approach, with only one show on my calendar for the month of March — DCAT Week '13 at the Waldorf-Astoria and Intercontinental Hotels in NYC, March 11 to 14. Now I know what you are thinking, "But Rob, in January you mentioned DIA Europe as being one of your top 10 shows. It's in March." This is true. DIA Europe is an important show, and if I felt I could effectively achieve work-life balance by attending it and DCAT Week '13 back-to-back, then I would. However, I believe that if you spread yourself too thin by trying to be everything to everyone, you end up being nothing to anyone. Showing up at DCAT exhausted or late is not an option. Especially when I plan on taking a deeper dive into the event, probably even attending a few sessions sponsored by *Life Science Leader*, such as "Beyond the Vial: Drug Delivery of the Future" and "Facilities of the Future: Single Use Technologies" which take place on Wednesday, March 13.

In addition, while I am in New York City, I have some other plans as well. On the evening of Wednesday, March 13, *Life Science Leader* will be hosting the CMO Leadership Awards reception and ceremony, starting at 8 p.m. at the W New York on Lexington Avenue. As master of ceremonies, I am looking forward to formally recognizing the 2012 CMO Leadership Award Winners. You can learn more about the CMO Leadership Awards by checking out www.cmoleadershipawards.com. Hope to see you in New York in March. Perhaps we can even see who is doing better with their NCAA bracket?

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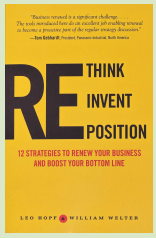

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Q: Should there be legislation to gain alignment between payors, providers, and drug development companies in an effort to facilitate more cost-effective drug development?

We are always open to looking at ways to bring down R&D costs for small, emerging biotech companies, but we are not convinced that legislation such as this would be appropriate for meeting this goal. Our goal must always be ensuring access to quality patient care and outcomes, which is the cornerstone of any payment system reform. We believe change needs to take place within the FDA regulatory approval process and within the reimbursement landscape. Further, we believe that we need to shift our innovation paradigm — the focus should be on the long-term goal of reducing the overall burden of disease through innovative new drugs to reduce the incidence of chronic disease. Despite the best efforts of industry, academia, and the FDA, new drug approvals are not keeping up with investment in R&D.

Alan Eisenberg
Alan Eisenberg serves as executive VP for emerging companies and business development at the Biotechnology Industry Organization (BIO).

Q: How have you been able to incorporate social media into your business model, given the lack of FDA guidance?

Working in R&D, there are a number of places where we have been able to incorporate social media today without waiting for formal FDA guidance. One example is our use of social media to engage stakeholders on diverse topics related to R&D without discussing specific products, such as our community of R&D bloggers at Pfizer Think Science Now (www.thinksciencenow.com). While comments are moderated to monitor for appropriate conversation as well as the potential safety reports, we are able to engage with diverse stakeholders on topics ranging from policy to technology to other relevant trends. Another area has been around applications for patient recruitment — from basic one-way advertising on social media sites to more sophisticated use of video or even engagement with patient bloggers. There are some ambiguities without proper guidance, but it is unrealistic to continue to sit on the sidelines.

Craig Lipset
Lipset is head of clinical innovation within worldwide R&D at Pfizer. In this role, he works across units and stakeholders to define Pfizer's vision for the future of clinical trials and enables the initiatives and investments to create that future.

Q: What company do you view as a model for learning from past experiences and improving development of new and innovative medicines?

I don't think there is just one model that can successfully translate cutting edge science into medicines. Companies of all sizes are already doing it (e.g. Novartis, Vertex, Biogen, virtual pharmas). These companies share two characteristics — embrace risk-taking and breakthrough science. These are the values that made the industry great. Fifteen years ago, many companies moved away from that model, hoping to lower risk and make innovation more predictable. It did not work and seriously damaged their innovation culture. Some companies, such as GSK, Sanofi, and Roche, have returned to real translational science and are again letting their scientists work on important problems, not just replacements to blockbusters. This will not only strengthen innovation, but also help burnish the industry's image.

Bernard Munos
Bernard Munos founded the InnoThink Center for Research in Biomedical Innovation, a consultancy that focuses on pharmaceutical innovation. He previously served as an advisor for corporate strategy at Eli Lilly and Company.

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By Wayne Koberstein

Centyrex

An entrepreneurial venture grows up inside Janssen R&D.

SNAPSHOT

Centyrex is a start-up platform and development company that originated inside J&J's biopharma R&D organization in 2008. Its platform consists of "alternative scaffolds" (AS), small simple proteins usually associated with monoclonal antibodies but engineered for superior stability. The company's AS molecules are called "Centyrins." Although the technology is still in its infancy, AS combined with modern protein engineering allows the design of exceptionally stable proteins that can be administered to patients in new ways. One of the original aims of Centyrex was to develop a normally oral asthma drug delivered directly to the lungs with an inhaler, a device formerly used only for small-molecule drugs. The company has since demonstrated successful inhaler delivery of the drug with its AS technology.

Robert Hayes, CEO

LATEST UPDATES

With the worldwide research collaboration and licensing agreement between Amunix, Inc. and Janssen, Amunix will combine its XTEN half-life extension technology with protein and/or peptide therapeutics selected by Janssen. The Amunix technology is expected to provide a half-life extension strategy for the small-protein scaffolds (Centyrins) created by Centyrex.

WHAT'S AT STAKE

Try googling Centyrex — go ahead, try it — and you will not find even the minimum press release-driven media coverage afforded most other life sciences start-ups with public announcements of funding and development progress. For, although the company operates and survives on its own merits like any other company, it does so as an entrepreneurial unit tucked away inside the great onion-layered edifice of Johnson & Johnson. Centyrex CEO and "Venture Leader" Robert Hayes and CSO Karyn O'Neil formed a team and presented a business plan for the "alternative scaffold" start-up, and they have run the company since they won initial funding from the Johnson & Johnson Development Corporation five years ago. Hayes's and O'Neil's background in protein engineering and previous work with mAbs and peptides had sparked their interest in AS development.

"Developing our own AS platform gives us the freedom to move alternative scaffolds into areas that are not being explored by other companies," Hayes says. "We have the luxury as a venture within Janssen and with broader J&J support." In the beginning, Centyrex focused on pulmonary drug candidates. Since then, it has steadily increased the number of new therapeutic applications of its proprietary Centyrin scaffolds.

"Recently we have been using alternative scaffolds in quite different ways, such as nanoparticle technology," he says. "We are combining material sciences and alternative scaffolds together to form novel drugs in therapeutic areas of interest. For example, scaffolds allow nanoparticles to be targeted to different tissue types or different organs, perhaps even including across the blood-brain barrier. Where biologics and material science meet is the future for drug development; it is truly innovative science that will provide translational drugs to patients in the future."

The application of Centyrins to nanoparticles is due to their simplicity — they can be easily attached to particles, and they have an exceptionally high tolerance of harsh manufacturing conditions. Centyrins can be "labeled" to bind to specific tissues and cell receptors, so they may be useful for imaging, specimen selection, and tumor analysis during surgery. AS technology may also offer advantages in formulation and stability, for example, eliminating the need for a cold chain for protein-based drugs.

Hayes is realistic about the potential of this platform as therapeutics: "The competitive barrier in AS development is the inherent technical challenge of creating scaffolds that don't fall apart when the proteins are tweaked for particular applications and ensuring that these molecules have the half-lives that allow convenient dosing to patients. Some AS proteins have also proved to be immunogenic or prone to aggregation, or cannot be manufactured in a cost-effective manner." He believes the promise of a superior AS platform was "something clearly appreciated by Janssen's senior management when it agreed to support the creation of Centyrex."

If Hayes is right, the advantages of alternative scaffolds will inevitably win over a large segment of the industry, and AS will become a dominant platform for many new drugs, devices, imaging technologies, and various hybrids of those categories. Centyrex is worth watching, both as a leader in the space and as an interesting hybrid in its own right — the venture inside the corporation.

VITAL STATISTICS

- Employees: 32; Headquarters: Spring House, PA
- Finances: Wholly owned internal venture of Janssen Research & Development, LLC, of the Pharmaceutical Companies of Johnson & Johnson
- Partnerships: Molecular Partners (Swiss-based) Amunix, Inc. (Mountainview, CA)

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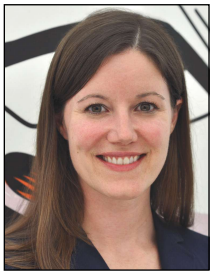

OUTSOURCING INSIGHTS

Outsourcing Clinical Research — Trends By Customer Group

By Kate Hammeke, director of marketing intelligence, Nice Insight

The practice of using CROs to conduct clinical trials is continuing to grow in popularity, especially as trials become more complex. Analysts estimate clinical research outsourced to CROs will grow from $31.8B in 2009 to a projected $60.8B by 2016. Beyond reducing sponsors' fixed costs, CROs have proven their ability to add value through expertise — from patient recruitment to navigating an increasingly tricky regulatory environment. And at the same time as drug makers have been focusing efforts on reducing the time and expense associated with bringing a new medicine to market, ironically it seems the FDA has been catching some blame for drug development costs increasing.

According to Avik Roy, author of *Stifling New Cures: The True Cost of Lengthy Clinical Drug Trials*, the primary source of rising costs over the past 15 years has been the regulatory process governing Phase 3 trials. He uses data from Tufts (from 1999 to 2005) to support his theory, reiterating that the length of a clinical trial has increased by 70%, and the average number of routine procedures per trial has increased by 65%, while enrollment criteria and trial protocols resulted in 21% fewer volunteers being admitted to trials and 30% of qualified participants dropping out before the study was completed. In order to keep up with these changes, it makes sense to engage the help of an external expert.

> Analysts estimate clinical research outsourced to CROs will grow from $31.8B in 2009 to a projected $60.8B by 2016.

BIG PHARMA IN SEARCH OF CROs

Fraught with a multitude of FDA regulations and an average duration of eight years, it's no surprise that clinical research is one of the most frequently outsourced elements of the drug development process. According to Nice Insight's most recent outsourcing survey, nearly half of Big Pharma respondents (46%) stated they would engage a CRO for clinical research during the next 12 months. Specialty pharma companies and emerging biotechs were just as likely to outsource clinical research, with 45% and 42% respectively. Emerging pharma and big biotech were slightly behind, with roughly 1/3 stating it is a service they will outsource in the coming year.

Not only do drug innovators from every buying category plan to engage a CRO for clinical research, they tend to have drug candidates in more than one therapeutic area for which they are looking for a CRO. Not surprisingly, Big Pharma companies had drug candidates in more therapeutic areas than the others. Oncology (55%), cardiovascular (47%), CNS disorders (43%), and infectious diseases (43%) were the most common therapeutic categories among Big Pharma respondents.

For Biotech companies, Oncology (39%), infectious diseases (36%), and metabolic disorders (24%) were the most popular therapeutic categories. Specialty pharma companies showed similarities to Big Pharma, outsourcing clinical research for drug candidates in infectious diseases (27%), oncology (26%), and cardiovascular diseases (20%). Emerging pharma (1.5) and emerging biotech (1.4) had slightly fewer therapeutic areas of focus for upcoming clinical research. Both emerging segments had cardiovascular therapeutics in development. However, emerging biotechs were much more likely to have infectious diseases candidates in development, whereas emerging pharma indicated oncology and respiratory diseases as additional therapeutic areas of focus.

If Avik Roy is correct in identifying the significant increase in costs occurring in Phase 3 trials, the question in the trend towards the use of CROs is whether their expertise can mitigate these rising process expenses. This will be fundamental to controlling overall development costs and getting therapies to market faster.

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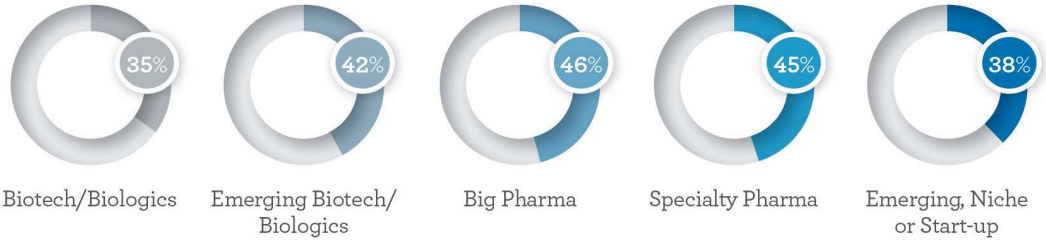
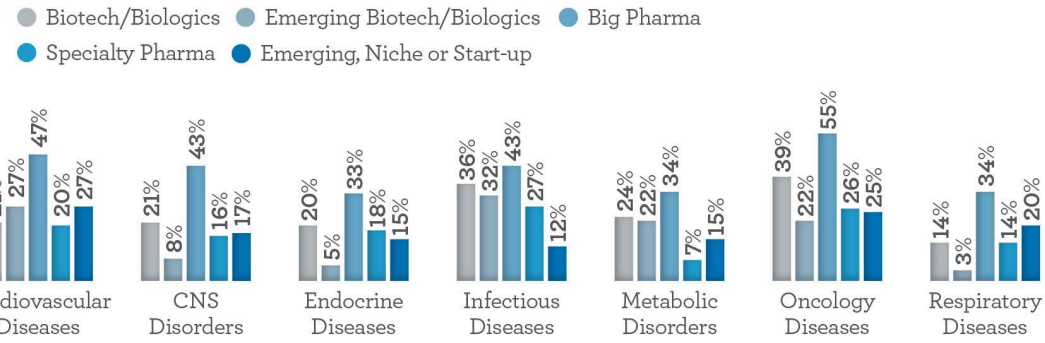


NI Average Number of Therapeutic Categories for Clinical Research

NI Outsourcing Clinical Research by Therapeutic Category



Survey Methodology: The Nice Insight Pharmaceutical and Biotechnology Survey is deployed to outsourcing-facing pharmaceutical and biotechnology executives on an annual basis. The 2012 sample size is 10,036 respondents. The survey is composed of 500+ questions and randomly presents ~30 questions to each respondent in order to collect baseline information with respect to customer awareness and customer perceptions on 170 companies that service the drug development cycle. More than 800 marketing communications, including branding, websites, print advertisements, corporate literature, and trade show booths are reviewed by our panel of respondents. Five levels of awareness from "I've never heard of them" to "I've worked with them" factor into the overall customer awareness score. The customer perception score is based on six drivers in outsourcing: Quality, Innovation, Regulatory Track Record, Affordability, Productivity, and Reliability.


Walker

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

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BIO INNOVATION NOTES

Innovation In Assays And Analytical Methods Urgently Needed

Industry Continues To Seek Better Bioassays

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

Biomanufacturers are increasingly demanding better analytical methods development as the industry expands its need to provide better metrics regarding process monitoring, comparability of products, quality, and a number of other critical areas associated with process improvement. In fact, when we surveyed the 450 global subject matter experts and senior participants on our Biotechnology Industry Council to identify the critical factors and trends they expect to be addressed over the coming year, 24% pointed to demands for better analytical methods.

To stay on top of the emerging trends in this important area, we also include this topic in our annual study of biomanufacturing, asking hundreds of global biomanufacturers from around the world to identify which assays are most critical and where improved testing methods are most urgently needed for biomanufacturing.

IMPROVED TESTING METHODS FOR BIOASSAYS

This year, preliminary results from our 10th Annual Report and Survey of Biopharmaceutical Manufacturers, due for release in April, show that the industry continues to look for improved testing methods for bioassays. We evaluated 30 different assay areas and found that assessment of potency for release of drugs topped the list again this year, with 42% of respondents to date indicating this to be an assay area urgently in need of innovation (see Fig. 1). This was also the leading area in need of innovation in last year's study, cited by 41% of respondents.

Next on the list this year is aggregation, indicated to be in serious need of testing innovation by 40% of respondents, a big increase from last year's 28%. Roughly 4 in 10 respondents also see the need for better testing in stability assays and biotech drug comparability (for in-house manufacturing changes as well as biosimilars), each at around 39% of respondents and each up from around 32% in 2012.

Rounding out the top five this year is glycosylation, an area which 37% of our survey respondents indicated to be urgently in need of new or improved testing methods, up from 33% last year.

Other trends we see developing this year (noting that our data remains preliminary) include:

- host cell-protein assays, which 36% of respondents see as urgently needing new or improved testing methods, up from 25% last year
- bioassays of proteins with multiple functional domains, also up this year
- bioassays for ADC (antibody drug conjugates) molecules showing an increase in cell viability, down somewhat in 2013
- precalibrated disposable sensors, down in 2013.

QUALITATIVE ANALYSIS OF INNOVATION FROM THE EXPERTS

When we asked our expert panel about this year's critical trends, those citing analytical methods mentioned a variety of micro trends, including high-throughput assays for high-level expression, therapeutic efficacy, improved high throughput, high-resolution glycosylation analysis, and better characterization tools for upstream analysis. The following are some qualitative analyses from respondents, diving deeper into the critical trends that will shape innovation in this all-important area.

According to a manager of technology development at a large biopharma company, developing better characterization tools for upstream analysis is critical. "The importance of in-process analytics means pushing the analysis of key product qualities further upstream in the process as opposed to relying primarily on end-product testing," the manager said. "This entails higher-end characterization tools such as mass spectrometry that provide multiple levels of information. The standardization and qualification of these information-rich assays are key to implementation of these assays for supporting process decisions."

Another senior scientist and group leader at a global biopharma noted that high-throughput assays that assess IgG (Immunoglobulin G) clones for expression levels and therapeutic efficacy are critical. "The overriding goal is to identify efficacious drug candidates. However, there are quite a few occasions where functionally selected candidate monoclonal IgG clones would not to be suitable for manufacturing," the scientist said. Ideally, assays should be developed to show this earlier, rather than after large investments of time and money. What is needed is a simple assay run during the early stages to guide the suitability of individual IgG clones for large-scale manufacturing. A number of industry experts believe there is substantial need for convenient high throughput assays that allow assessment of physicochemical properties of

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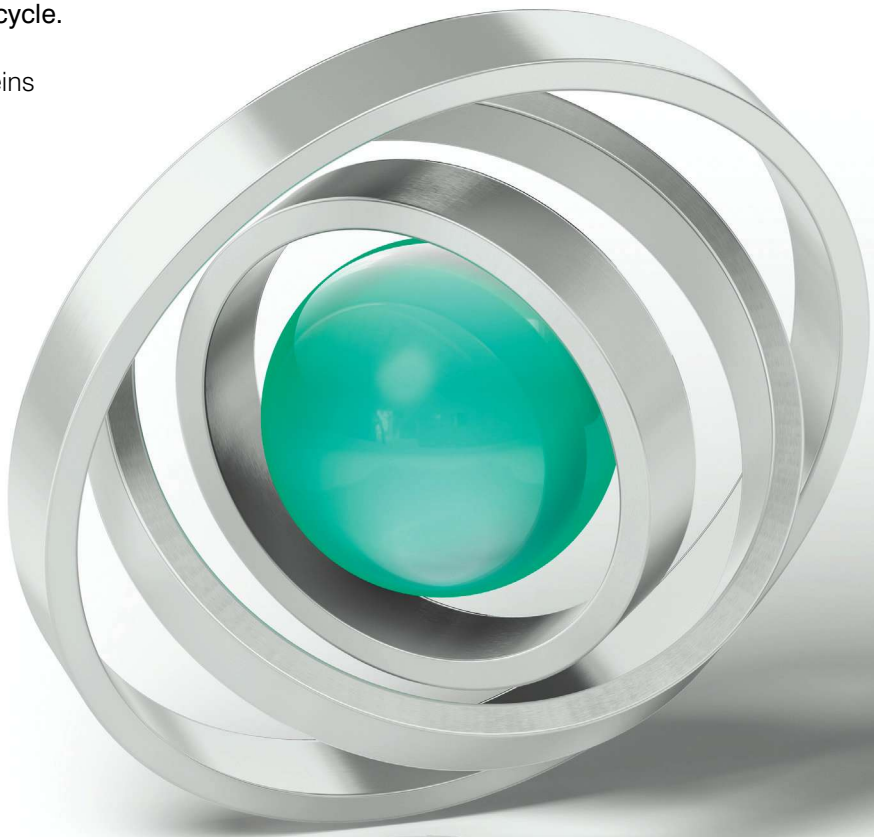

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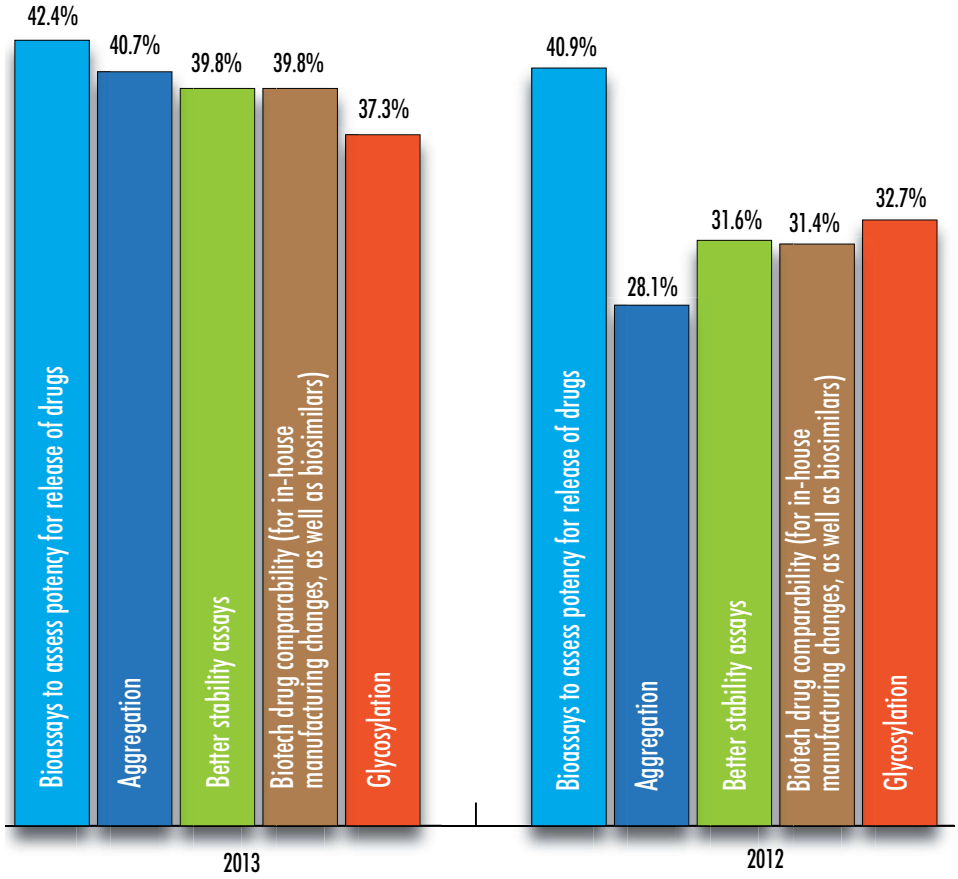
individual IgG clones for high-level expression to evaluate therapeutic efficacy.

With at least ¼ of our survey respondents to date seeing an urgent need for new or improved testing methods across eight assay areas, it's clear that significant attention from an innovation angle is needed. Yet innovation in assay services may still be a few years away.

In coming articles, we will discuss how suppliers and assay innovators are focusing (or not) on new technologies. For example, last year, only about 1 in 10 vendors said they were working on new technologies related to testing and assay services, whether for impurities detection, raw materials testing, glycosylation analysis/characterization, etc. We will be discussing whether assay innovators this year plan to take on a new commitment to improved testing and assay services. What we do know is that the industry is definitely seeking innovation, and as our preliminary study results show, that interest does not appear to be waning.

Figure 1: Selected assays of 30 evaluated areas most urgently requiring new or improved testing methods



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

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Andrew Callos (left), VP of commercial development for Pfizer's Specialty Care Business Unit, and Kevin Lee, Ph.D., VP and CSO for Pfizer's Rare Disease Research unit

Pfizer's Approach To Developing A Sustainable Business In Rare Disease R&D

By Rob Wright

Driving down Route 422 a few miles away from Pfizer's Specialty Care Business Unit headquarters in the eastern Pennsylvania town of Collegeville, you might notice the remnants of a dilapidated farm. Past the rotted out, collapsing walls of the barn, you can still see the faded white top of a silo that once was used to store and isolate one type of grain from another. The image serves as a grim reminder for Pfizer employees Andrew Callos and Kevin Lee that in order to avoid a similar fate, their two business units, commercial operations and rare disease R&D, cannot operate in "silos" but must collaborate.

If you have worked in or studied business, you have probably observed, or perhaps experienced firsthand, the "silo syndrome," whereby divisions within a company work in a vacuum with little or no communication between them. The end result is often a colossal failure, and you find yourself asking, "Who thought this was a good idea?" At Pfizer, about three years ago, it was recognized that there needed to be an active collaboration between commercial operations and the rare disease R&D unit. This was especially evident since the company was fresh off its $68 billion acquisition of Wyeth in 2009 and a subsequent acquisition of FoldRx, a little-known privately held Cambridge, MA-based biotech focused on developing treatments for conditions caused by the improper folding of proteins. But in order to leverage the collective strengths of the combined organizations toward rare disease drug discovery, the company needed to appropriately balance the desire for scientific innovation with the practicality of business. "Most importantly, we want to innovate where there's a high unmet need, while making sure we generate a reasonable return," says Callos, VP of commercial development in Pfizer's Specialty Care Business Unit. "It's got to be both." Kevin Lee, Ph.D., VP and CSO for Pfizer's Rare Disease Research Unit, agrees with Callos on the need for balance between scientific intrigue and commercial practicality. "There's a healthy tension that exists between the scientific desire of the researchers to take on new programs and the commercial team providing a reality check," states Lee. "It's a great dynamic that we should strive to maintain." Callos and Lee explain how the internal collaboration between their two teams serves as the foundation for developing a sustainable business in rare disease research.

THE RARE DISEASE OPPORTUNITY

The FDA Office of Orphan Products Development (OOPD) is charged with encouraging companies such as Pfizer to develop orphan drugs for the treatment of rare diseases. Encouragement by OOPD takes the forms of simplification of marketing authorization procedures, tax credits and research aids, and seven years of market exclusivity after FDA approval of a drug. Incentives aside, Callos and Lee affirm that pursuing drugs for rare diseases has to start with the patients and the science, not the incentives.

In 2010, Callos observed the number of rare disease drug approvals was approaching 40% of all U.S. drug approvals. According to Lee, the science was evolving, resulting in a de-risking of rare disease research, making it more tractable. Further, of the 7,000 rare diseases, only about 5% presently have approved therapies. There seemed to be a growing opportunity for success in the rare disease space. Through many of its legacy companies, Pfizer already had a long-standing presence in rare diseases, including approved treatments for hemophilia and rare endocrine diseases. "If we continued the way we were going, perhaps we would have created new therapies for rare disease," Callos matter-of-factly states. "However, there was recognition that rare diseases are a different business model, requiring a different approach in terms of the way we think about investing in R&D, conducting clinical trials, engaging patients, and bringing products to market." Callos needed to bring these rare disease differences to the forefront to improve the ability to compete for internal resources and investment in both the commercial and research sides. Given the size and

DON'T UNDERESTIMATE THE IMPORTANCE OF COLLABORATIONS BEING SEAMLESS

"I think from a scientific perspective it is hard at times, but yet so crucial to the success of a drug discovery program, to keep in mind that if you want to make medicines, you have to have good alignment with the medical and commercial groups," surmises Kevin Lee, Ph.D., VP and chief scientific officer for Pfizer's Rare Disease Research Unit. Lee's advice to avoid having to learn lessons the hard way is to start projects by asking the tough questions at the beginning, rather than halfway through, or worse yet, at the end.

That being said, Andrew Callos, VP of commercial development in Pfizer's Specialty Care Business Unit, admits that even with trying to proactively address the tough questions up front, some lessons remained to be learned the hard way. "The organization between the research and commercial units needs to be seamless," he testifies. "We need to be operating and thinking as one, not two distinct units. I think we probably underestimated the importance of that in the beginning," confides Callos. "We've done a lot in the last year and a half, two years, to make the communication more seamless between rare disease R&D and the commercial organization, to make us operate more as one group. We went back to basics like high frequency face-to-face interactions despite our different locations. In addition, we align early on potential collaborations and internal programs vetting the science, the unmet need, the chance of success, and commercial viability, and we go forward with recommendations as a single unit." As a result, the two organizations are now functioning as one. "Like a company within a company," he analogizes. According to Callos, every large company, including Pfizer, has a way in which it assesses and thinks about decisions, investments, and how to approach problems and opportunities. "Pfizer has a very robust, well-thought out approach," he states. "But I don't know that we really thought through that decision process, relative to rare disease investment, where clinical trials can generally cost less than trials in other areas, but where the disease and regulatory endpoints are perhaps not as well-understood." Callos and Lee admit they may have stumbled a bit in the beginning in their approach to decision making, understanding investment decisions, and gaining seamless alignment of the units. However, by having open dialogue and transparent communication, these areas have been rectified.

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scale of Pfizer, he thought a greater strategic and more specific rare disease focus, as opposed to lumping rare diseases in with specialty care, would provide the opportunity to make a much larger impact for patients and Pfizer.

Orphan diseases are defined as affecting fewer than 200,000 people in the U.S. Because the populations can be relatively small, there is a risk that companies investing in developing cures and treatments for rare diseases may not see a reasonable return, possibly even lose money. "We can't just generate therapies for patients without getting a return, because we won't be a company of the future, to generate more medicine," Callos explains. There needs to be a balance between scientific intrigue to finding cures and commercial practicality of providing a reasonable return.

ACHIEVING BALANCE BETWEEN SCIENCE AND BUSINESS

When you are dealing with 7,000 possible rare diseases, you can't build infrastructure for every single malady. You need focus. "We needed to focus on the areas where we have capability and knowledge and ideally, existing assets," says Lee. Callos described the team applying an analytical filtering process, viewing the opportunities through a series of "lenses" — scientific tractability, risk assessment, unmet need, and commercial viability. The first filtering pass removed oncology, given that a separate unit within Pfizer focuses on this area. This initial filter cut the number of potential rare disease targets to around 3,500, still a pretty large number. To narrow it further, they began the iterative filtering process anew, beginning with science and risk. This was accomplished through the creation of a cross-functional team, which included research unit, medical, regulatory, portfolio analysis, and commercial colleagues. "We had a lot of discussions with internal, and sometimes external, experts in both clinical practice and academia," he explains. "We really looked at which diseases are well-categorized." This was done by asking a number of questions to determine the diseases of interest, such as, "Do we really understand the pathogenesis of the disease?" "Is there a good understanding of the natural history of the disease?" "Are the diseases being studied?" "Are the regulatory pathways somewhat established?" "If not, could a regulatory pathway with defined endpoints be established, given the understanding of the disease?" "Are there 'drugable' targets available from mechanisms that have been described?" Through this drilling-down process, the team created a database of potential target diseases. "We tried to look at each one to determine the tractability from a research and risk point of view," Callos explains. "We also focused on diseases that were monogenetic." Through their collaborative analysis, the list was narrowed to around 40, though Callos and Lee note that Pfizer continues to evaluate every opportunity, as the science can change quickly.

Once the team had a thorough understanding of the risk and scientific tractability of the approximately 40 potential targets, they began to look at the unmet medical need of each disease. The group wanted to be sure the target diseases were very debilitating, with high morbidity and/or mortality rates. In addition, the team looked at diseases that affected children. "We really wanted to make sure that we were focused on where we could have the potential to significantly improve patients' lives and outcomes," Callos affirms.

The last filter the team applied was the viability from a commercial point of view. "What kind of investment do we need to make in each one of these disease areas?" he pondered. "What is a reasonable return, and will the investment we make cause us to compete for internal resources or could we partner externally?" The end goal, according to Lee and Callos, is to generate a meaningful return that would continue the investment, resulting in a robust disease area within Pfizer that is fully functional, growing over time, generating a meaningful difference to society, as well as a meaningful difference to shareholders.

MEASURING SUCCESS

Due to confidentiality constraints, Callos and Lee were unable to share what Pfizer considers to be a "reasonable return." However, Callos says, "One way to look at it is to ask, 'Are we getting appropriate return on our investment relative to other investment options within Pfizer outside of rare diseases?'" According to Lee and Callos, the fact that the rare disease units, respectively, continue to sign external collaborations and launch new rare disease products while progressing a number of programs in development demonstrates the commercial/rare disease R&D collaboration as being a success. They point to the fact that the rare disease pipeline now includes a number

STEPS TO PREVENTING SILO SYNDROME

The purpose of agricultural silos was to keep one type of grain isolated from another. The same approach in business, having departments operate in isolation from one another, can be detrimental to successful innovation. Commonly referred to as "Silo syndrome," it can hamper any type or size of organization from achieving its true potential. Here are a few simple steps to encourage cross-departmental cooperation.

Step 1 - Change your style of management, taking more of a consultant approach.

Step 2 – Update your company's core values, focusing on collaboration, communication, innovation, and teamwork. Communicate these, and then live by them.

Step 3 - Create cross-functional teams based on shared company goals, being sure to provide them with proper leadership.

Step 4 - Change performance metrics so that they are aligned, and reward collaboration/innovation.

Step 5 - Focus on the customer, placing them above all else, and share relevant information throughout the entire organization. Having an external focus tends to diminish the development of internal silos.

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of investigational compounds in development for ailments such as Duchenne's Muscular Dystrophy, Pulmonary Sarcoidosis, and vaso-occlusive events in patients with sickle cell anemia. "We have developed a partnership with a company called GlycoMimetics, for an exclusive worldwide licensing agreement for a drug candidate, GMI-1070, currently in research for patients experiencing vaso-occlusive crisis associated with sickle cell disease," relays Callos. GMI-1070 just completed enrollment for Phase 2 and has received Orphan Drug and Fast Track status from the FDA. Callos also notes the EU approval of Vyndaqel (tafamidis) for the treatment of transthyretin familial amyloid polyneuropathy (TTR-FAP) in adult patients with Stage 1 symptomatic polyneuropathy, a rare neurodegenerative disease that is estimated to affect 8,000 people globally. Unfortunately, Pfizer received a Complete Response Letter from the FDA on its NDA (new drug application) for tafamidis this past June. Pfizer is currently in dialogue with the FDA to discuss a potential path forward for tafamidis in the U.S. Despite this setback, the units continue to press forward. For example, Pfizer signed an agreement last year to expand on its relationship with Cystic Fibrosis Foundation Therapeutics, Inc., whereby the foundation will invest up to approximately $58 million into cystic fibrosis research at Pfizer. Additionally, "We have progressed assets in Phase 1 research for Factor VIIa and Duchenne Muscular Dystrophy," Callos adds, further noting the license agreement brokered with Repligen for research in spinal muscular atrophy. "I think you can see from our internal investment that we have multiple investigational compounds now in the clinic." By taking a focused approach to rare disease drug discovery — balancing the scientific curiosity for wanting to find cures, with the commercial practicality of generating a reasonable return — Pfizer has created the foundation for a sustainable business model for rare disease research.

> "We can't just generate therapies for patients without getting a return, because we won't be a company of the future."
>
> *Andrew Callos, VP of commercial development for Pfizer's Specialty Care Business Unit*

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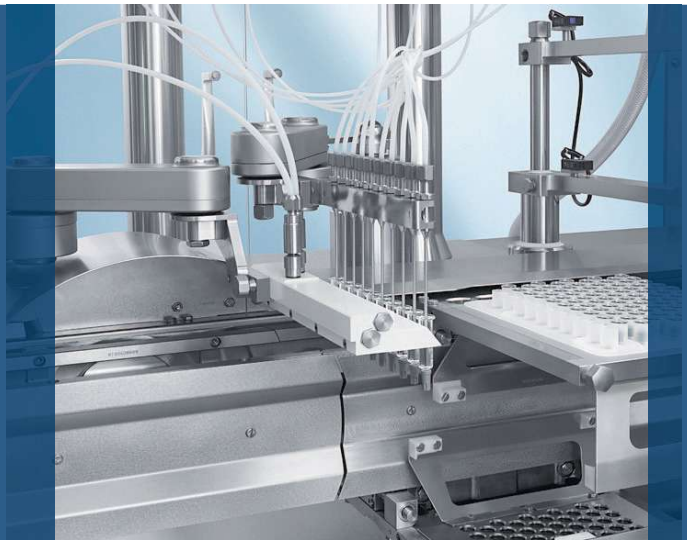

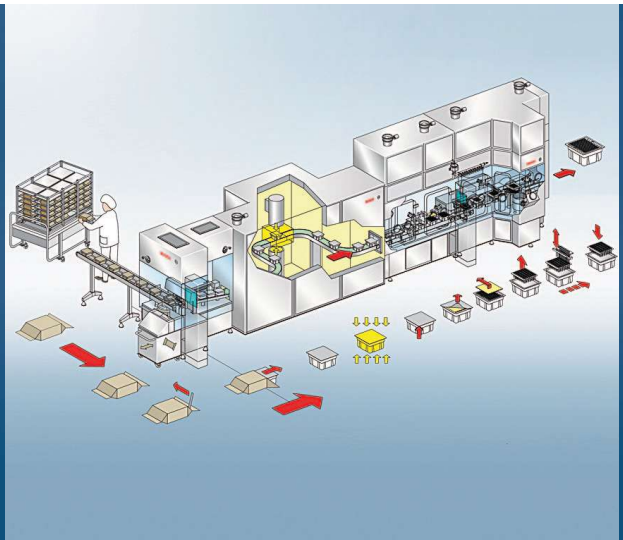

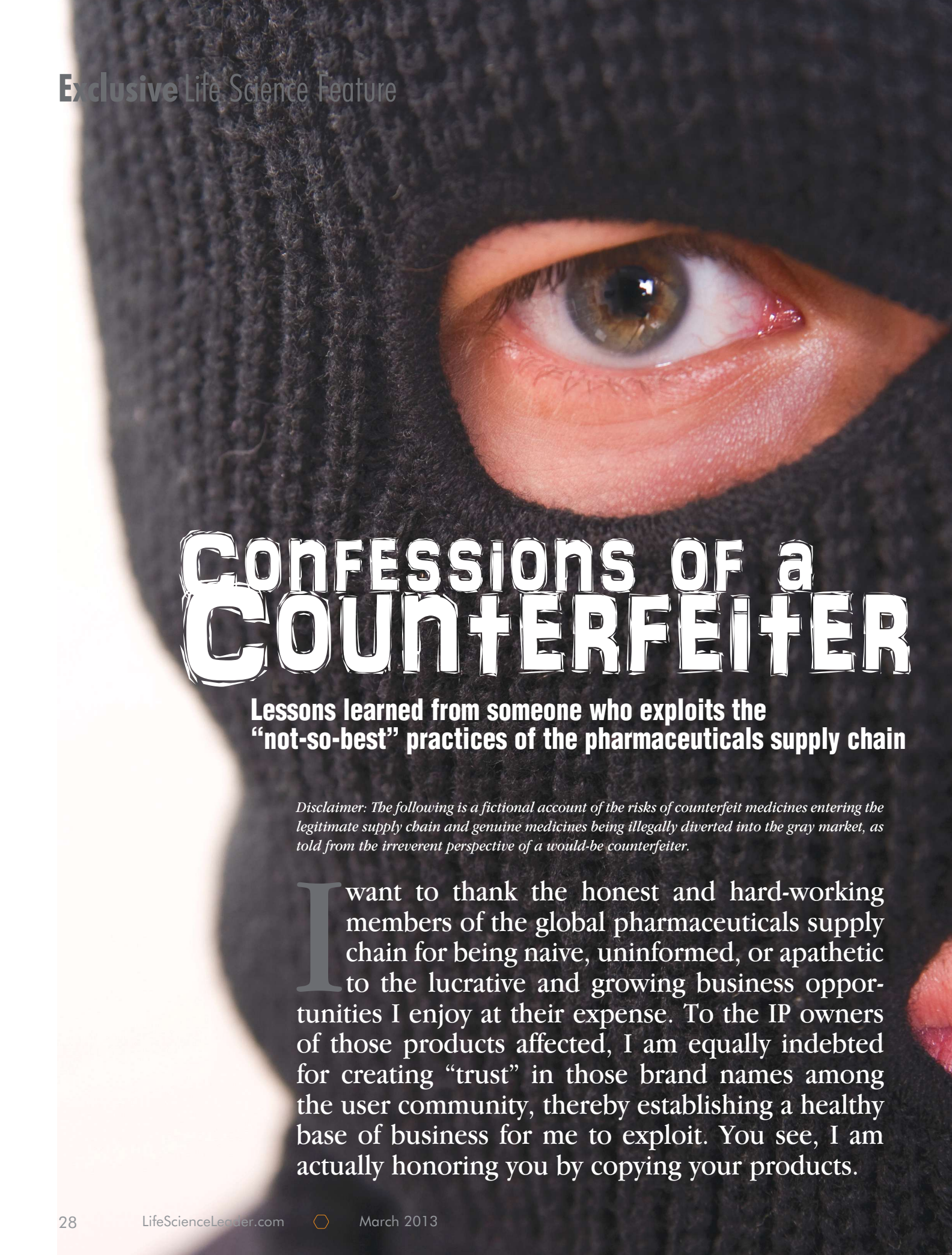

Confessions of a Counterfeiter

Lessons learned from someone who exploits the "not-so-best" practices of the pharmaceuticals supply chain

Disclaimer: The following is a fictional account of the risks of counterfeit medicines entering the legitimate supply chain and genuine medicines being illegally diverted into the gray market, as told from the irreverent perspective of a would-be counterfeiter.

I want to thank the honest and hard-working members of the global pharmaceuticals supply chain for being naive, uninformed, or apathetic to the lucrative and growing business opportunities I enjoy at their expense. To the IP owners of those products affected, I am equally indebted for creating "trust" in those brand names among the user community, thereby establishing a healthy base of business for me to exploit. You see, I am actually honoring you by copying your products.

You may not know me, but I certainly know you very well. In fact, it is easy to become acquainted with you by simply observing your predictable routines and trusting behaviors. I am amused by your preoccupation with service levels, fill rates, global sourcing networks, and speed of delivery. Ah yes, I enjoy the way you process countless transactions and inventory transfers without that verification part — my fortune is built upon your trust-sans-verification habits.

Nevertheless, I do feel obligated to share some of my practices with you, because I get the feeling you think that counterfeiters cannot be stopped or even deterred away from dangerous medicines to other more benign product categories. And you pathetically believe that you, the legitimate trade masters of the pharmaceutical industry, are simply victims of my success rather than accomplices. As you will learn, all you have to do to render me powerless is to get your collective acts together, share control of the supply chain with each other, and add visibility to information you feel you must hide from each other.

What I am offering you is a chance to see how you unknowingly contribute to a not-so-secure pharmaceuticals supply chain … from the vantage point of a business opportunist. So let's get started with my confessions.

CONFESSION #1: MY MARKET SPACE IS THE FACILITY OF GLOBAL COMMERCE

The global market for prescription medicines is rapidly approaching $1 trillion according to recent IMS data. The key is cross-border trade facilitated by a growing percentage of production taking place in a country in which those goods are not consumed. This is the case with pharmaceuticals.

Stimulated by free trade agreements and geopolitical will for a single global economy, Asia, in particular, has become the "factory" for the world. The growth and capitalization of emerging markets, combined with a relative lack of respect for and protection of IP in some countries, has created a cornucopia of opportunity for those of us who understand international trade. And if the situation wasn't easy enough to exploit, there is a perpetual shortage of regulatory and enforcement resources around the world. In the unlikely event that my goods are confiscated in transit, the risk of prosecution is much lower than the reward. In fact, I can't think of any form of commerce that has a more attractive risk/reward profile than sending branded drugs across borders. If such illicit endeavors still appear risky, the safe haven of e-commerce is always available to me. With the lack of international regulations and oversight policing Internet sales, taking Internet orders and sending the goods through parcel services is perhaps the easiest and least risky trade route available to those of us in this profession.

10 Best Practices To Counter The Counterfeiter

Since I like making money at my job as a drug counterfeiter, I'm hoping you don't follow these guidelines, which demonstrate some of the countermeasures currently in place or under development to help pharmaceuticals manufacturers prevent counterfeits from entering the legitimate supply chain.

1. Establish a companywide business culture of trust with verification.
2. Respond aggressively to all reported incidents.
3. Rewrite agreements with intermediaries to assure your branded products are only purchased from your authorized sources.
4. Enlist the support of government agencies in authenticating your brands as they cross borders.
5. Utilize authentication technologies interoperably with track-and-trace systems to identify where and when counterfeits enter the supply chain.
6. Apply stringent reverse logistics procedures to assure that returned goods are genuine and destruction is witnessed and documented.
7. Market monitoring and supply/demand analytics can identify potential brand attacks.
8. Ensure suppliers and contract manufacturers are not supporting shadow operations.
9. Protect your facilities and cargo from pilferage, theft, and other security breaches.
10. Prevent your excess and retired equipment from being acquired by counterfeiters.

CONFESSION #2: MY TARGETS ARE MULTINATIONAL BRANDS IN HIGH DEMAND

Why spend time and money falsifying obscure brands with limited demand when you can exploit reputable, highly recognizable brands which are registered for trade virtually everywhere? My experience tells me that price is a plus, but not as important as volume, particularly considering my low cost of goods. Areas of prime interest in counterfeit trade include branded apparel, media products, software, electronics, and healthcare products. All are money-makers for the same reason — high-volume, popular brands attract less scrutiny than specialty items and are easier to move throughout their respective supply chains.

CONFESSION #3: AS A RULE, NEVER BE SEEN WITH THE GOODS

My success in remaining undetected as a counterfeiter is largely attributable to ensuring that my manufacturing site not be visible to the legitimate supply chain. Once I manufacture my goods, I want to cross a border as soon as possible. In so doing, I am able to utilize gray-market diverters to "dilute" fake products among genuine goods. In addition, I always ship my goods across borders in multiple small quantities rather than bulk so that, in the unlikely event that they are intercepted by the authorities, my investment is not totally lost. For added protection, I use my friends and family for import/export operations, regularly "transplanting" trusted colleagues to port cities to serve as trading brokers.

CONFESSION #4: MY TECHNOLOGY INVESTMENTS ARE LARGELY IN PACKAGING

I spend at least 80% of my operating budget on packaging. I always begin by purchasing genuine products to use as a template and utilize the latest Web-based printing tools to replicate packaging. Even better, I try to secure discarded genuine packaging to encase my fakes. I am not admitting to the art of "dumpster-diving" as a means of procuring spent packaging, but I do know colleagues who enjoy the fruits of such practices. Whenever possible, I source containers, caps, inks, and labels from the same suppliers used by my targeted brands, unless of course the legitimate rights holders are prudent enough to track inventories of such supplies into and out of their providers.

I'm most amused by the term "anticounterfeiting technologies." Do you really believe that just because you bury some secret foo-foo dust deep into your printing inks, I will be deterred? If no one can find such authentication markings because the required high-tech scanners are located halfway around the world, or if no one even knows what to look for, I thank you for investing in such a false sense of security. Remember, my objective is to fool the inspectors, not the users of the product or the company's security ink brigade.

More broadly, when it comes to technology,

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- Glenn R. Siegele, President
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I have been fortunate to be in practice at a time when excess capacity exists across the pharmaceuticals industry. Plant closings offer me a plethora of equipment, from printing plates to dies to pill-making equipment. Online auction sites routinely offer the equipment I need to reproduce anything, usually at a fraction of the original cost. Oddly, the legitimate drug manufacturing industry is ostensibly handing me the know-how, supplies, and hardware I need to become a so-called third-party manufacturer of their most cherished brands. Regardless of how I choose to make a fake, I always check for mistakes using sound quality control practices. Most arrests begin with someone identifying subtle packaging flaws.

CONFESSION #5: MY FAVORITE SUPPLY CHAIN CATEGORY IS REVERSE LOGISTICS

People in my line of work know that famous brands have liberal returns policies. Perhaps the easiest way to make money in counterfeit trade is to sell the fakes to the company whose brands you are falsifying! I know this seems absurd, but consider this: Returned prescription medicines aren't generally restocked and resold. There is no need to worry about such fakes reaching the patient. Furthermore, the administrative tasks involved are usually too overwhelming to include any significant authentication, particularly when returned drugs are quarantined for destruction anyway. Typically, my returned goods are sent back to the company through enterprising returns processors or aggregators, providing a natural fence between me and the IP rights holders.

"Do you really believe that just because you bury some secret foo-foo dust deep into your printing inks, I will be deterred?"

Lastly, I want to point out a major deficiency in the way returned goods are processed by legitimate supply chain managers. Destruction of damaged, expired, or obsolete pharmaceuticals is typically orchestrated through a third-party contractor which picks up the inventory and brings it to a remote site for destruction, burial, or incineration. Yet many of your company's practices simply require the driver to sign for the load or, more securely, photograph the act of destruction. I have found it relatively easy to repurchase such inventory from your third-party contractors for a fraction of the market value and reintroduce those products into the reverse logistics network. I often wonder if such drugs are ever returned for a second trip to the dump.

CONFESSION #6: I AM INSPIRED BY THE LACK OF PHARMA SUPPLY CHAIN VISIBILITY

I am almost embarrassed to share my observations about how the lack of visibility to transactions in the downstream supply network allows me to become wealthy. First, as long as those within pharmaceutical supply operations continue to call it a "chain," instead of recognizing it as the "network" it really has become, transparency of transactions will remain an aspiration but never a reality. The history of pharmaceutical trade explains the lack of visibility. Manufacturers are motivated to rapidly sell and distribute their remarkable innovations in medical science to all dispensing outlets utilizing all reasonable means to do so. Consequently, the "chain of custody" or pedigree of a given inventory unit is lost among a sea of transactions with little coordination of events across trading entities. Authentic products visit wholesalers, secondary distributors, repackagers, and third-party logistics parties across many boundaries and regulatory jurisdictions before arriving at the patient's side. Separately, financial records are generated and processed by

some of the same entities as well as by importers, exporters, retailers, clinics, and brokers along the way. In short, records of trade are asynchronous to money and inventory flows, leaving a myriad of opportunities to insert falsified product into such a web of unregulated trade. Each legitimate player in the network contributes to the problem by acting independently of others. IP rights holders quickly "sell out" their brands to intermediaries in order to register revenue, but this creates attractive gray zones outside their purview. Intermediaries are reluctant to share trade data for fear of being disintermediated from the network. External manufacturing sites require separate flow lanes for legitimate trade while opening the door for shadow operations to arise. Suppliers of legitimate components and services openly seek new customers to leverage available capacity. Trivial checks by government agents create a false sense of security. Trusting retailers and consumers don't worry about integrity of supply. Lastly, Internet purchasing is attractive to consumers, yet the most difficult to regulate. With so many opportunities to insert fake goods into what is perhaps the most complex of all global supply networks, the only logical way to illuminate the supply chain is to implement and enforce a real-time track-and-trace system.

CONFESSION #7: LAISSEZ FAIRE PROVIDES A SUPPORTIVE BUSINESS ENVIRONMENT FOR COUNTERFEITERS

Controls, regulations, audits, certifications, and intellectual property rights all impede free commerce, and therefore, they will usually be denied or minimalized in favor of allowing business success to drive economic growth. There is a natural bias of local authorities to favor their own economic development over international trade rules. Inbound customs inspections, for example, are more rigorous than scrutiny of exported goods.

Some governments actually endorse local production of unauthorized generics in the interest of jobs creation. An argument can be made for the value of knockoffs in stimulating local economies and generating new tax revenue. In most industries, while genuine brands establish demand for a product category, "generics" will usually suffice. Consumers tend to be trusting and/or apathetic about the dangers of fake goods. Although this is not necessarily the case for pharmaceuticals, given a choice, the public tends to favor economic stimuli over concerns for supply integrity.

So there you have it — my true confessions! I do feel bad about all of you honest people trying to figure out how to safeguard the supply chain. Maybe I can take a pill for that.

About the Author

Ron Guido has 36 years experience in the healthcare industry with Johnson & Johnson. His current role is VP of global brand protection and supply chain integrity where his international team is responsible for anticounterfeiting programs and policies.

ADC: The Next Big Opportunity For Oncology Drugs

Cliff Mintz, Ph.D., contributing editor

The commercial success of mAb products, such as Rituxan for B cell lymphomas, Erbitux for colon cancer, and Herceptin for breast cancer, has catapulted mAbs to the forefront of modern molecular medicine.

According to a recent report by GBI Research entitled "Monoclonal Antibodies Market to 2017," the size of the global mAb market was estimated at $16 billion in 2011 and is expected to grow to almost $32 billion by 2017.

While engineered mAbs like Rituxan and Herceptin have proven to be effective therapeutic agents, researchers are increasingly evaluating the use of antibody drug conjugates (ADCs), or so-called "empowered antibodies," as potential new treatments for a variety of cancers. But the size of the ADC market is difficult to accurately assess because there is only one approved product on the U.S. market today. Nevertheless, many pharmaceutical and biotechnology companies believe that ADCs represent an opportunity in the global oncology market in the not-too-distant future. At present, there are over 20 ADC products in various stages of clinical development at a variety of pharmaceutical and biotechnology companies.

MORE FDA APPROVALS EXPECTED

ADCs involve attaching toxins or cytotoxic small molecules to mAbs that are directed against specific antigens found on cancer cells. The toxin or cytotoxic drug kills the cancer cells but leaves normal cells largely unharmed and intact. The delivery of toxic payloads directly to tumor cells improves the killing effects and therapeutic efficacy of ADC molecules as compared with mAbs themselves.

The idea of "arming" antibodies with toxins or cytotoxic molecules dates back to the early 1980s. However, it took almost 20 years before the first ADC product — Pfizer's Mylotarg — was approved (2000) as a treatment for acute myeloid leukemia (AML). However, within the first year after its approval, Mylotarg showed signs of serious toxicity; this ultimately led to its removal from the market in 2010.

Shortly thereafter, in August 2011, Seattle Genetics received FDA approval for its ADC Adcetris. Unlike Mylotarg, Adcetris exhibits minimal toxicity, is well-tolerated by patients, and represents an incremental improvement as a treatment for patients with Hodgkin lymphoma and anaplastic large cell lymphoma (ALCL).

The approval of Adcetris signaled the beginning of the ADC era. Like Seattle Genetics, Massachusetts-based Immunogen has been a pioneer in developing ADC technology.

While Immunogen has yet to garner regulatory approval for one of its own products, one of the company's technology partners, Genentech, recently submitted a biologics license application (BLA) to the FDA for T-DM1, an ADC molecule designed as a new treatment for HER-2 positive breast cancer. Many industry analysts expect Genentech, the current world leader in developing mAb-based cancer treatments, to be a large purveyor of ADC products.

WHAT WILL DRIVE THE UPTAKE OF ADC MOLECULES AS CANCER TREATMENTS?

Before pursuing the development of an ADC product, it's important to understand that the linker chemistry that binds the toxin/cytotoxic agent to an antibody is vitally important for ADC molecules. And that chemistry doesn't always come easily. "It took us many years of laboratory research to develop the optimal linker chemistry necessary to commercialize our products," said Clay Siegall, CEO of Seattle Genetics, who oversaw the development, FDA approval, and commercialization of Adcetris. Further, Siegall adds, "We learned a lot about the importance of linker chemistry with our first ADC molecule, SGN15, which had a linker similar to Mylotarg. Even though SGN15 failed in the clinic, we would not be where we are today without the experience."

Like Siegall, Daniel Janus, CEO of Immunogen, contends that advances in

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linker chemistries will help drive uptake of ADC molecules as cancer treatments. In fact, he says, "Immunogen has developed four different types of specific linkers because we have learned that different linker chemistries may be required for different cancers and tumor types."

The cytotoxic payloads delivered by most ADC molecules are, for the most part, tubulin inhibitors because these are proven cancer chemotherapeutic agents. However, there are concerns among ADC developers that other anticancer treatment payloads should be considered. Immunogen's Janus says, "We and others recognize the need to expand our ADC payload repertoire beyond tubulin inhibitors. However, for the moment, there are a broad range of cancer indications that will clearly benefit from antitubulin ADC molecules."

PARTNERSHIPS ARE KEY FOR THE NEXT GENERATION OF ADC MOLECULES

U.K.-based Spirogen, and MedImmune, a U.S. subsidiary of Astra Zeneca, also recognize the need to expand ADC technology beyond tubulin inhibitor payloads. Spirogen scientists spent the past 10 years optimizing the use of PBDs — naturally occurring antibiotics that covalently bind to the minor groove of DNA with minimal disruption to the DNA helix — as antitumor agents to treat chemotherapy-refractory or -resistant cancers. The company has two PBD products already in clinical development as stand-alone cancer treatments.

Spirogen CEO Chris Martin says, "Many of the drugs used in the current generation of ADC molecules are susceptible to resistance by tumors, and the use of next-generation toxins like the PBDs holds promise in these disease settings." He emphasized that PBDs by themselves have a good therapeutic index and are not as toxic as other chemotherapy agents, making them ideal for ADC use. Recently, Spirogen entered into research collaborations with Seattle Genetics and ADC Therapeutics to develop ADC molecules using its PBD technology platform.

Unlike most other ADC companies, MedImmune is evaluating the use of bacterial toxins and other biologics as payloads for its ADC products. Herren Wu, VP of R&D, believes that one of its products — a cancer antigen-specific mAb fragment — will be useful to treat a variety of cancers. However, he cautioned, "Immunogenicity will always be a consideration with ADCs regardless of whether or not the payload is a small-molecule drug or a biologic." Wu believes MedImmune's long history in biologics drug development, coupled with AstraZeneca's expertise in small-molecule drugs, may provide the company with an edge in the current ADC development race. Still, he says, "We are always looking for new technologies and partners to develop the next generation of ADC molecules."

Although full-length mAbs are routinely used as ADC delivery vehicles, their large size can sometimes block access or hinder binding to many solid tumors. This has forced ADC developers to consider using smaller antibody fragments or engineered protein scaffolds as delivery vehicles for solid tumors and other difficult-to-treat cancers. One such company is Cambridge, MA-based Mersana Therapeutics, a five-year-old biotechnology start-up that developed a novel ADC technology platform that allows multiple drug payloads to be attached to a highly water-soluble, biodegradable polymer which can then be attached to antibody-derived fragments, engineer protein scaffolds, or full-length mAbs. Last March, Mersana entered into a $270 million ADC research collaboration with Endo Pharmaceuticals and, more recently, inked a development deal with Adimab, a leader in mAb discovery and development.

REGULATORY CONCERNS

Despite the previous well-publicized toxicity issues of Mylotarg, both Seattle Genetics' Siegall and Immunogen's Janus believe that the FDA has been extremely helpful and supportive of their efforts to develop new ADC treatments. Siegall offered, "We experienced little difficulty in getting Adcetris approved because regulators recognized during Phase 2 clinical studies that it was safe and represented a significant improvement in current treatment options for patients with relapsed or refractory Hodgkin lymphoma."

Likewise, both men agree that since ADC products are still new, it may take some time for regulators to craft definitive regulatory guidance for approval of these molecules. Nevertheless, neither of them envisions any unusual regulatory approval hurdles for ADC products in the foreseeable future.

IT'S A HOT MARKET, BUT CONSIDER THESE LIMITATIONS

Like most new promising technology platforms, ADCs are not without their limitations. First, not all cancer cells or tumors express or over-express tumor-specific antigens which can limit the use of ADCs or mAbs as treatment options. Second, the number of potent cytotoxins (with acceptable safety profiles) that can be used as ADC payloads is still somewhat limited. Third, the effectiveness of ADC molecules as treatments for solid tumors may be limited because solid tumor cellular antigens may be difficult to access because of the large molecule size of most engineered therapeutic mAbs. Finally, the potential immunogenicity of newly developed ADC conjugates remains a regulatory concern that may affect these molecules as treatments for chronic diseases, mainly because of multiple injections over a patient's lifetime. Nevertheless, ADCs are still in their infancy and, as new products are developed, garner regulatory approval, and are commercialized, it is likely that many of these limitations and challenges will be overcome.

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The Role Of Language Translation In Clinical Trials

By Matthias Steiert, Ph.D., Elanna Mariniello, B.A., and Afaf Steiert, M.Sc.

Nowadays, clinical trials are governed by strict guidelines, a declaration outlining standardized ethical practices, mountains of paperwork, a heavy review process, and the ability to affect a multibillion dollar pharmaceutical industry. Every new drug must go through a clinical trial, Patient Reported Outcomes (PROs) must be evaluated, and the drug deemed safe for humans to consume and doctors to prescribe. The failure to do so within the ethical and specified guidelines could result in serious health risks, including patient fatality. Thus, designing and implementing a well-designed clinical trial is critical.

AN UNDERRATED COMPONENT OF GLOBALIZING CLINICAL TRIALS

There are, indeed, clinical trials that take place in their country of origin; however, in recent years clinical trials have become an increasingly global affair, and the trend to delocalize clinical trials into emerging countries continues. Both translation and localization services are necessary to accurately represent the implementation and outcomes of these trials. Many times, clinical trial protocols (CTPs) are developed in one country and then implemented in locations with vastly differing languages and cultures. The importance of clinical translators thus becomes a key element in the implementation of these trials and the way pharmaceutical companies interpret PROs.

Although the consequences of an inaccurate translation can be extremely serious in terms of human lives, credibility, and economic revenues, translation is often the last step in the planning of an international clinical trial, and it is rarely given the attention that it requires. Faulty translations may entail the "failure of the participant to act as instructed, disparities in prescription and administration of the study preparation, and reduced likelihood for appropriate follow-up and treatment of the underlying conditions and/or of side effects of the trial," (Eldar and Wexler 2009: 15), not to mention physical or emotional damage, misconduct of the experiment, time, and money.

The obligation to translate clinical trial-related documents varies from country to country. In the United States, all documentation for all participants and investigators must be in the local language. In other countries, it is often taken for granted that most researchers are able to read and write English, and this is one of the reasons why it is not compulsory to translate the texts specifically addressed to them, even though most regulatory bodies and ethics committees still require local language documents to be submitted for review and approval.

With differing worldwide clinical trial regulations, some trials are conducted without being completely translated, sometimes even as a way to shorten the time before approval and reduce costs, to the detriment of the outcome. Since translation needs to be involved at many stages, from clinical research and regulatory submission and review to production and marketing, improving the quality of the translation services can actually reduce timelines and even save money. The role of translation in affecting the likelihood of lawsuits or rejection by regulators and in the safety and efficiency of the final product should not be underrated either.

THE IMPORTANCE OF TRIAL PARTICIPANT UNDERSTANDING

Every clinical trial requires a protocol, which assists communication among all individuals in the trial. Each protocol describes the objectives, design, methods, statistical aspects, and organization of a trial. Clinical trial protocols are formal, written documents of a very specialized nature which show a high degree of technical complexity and require a clear, concise, and accurate style so that any ambiguity can be prevented. The language used in CTPs is becoming more and more differentiated, as it blends medical, administrative, and technical jargon (for instance, statistical terms), and it involves many traits which are not seen in other medical documents. Thus, terminology from any field of medicine mingles with that from laboratory practice and from the Medical Dictionary of Drug Regulatory Activities or MedDRA (Maintenance and Support Services Organization, 2011)

and is very often unique to every individual trial.

However, not all documents related to clinical trials involve highly technical content, and the recipients of the translation must be taken into account. Clinical trial documentation producers and translators must be aware of the fact that each participant is supposed to have a different level of understanding of the development and use procedures of clinical trial-related documentation, which is best illustrated if we compare that of participants and the specific site researchers. For instance, in order to standardize the conduct of the trial and to facilitate communication between all the individuals involved, several types of instructions, which may be placed in an appendix or in the data collection forms, can be created.

In addition, informed consent forms record dated and signed decisions to take part in a clinical trial, which are freely undertaken by individuals once they have been informed of its nature and risks. These documents must be easily understood by study participants.

LOCALIZING CLINICAL TRIAL PROTOCOLS

CTP translation requires a multistep process to meet clinical trial goals. Unfortunately, budgets and timelines often reduce the number of steps required for best practice. The steps outlined below are recommended for best outcome:

Create translation memory. Source materials, existing translations and translation memories, glossaries, and public databases are used to compile a translation memory.

- Create a terminology base from the translation memory.
- Translate, edit, and proof first round of translation.
- Clinical review.
- Harmonization conference.
- Final proof.

Today's pharmaceutical companies need more and more services that go beyond simple translation and enter the realm of localization, that is, the modification of a product or a service to account for differences in different countries, markets, or locales. Outsourcing to localization and globalization service providers has been a strategic decision, so that pharma companies could remain focused on their core businesses. Involving not only linguistic transfer but also content, cultural, and technical issues, localization accounts for changes in information, functionality, instrument design, and all necessary aspects in an organized manner, thus facilitating quality assurance and control . This is particularly the case when it comes to trials being conducted in emerging and culturally distant countries in Asia, Africa, Eastern Europe, or Latin America.

In recent years, pharmaceutical companies have begun to contract language service providers not just for translation, but for all language and globalization needs in the form of consulting services with reference to regional regulatory requirements, interpreting services, asking experts as technology advisors, etc.. When translation is taken into consideration from the beginning of a study, it is more likely that all resources can be more efficiently assigned, delays can be avoided, and the documentation provided will be readily understood within the cultural context.

CONSIDER QUALITY ASSURANCE & CULTURAL ASPECTS

It has been stated that the quality of the translation of clinical trial-related documentation is rather poor nowadays; this is perhaps the case because of the relatively short time frame given to translators in which they must complete their work. It may also be due to the fact that the rare combination of professional translation skills and biomedical knowledge is not very common among professional translators, or alternatively, because the needs of the target reader of the translated document are not sufficiently taken into consideration. A sound review process once the translation is complete can take as long as 7 to 15 weeks, while providing reviewers with online tools or even outsourcing the review to an independent third party could improve this situation.

Cultural values and behavior may present benefits and/or challenges for the sponsors of multinational clinical trials with respect to management of relationships with subjects, investigators, and regulatory bodies. As for the benefits, some cultures, such as Japan and Russia, are "cultures of compliance" and participants belonging to them tend to follow doctors' instructions to the letter. However, that very same trait can become a challenge when they do not easily complain or report adverse events. Undeniably, accurate translation of study documents by native speakers from each country or locale plays an important role in the success of trials in any particular region.

With so many different steps to be completed by so many different team members, validation of CTPs and PROs may take months. For clinical trials where a cognitive review workflow is necessary, delays can seem endless. The worst possible outcome of a poor translation process is a serious adverse event. More common is the expensive price of delay. As regulatory bodies demand greater scrutiny over drug discovery and clinical trials, costs and risks will increase. As sponsors and CROs look for efficiency wherever they can find it, clinical trial language management offers a key competitive advantage. As trials become more global, sponsors and CROs that can rapidly deliver good data will enjoy a market advantage. Translation best practice is critical to the effort of cultural consulting, cultural adaptation, and localization.

About the Authors

***Matthias Steiert**, cofounder of Afaf Translations, specializes in German pharmaceutical translations. He holds a Ph.D. in biochemistry from the University of Basel. **Afaf Steiert**, president and cofounder of Afaf Translations, works as a conference Arabic interpreter and translator. She holds a M.Sc. in molecular biology from the University of Basel. **Elanna Mariniello**, Spanish project coordinator at Afaf Translations, has a B.A. in translation studies and Spanish language interpretation and translation.*

FDA, Suppliers, & Process Changes

By Wayne Koberstein, contributing editor

Most of the questions posed in this article might well be addressed to an expert. But the actual function of the article is to arbitrate already well-known expert opinions rather than add to them. The two best-known bodies of opinion on this month's topic represent the perennial dichotomy between industry and FDA supporters.

If you subscribe to the view that the FDA is an ever-more opaque miasma of bureaucratic obstruction, you may be in the industry camp that believes process changes in drug manufacturing should be left to the plant engineers. From the agency's perspective, however, the current procedures for validation of process changes simplify regulation and make it more transparent — precisely by giving you and your suppliers responsibility for deciding when a particular change in process is sufficiently significant to trigger FDA involvement. If any cooperation among all three parties is going to take place, its success will hang on that decision.

I will get to the matter of cooperation with your supplier in a moment. But first, let's consider how the process-change procedure might look from the FDA perspective.

IS IT MORE OR LESS REGULATORY OVERSIGHT?

One of the industry's chief complaints about the massive agency is its lack of personal continuity. As with the help department for your computer vendor, every time you call the FDA about a pending matter, you get a different person, often with a much different disposition, and varying from helpful to disdainful. But what you are seeing may be an artifact not of more but less regulatory oversight.

Since the early 2000s, the agency has operated on the principle of "risk-based regulation," meaning it would leverage its meager resources by putting companies on their honor to monitor and report many quality-related data points in lieu of previously customary inspections. Despite changes in administration, budgetary pressures alone have been enough to keep the risk-based approach in motion. The fact that the FDA now waits for a producer to report a significant process change determines the structure of the agency organization charged with responding. It is unlikely to be linear and continuous; it is quite likely to be the opposite.

Nevertheless, I can see that the agency is making a serious effort to map the way — to elucidate the right steps to take with process changes. Last May, the FDA's Susan Kirshner gave a presentation at the AAPS National Biotechnology Conference. Perhaps ironically, my attempts to contact Kirshner for this column went unanswered — but maybe that's because I'm the press. In any case, she was authorized at AAPS to elaborate on FDA guidances, add her own insights, and answer audience questions. (I can't give you a simple url link to Kirshner's slides, but if you search for "Ask the Regulator AAPS Susan Kirshner," you should see a PDF download close to the top of the results.)

The session began with a focus on process changes and paid particular attention to federal regulation 21 CFR 601.12, which provides risk-based reporting categories for changes to an approved biologics application. A Kirshner slide quoted the Guidance for Industry Changes to an Approved Application: Biological Products 1997: "Applicants are required to demonstrate … the lack of adverse effect of the change on the identity, strength, quality, purity, or potency as they may relate to the safety or effectiveness of the product." Moreover, §601.12 presents the three main categories of changes that require reporting, in order of how much a change could potentially have adverse effects. If the potential is minimum, you must merely describe it in your annual report; if moderate or substantial, supplements are required.

Unless I'm reading it wrong, what that seems to say is that you — the big collective that includes your entire company and your supplier — must decide when to report a change based on your assessment of its adverse potential. Because you — this time the company *you* — ultimately hold the bag if you don't happen to report something that later turns out to be harmful, or maybe

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an inspector happens to stumble upon it some day and thinks it might be harmful. That's where the "how you can work with your supplier" comes into play regarding cooperation with the FDA.

PAT IS SCARCE

If you're not sure about a change, there are some objective ways of settling the matter. Regulation section §601.12(e) describes a "comparability protocol" of tests and "acceptable limits" sufficient to prove a change lacks adverse effects on safety and efficacy. The protocol is meant for changes already reported, but if you or your supplier is contemplating any change in process, there are ways nowadays of modeling the process on a small or virtual scale before spending the money to implement. It's called PAT (process analytical technology), but you won't see much of it around this industry, yet. Used in all kinds of other industries, yes, even those where process changes can be a life-or-death concern, PAT is a rational and flexible technology that can be applied broadly or incrementally on the plant floor.

It's called PAT (process analytical technology), but you won't see much of it around this industry, yet.

Perhaps the small-molecule crowd is feeling a bit overlooked at the moment. It's true much of the material cited above is directed at biologics, but I have a sense that much of it still applies to everything from API to finished product in the traditional pharmaceutical lines. Like the regulatory requirements, the solutions largely apply to both sides, biologics and pharma. My closest look at a PAT application in this industry has been a changeover to real-time automated monitoring and control of moisture in a fluid bed dryer. (By the way, if you want to know more about PAT, search for it on the FDA website.)

Often lost in the perennial debate about the recalcitrant regulators at the poor old FDA, the other two main elements in the equation of cooperation are you and your supplier. If you haven't already, make it your business to bring those two elements together. Start with the easy stuff — fund some pilot projects — but work steadily and persistently toward the level of cooperation that allows you to make smart choices about process changes.

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Online Patient Communities: Accelerating Clinical Trials, Improving Patient Outcomes

Patients are taking an increasingly active role in managing their own healthcare. This continues a trend that 65% of physicians believe is linked to better outcomes. In this environment, online communities are becoming a powerful tool for clinical research — even raising the interesting possibility of carrying out elements of clinical trials without involving physicians.

This radical shift, where patients are becoming their own advocates rather than relying on their healthcare provider's advice for managing their health, is largely the product of the Internet and the wide availability of medical information. The role of patient advocacy groups is also evolving, often focusing on driving traditional biopharma research to benefit their constituents, while individual patients are seeking practical guidance online to help manage their health. Online patient communities, which may be sponsored by a variety of groups, provide many benefits to patients, including connections with other people coping with similar conditions, advice on disease management, and information about clinical trials. These communities — for example, MediGuard.org and ClinicalResearch.com — also have the potential to improve trials and accelerate patient recruitment by prescreening potential participants online and by allowing protocol feasibility and messaging to be tested directly with patients.

During a trial, online tools, such as email communications providing disease updates and appointment reminders, can keep patients engaged with the study, help optimize participant retention, and may allow patients to have virtual visits (for example, submitting patient-reported outcomes, the contents of a patient diary, or progress on lifestyle changes). Virtual visits can reduce the burden of trial participation for both patient and physician and can also reduce costs such as site monitoring and investigator grant fees. Once the trial is complete, creation of "alumni communities" can keep participants informed about the findings of the trial and may provide a pool of engaged and willing volunteers for future research.

DIGITAL OBSERVATIONAL RESEARCH

Much experience to date with patient communities has involved observational research. A recent study aimed to test the perception that patients who are highly engaged in their healthcare have better outcomes than those who are not engaged in their healthcare. The study needed 500 patients with a chronic ambulatory disease to fill out a patient-reported outcome questionnaire indicating their level of engagement and motivation to take care of their health. The participants were recruited online through patient communities. As an indication of the promise of this approach, the first patient was recruited in six minutes, and all 500 were signed up within six business days. To recruit this many patients through the traditional physician-based approach would have taken months.

As part of the study, all participants were asked to give informed consent and were asked to fill out an online psychodemographic survey, which segmented them by behavioral characteristics related to control, emotion, and agency/action. With permission from these patients, the researchers then examined the patients' medical records (MR). The actual medical outcomes for each patient were compared with the segmentation results of survey, allowing researchers to determine whether there was a correlation between the MR and the patient-reported outcome (PRO). Although concerns exist regarding the validity of self-reported diagnosis, this pilot showed that nearly all data collected by physicians confirmed the data provided by the patients, with those who are highly engaged in their healthcare recording the most positive outcomes. The study broadly validated PRO instruments used to evaluate adherence to medications, treatment satisfaction, and other drivers of actively managing a patient's health.

This interesting result illustrates the promise of obtaining data directly from patients and comparing this with the outcome recorded in their health record, requiring minimal involvement from physicians. This approach has particular promise in postmarketing surveillance of products that are taken over extended periods, such as products for diabetes or pain, and could come close to real-time clinical research. Alumni communities could be helpful in risk evaluation and mitigation strategies (REMS) programs required by the FDA, allowing immediate feedback from trial participants. If used in the appropriate setting, online communities may be a rapid and relatively inexpensive source of essential data in the future.

Jim Kremidas

Jim Kremidas is VP of market development for Quintiles' Digital Patient Unit. Previously, he served at the company's head of patient recruitment. Prior to Quintiles, he worked 24 years at Eli Lilly where he led patient recruitment and retention efforts.

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How The FDASIA Can Affect Your Supply Chain

Junan Guo, Ph.D.

Dr. Guo is VP of pharmaceutical and quality services at AMRI. He is responsible for the scientific direction and P&L of AMRI's pharmaceutical development business and AMRI's quality affairs.

The supply chain for active ingredients and drug products in the pharmaceutical industry is becoming more complex as globalization in the world economy continues. Globalization provides benefits for cost-effective solutions, enhanced security, and stability for the supply chain. On the other hand, companies therefore need a more sophisticated approach to manage their global supply chain. After all, suppliers in individual countries operate under their own regulatory, environmental, and cultural norms and requirements.

KEY INFO ABOUT THE FDASIA

As part of the U.S. effort to modernize regulation for the 21st century, the U.S. FDA Safety and Innovation Act (FDASIA) was enacted in July 2012. This act reauthorized/authorized user fees for various submissions to ensure that the FDA is adequately funded for its mission. Another part of this act covers the supply chain.

First, the FDASIA introduced the *"risk-based inspection"* concept for drug establishments, which shall be inspected according to known safety risks, based on risk factors such as:

a) compliance history of the establishment

b) the record, history, and nature of recalls linked to the establishment

c) the inherent risk of the drug manufactured, prepared, propagated, compounded, or processed at the establishment

d) the inspection frequency and history of the establishment

e) whether the establishment has been inspected by a foreign government.

Second, the FDASIA clarified the term cGMP (current good manufacturing practice), defined specifically to include *"the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products."*

RISK-BASED MANAGEMENT OF THE GLOBALIZED SUPPLY CHAIN

Risk-based management of the supply chain is increasingly important considering the increased complexity of the globalized supply chain and the FDA's expectation that market authorization sponsors manage the risk to and establish the safety of drugs — including all materials used in manufacturing. This is equally important for pharmaceutical companies or contract manufacturers.

Risk factors considered in the FDASIA provide a good basis for a company to establish a risk-based management program. This program should cover the life cycle of the supply chain — from selection, inspection, and qualification to ongoing quality monitoring and requalification or disqualification as appropriate.

For this risk-based program, it is important to first research and evaluate a supplier's history. This analysis should review the supplier's registration and inspection history, including establishment inspection reports, agency databases for objectionable actions including recalls, and product lists (especially for known sensitizers, sex hormones, or animal-originated materials). Second, it's important to evaluate the inherent risk of a drug or intermediate manufactured, prepared, propagated, compounded, or processed at the establishment. The inherent risk increases from GMP starting material, to GMP intermediates, to GMP active pharmaceutical ingredients, to GMP oral drug products, and to GMP injectable drug products. The suppliers for each type of material or product shall be risk-assessed and managed as appropriate. For example, although a GMP starting-material supplier may have less inherent risk in comparison to a GMP injectable-drug product supplier, the risk assessment is still important for such a supplier. Otherwise, a contaminated starting material could carry such risk all the way to the drug product. Often, starting materials are supplied by a chemical or other company instead of a GMP establishment, and quality systems can sometimes be weak.

With a comprehensive risk assessment of multiple factors, companies should develop supplier qualification standard operating procedures. A supplier qualification and inspection plan should also be evaluated periodically to reflect the dynamic nature of the globalized supply chain and industry best practices.

The FDA clearly expects that market authorization sponsors shall be responsible for the quality of the entire supply chain starting from raw materials. Establishing, following, and continuously updating a risk-based assessment process is highly recommended.

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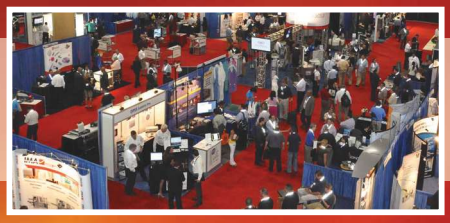

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How To Avoid Pharma/Bio Cargo Theft

If your job is even remotely related to the transport of your company's pharmaceutical or biologics products, you need to be familiar with the Supply Chain-Information Sharing and Analysis Center (SC-ISAC). That's because this organization has been collecting and analyzing cargo-theft data for industries just like yours since 2005. And don't be naive — thieves *are* targeting your products.

What you need to do is use the insights gleaned from the SC-ISAC's data to better understand how cargo is targeted and then drive that awareness to your logistic providers. Having such a proactive, preventative approach to your supply-chain logistics is essential to avoiding the costly recovery fees associated with stolen product and equipment.

WHAT TO KNOW REGARDING CARGO THEFT

One of the first valuable pieces of information to know about cargo theft is where it most commonly occurs. For instance, when we look at the past three years of the SC-ISAC Cargo Theft reports, we see that the top states for these thefts include California, Florida, Texas, New Jersey, and Georgia with Pennsylvania and Illinois occasionally entering the top five. When you dig a little deeper into the research, you find that the type of location involved in each particular theft includes truck stops, carrier facilities, lots, yards, and streets. And in almost every case at each location type, the thieves are waiting for the opportunity when the loaded vehicle is left unattended.

It's also beneficial for logistics professionals to know when cargo thefts are likely to happen. The SC-ISAC's results continuously show that the majority of cargo crime occurs on weekends, especially on three-day weekends. If you add in Monday and Friday, statistics show about 70% of cargo crime happens during that part of the week.

Working with law enforcement, especially with the current cargo task forces and officers assigned to cargo crime investigations, we have come up with the following list of groups who target the industry:

1. organized cargo theft crews — full truckload
2. organized cargo theft crews — fraudulent pickup
3. opportunistic cargo thieves
4. high-value warehouse burglary
5. truck-stop crime

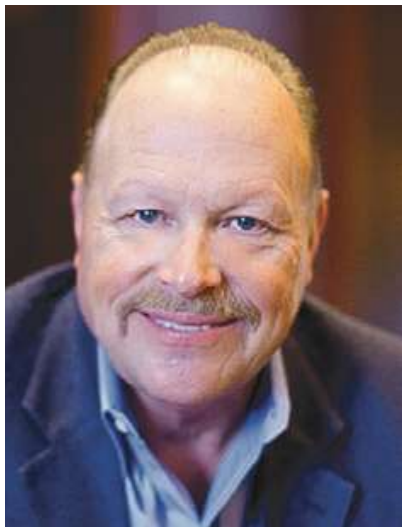
Although there is some overlay in how the groups operate, these are the main organized and loosely organized groups who target freight in-transit.

KEY COMPONENTS OF YOUR LOGISTICS/ TRANSPORTATION DEPARTMENT

Knowing all of this information and recognizing that the pharma/bio products you distribute are a target of cargo thieves is just the first step. Next, you need to determine if your logistics providers or internal transportation departments are aware of the risks and are organized to prevent — and if necessary — react. Some of the things you should consider include:

1. Do your transportation and logistics providers have a security function, including a written security/recovery plan for in-transit and warehouse operations?
2. Do they have a dedicated security department or manager?
3. How do they select their carriers, and do they require their carriers to meet any minimum security/ insurance requirements?
4. If transportation brokers are used, what requirements are being used for the vetting of the carriers for your account?
5. Do they have specific guidelines to fully protect in-transit freight on the weekends, including dropped trailers and unattended loads?

These are all very important issues when dealing with the loss of a load. Establishing prevention protocols and maintaining a visibility of the shipment from origin to destination are the best policies. If these fail, history tells us that when a full-load theft occurs, you have a limited amount of time to recover the cargo. The equipment is usually recovered within a few days of the crime, but the cargo is a different story. Having the correct business partners operating with contractually defined security requirements can make all the difference when an incident occurs. If you received a call right now that a theft had occurred, would you be ready to act, and do you have all of the information and resources you need to have a chance to recover?



JJ Coughlin

Coughlin is a VP at LoJack SCI, director of the Supply Chain-Information Sharing and Analysis Center and chairman of the Southwest Transportation Security Council.

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Building Organizational Focus With A Leadership Agenda

By Leo Hopf

One of the most important decisions you can make as a leader is how you allocate your time and attention. And yet most leaders do not explicitly make this choice. Instead, they allow the demands of the day to drive their attention. They are always busy, but they are not always busy on the topics that add the most value to their organization.

Creating A Leadership Agenda

Begin by creating a list of topics you could address in the coming months. Next, take a blank sheet of paper, and draw a line across the middle of it. Then go down your list one topic at a time, and place each topic either above or below the line on your paper. Placing a topic above the line means you are committed to spending time on it. You are doing so because you believe the topic truly matters and because you believe it is best dealt with at your level in the organization. Placing a topic below the line means the topic could be delegated, delayed, or not addressed at all. Placing it below the line does not mean it has no value. Instead, it is simply an acknowledgment that spending your time on this topic will have a lower return than spending it on a higher-value, above-the-line topic.

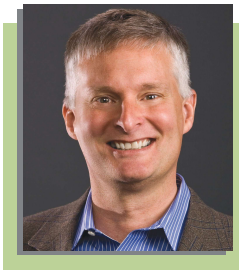
The value of the leadership agenda is that it provides clarity on how you should and should not spend your time. First, it produces a manageable number of above-the-line topics upon which you should focus. Second, and perhaps even more importantly, it identifies the many below-the-line topics upon which you should not spend your time and attention. Above-the-line topics get on your calendar; below-the-line items don't.

A leadership agenda provides a principled reason to say "no" when someone requests your time for a below-the-line topic. This puts you in control of your calendar and enables you to focus your time and attention on the small number of topics for which you can add the most value.

Using A Leadership Agenda To Align Your Organization

Once you have drafted your leadership agenda, discuss it with your boss. Do they agree with your above-the-line priorities? Are there any below-the-line topics they think should be elevated? Once your boss is satisfied with it, share it with your subordinates. This enables them to understand your priorities and lets them know why you will be saying "no" to some of their requests for your time. Then have your subordinates create their own leadership agendas. As they do so, you can discuss with them which of your below-the-line topics should be above-the-line topics for them.

Cascading leadership agendas up and down in an organization lets everyone know where and by whom each topic will be addressed. This results in the organizational alignment and focus necessary to move quickly and effectively.



Leo Hopf is the author of *Rethink, Reinvent, Reposition*, which was named the book of the month by the Institute for Management Studies. He can be reached at leo@teamhopf.com.

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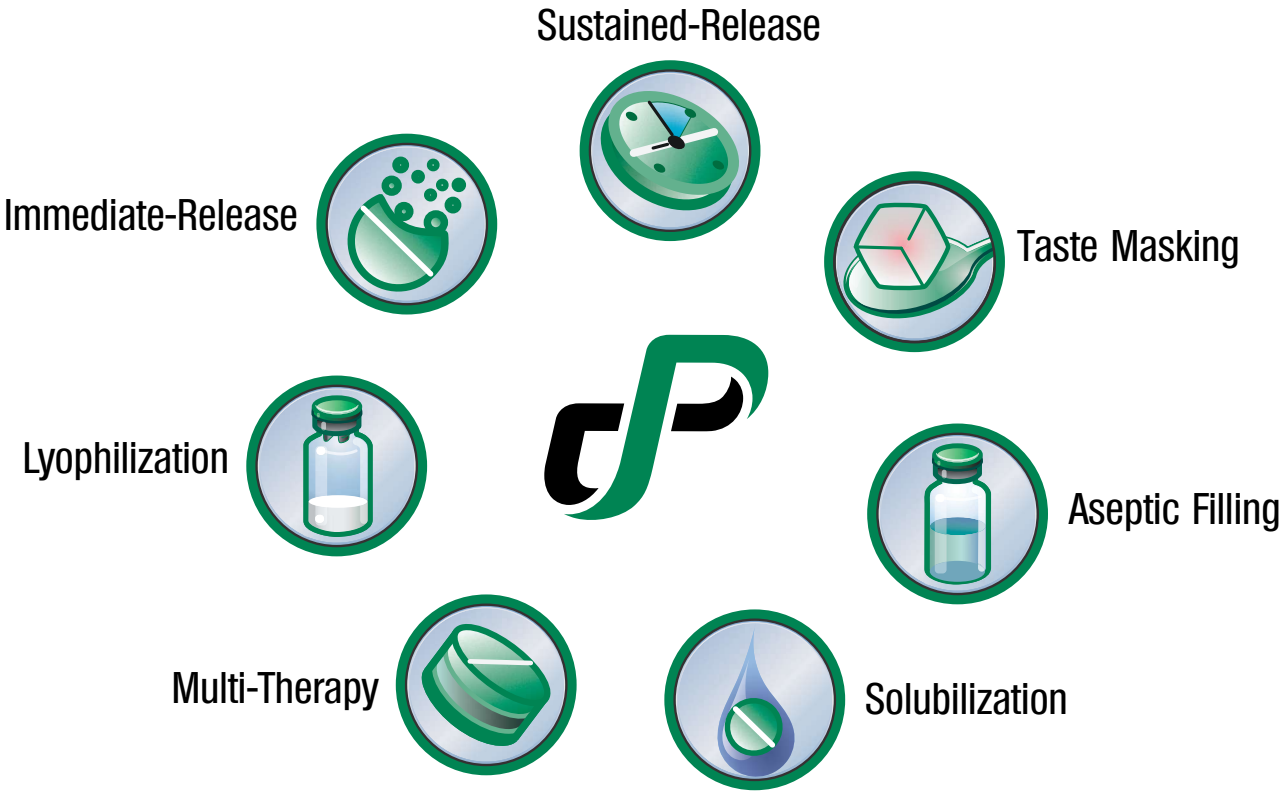

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