The Official Magazine of ISPE

PHARMACEUTICAL ENGINEERING®

November-December 2016 | Volume 36, Number 6

2016 Member of the Year Maurice Parlane

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Bethesda, Maryland
25–26 April 2017

Quarterly Report: Quality Culture

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Collaboration Key in the Quest for Quality

This issue celebrates ISPE members around the world who have given tirelessly of their time, intellect, and compassion to one another and to the industry. Ours is an industry of collaboration, and ISPE members are its best ambassadors. From Maurice Parlane (Member of the Year) to Mike Rutherford (2016 Professional Achievement Award recipient) to Param Bhatter and Sara Sukenik (Student Poster winners), our members are shining examples of the values we espouse.

Chief among those values is quality. Our members are relentless in their pursuit of it and we all benefit, in the form of Guidance Documents, conference presentations, reports, and training, as we do from the intellectual collaborations that occur within our many networks. The ultimate goal of this pursuit is the creation of quality medicine and quality solutions for patients around the world.

Quality, as it affects patients, data, processes, manufacturing, packaging, employee and organizational performance, has been top of mind throughout 2016, and we have presented this topic's many facets in this magazine.

So it's fitting that this last issue of the year contains our second annual Quarterly Report on Quality Culture. It provides a glimpse of what you may expect at the 2017 ISPE Conference on Excellence in Quality Culture and Performance: Powerful Tools to Shape Quality Excellence to be held 25–26 April 2017 in Bethesda, Maryland. The conference, which coincides with the publication of the ISPE Cultural Excellence report, a collection of practical powerful tools, will outline a comprehensive behavior-based approach to improving quality culture as a means of delivering enhanced quality outcomes.

Equally fitting is the announcement of a new research program on Pharmaceutical Manufacturing Quality Metrics between the FDA and the ISPE's new collaborators, the Pharmaceutical Operational Excellence Benchmarking Team at St. Gallen University, Switzerland, under the leadership of Professor Thomas Friedli.

Throughout 2017, you'll be hearing from members around the world on topics that are changing the way we approach what we do, so that patients everywhere may have easy access to medicine. But I'm getting ahead of myself. Until then, thank you for reading and may 2017 bring peace, love, and understanding (thank you, Elvis Costello!). ■

Anna Maria di Giorgio, editor in chief

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PHARMACEUTICAL ENGINEERING®

Volume 36, Number 6
Published since 1980

Editorial Policy

Pharmaceutical Engineering inspires engineers and regulators around the world with engaging and useful articles. From technical articles that provide practical how-to advice to thought-provoking features on current issues, *Pharmaceutical Engineering* offers readers a global picture of the profession and the industry. Opinions expressed herein do not necessarily reflect the views of ISPE.

Pharmaceutical Engineering is published six times a year by ISPE.

ISPE Headquarters
7200 Wisconsin Ave., Suite 305
Bethesda, MD 20817 USA
Tel: +1-301-364-9201
Fax: +1-240-204-6024

ISPE Operations and Training Center
600 N. Westshore Blvd., Suite 900
Tampa, Florida 33609 USA
Telephone +1-813-960-2105
Fax +1-813-264-2816

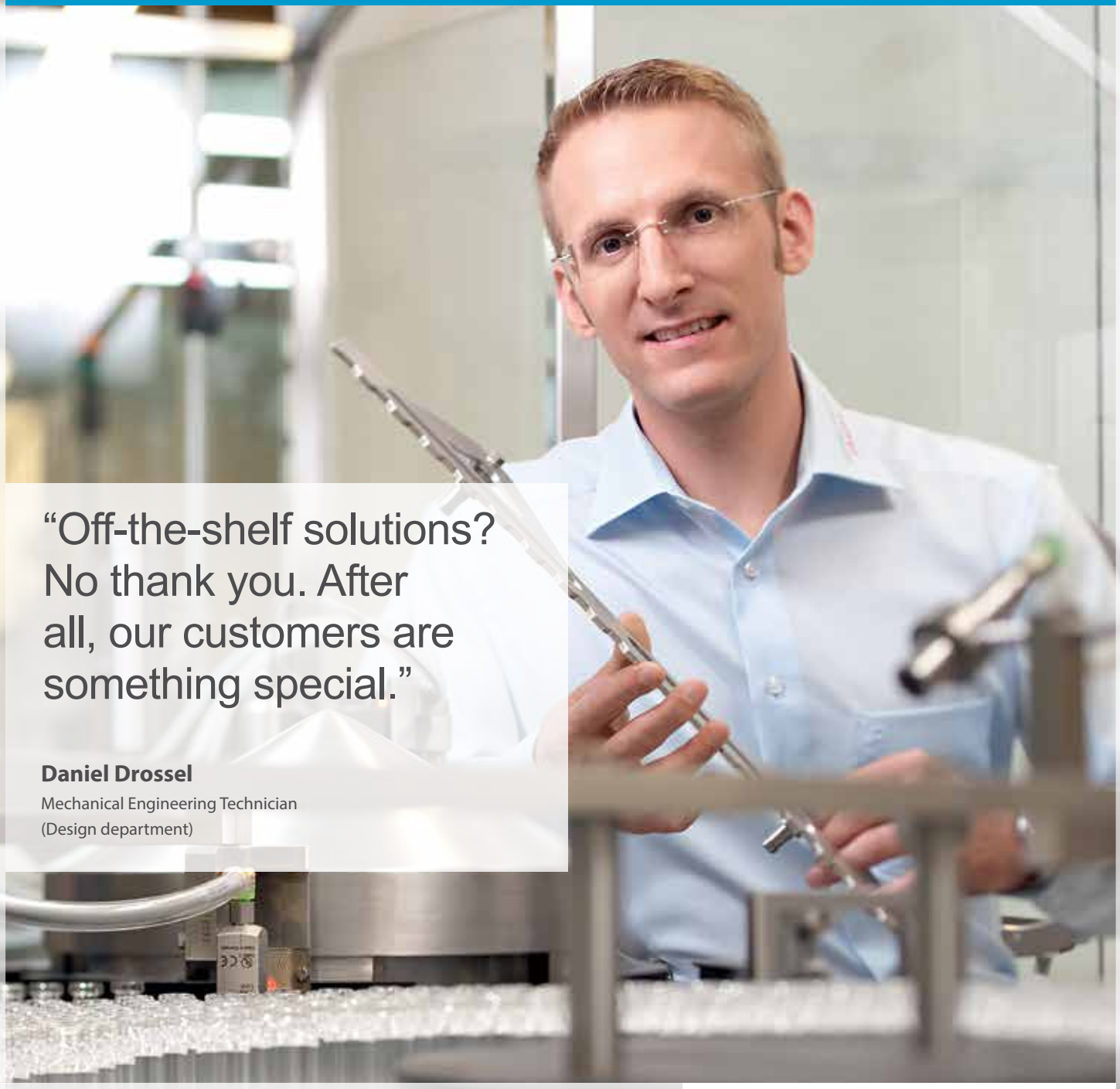
ISSN 0273-8139

US Postmaster
Send change of address to:
Pharmaceutical Engineering Magazine
600 N. Westshore Blvd, Suite 900
Tampa, Florida 33609

Periodicals postage paid at Tampa, Florida, US, and additional post offices

Canada Postmaster
Send change of address and undeliverable copies to:
Pharmaceutical Engineering Magazine
PO Box 122
Niagara Falls, ON L2E 6S8 Canada

Canada Post mail agreement #40012899



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Quarterly Report: Quality Culture

Technical Articles

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ISPE

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Letters to the editor
Pharmaceutical Engineering welcomes readers' comments. Letters must include the writer's full name, address, organization, and years of ISPE membership. If published, letters may be edited for length and clarity. Please address editorial correspondence to: The editor, Anna Maria di Giorgio (amdigiorgio@ispe.org).

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San Diego Chargers vs. Tampa Bay Bucs
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Suppliers Qualification
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Brazil Affiliate Training
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Basic GAMP® 5, Annex 11/Part 11 (T45)
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ISPE Training Institute
Tampa, Florida

24 Rocky Mountain Chapter
Ski Day!

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Ending on a High Note

Mike Arnold, Senior Director at Pfizer, and Chair of ISPE's 2016-2017 International Board

On behalf of your International Board of Directors, I would like to congratulate our members, volunteers, staff, sponsors, and vendors for a very successful Annual Meeting. Congratulations also to our award winners and the GAMP® Community of Practice on their 25-year anniversary.

In the five weeks since our Annual Meeting ended, activities in each of the four focus areas I spoke about have been initiated. Today I would like to share with you some recent activities related to "collaboration."

On 5 October, I had the pleasure of attending our Boston Area Chapter Annual Product Show. Joining me were Board Members Tim Howard and Joe Famulare, as well as our CEO and President John Bournas. We had the opportunity to engage with ISPE colleagues, students, and Young Professionals (YPs). It was great to see past International Board Director Doyle Johnson receive the Chapter's prestigious Hank Moes Lifetime Achievement award. Congratulations to Doyle for winning this award and to our Boston Chapter on a successful product show!

The New Jersey Chapter, ISPE's oldest, celebrated its thirtieth anniversary on 6 October. John Bournas and I joined more than 100 attendees to celebrate this important milestone. I had the distinct pleasure of sitting with and getting feedback from several YPs who were very enthusiastic about ISPE. Congratulations to our New Jersey Chapter for its 30-year accomplishment and a successful event. Here's to 30 more years!

At both the Boston and New Jersey events, I saw a number of "Women in Pharma" lapel pins (see pages 26–28). These buttons highlight the success of the inaugural "Women in Pharma" event at the 2016 Annual Meeting.

Mike Arnold (left) talks with Young Professionals at the New Jersey Chapter 30th anniversary celebration.

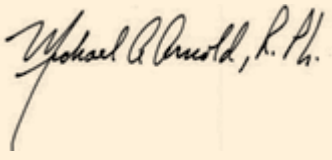
I encourage you to take advantage of opportunities with ISPE to expand your pharmaceutical knowledge and interact with industry professionals who are at the top of their field

Many thanks to Fran Zipp and Charlotte Enghave Fruergaard for leading this important initiative.

A request for YP representation on key ISPE committees has been issued and Brody Stara, ISPE International Young Professionals Chair, is working with committee chairs to identify interested YP representatives to serve on them. Brody and I have initiated discussions for a brainstorming event in August 2017. Watch for more information in upcoming communications.

As 2016 winds down, I encourage you to take advantage of opportunities within ISPE to expand your pharmaceutical knowledge and interact with industry professionals who are at the top of their field. With two new conferences—Facilities of the Future in November and Biopharmaceutical Manufacturing in December—plus classroom training opportunities in warm and sunny Tampa, Florida, you can hit the new year running, armed with practical, real-world knowledge to build on your company's current best practices and meet or exceed FDA regulatory requirements. Get started today!

Mike Arnold



2016 Member of the Year Maurice Parlane

We met with ISPE's 2016 Member of the Year, Maurice Parlane, just before he headed out to the PV/PV Stats conference in Bethesda, Maryland, in October. This is an edited version of our conversation.

How does it feel to receive this award?

I wasn't expecting this. It feels great to be recognized. I feel quite humbled as there are so many members who contribute a lot to ISPE.

How did you get involved in pharmaceutical manufacturing?

I have to admit there was no real strategy. I had worked as an engineer in a couple of other sectors prior to joining Glaxo in a small New Zealand city called Palmerston North, where Glaxo was the largest employer. I was trained as an electrical draftsman, and then completed a qualification as a mechanical engineer. I was a bus designer of all things! The Glaxo role turned out to be a job that suited me as there were lots of new projects involving building and process equipment. I was there for nine years in various engineering roles, and then moved across to manufacturing management roles. During the time I was at Glaxo, they sent me back to university for two years, which was pretty cool. I had to fund it, but they graciously gave me work over the holidays and said, "You've got a job at the end of it." At that time, they must have seen something in me. To go into management roles, you really needed a degree and I didn't have one at that time. I had only technical qualifications.

What degree did you obtain?

A bachelor of technology specializing in manufacturing and industrial engineering. And that was another stroke of luck: It was the perfect degree, because it was about quality by design, risk, statistics, manufacturing operations management, and personnel management. Unfortunately, the degree doesn't exist anymore.

To go to a university as a 30-year-old, with all the resources of Glaxo behind me, and then to be able to apply the degree, it was a revelation. I could see how I could use it anywhere. And when I went back to work I did get to use it a lot. I got deeply into process validation, process understanding, and quality improvement.

When did you first hear about ISPE?

We built a new dry powder inhalations manufacturing at the site in New Zealand, which was a strategic product for Glaxo at the time, so it had oversight from the UK head office. I met some of the project engineers from the UK who were involved in ISPE. It was probably those guys that influenced me—Simon Shelley, Chris Woods, and Nick Haycocks, I've been a member since then and still catch up with these guys via ISPE. Nick still "volunteers" me for roles at ISPE.

Why was it important to become an ISPE member?

It's my need to be connected. My ISPE life really took off when I got into consulting. In my previous work, my involvement with ISPE was mostly technical, but as I moved into consulting it was also great for networking. ISPE is really important to understanding what is going on globally because we can see what is coming even if we won't be able to apply it for a few years' time. It is essential when you are so far away from the hubs of pharma manufacture to be aware of what is going on. *Pharmaceutical Engineering* is always beside my bed or in my briefcase, and I read the whole thing from cover to cover, every issue.

How did New Wayz Consulting come to be?

Not long after Glaxo acquired Wellcome in 1995 they realized they had too much manufacturing capacity. Essentially, Glaxo ended up with twice as many factories, which were underutilized and inefficient, so Glaxo Wellcome decided to tighten their belt. And ours was one of a number of sites to close.

In a weird way that was a lucky break. As we closed the site over two years, senior management slowly left and I took on more responsibility. That was the first stroke of luck. I wasn't site manager or anything like that, but I managed the closing with another colleague. It gave me connections to a lot of people I would not have met otherwise. The process of dealing with the site closure broadened my horizons significantly. Secondly, as a result of the closure we shifted the sales and marketing, clinical/R&D and admin functions to another city and set them up in a commercial building. As the manufacturing operation wound back and eventually closed, I ended up with more responsibility. Because the corporate executive staff were based in another city, I ended up dealing directly with commercial matters that were well beyond my previous responsibilities.

That's how New Wayz came to be as well. Glaxo basically said,"We still have a lot to do. How about you hang on for another year and work for us on contract?" They encouraged me to set up a company and gave me and my business partner work for a year, dealing with the site sale and tech-transfer processes. New Wayz has grown from that.

What kind of consulting does New Wayz do?

The pharmaceutical sector in New Zealand is not big at all, so we cannot survive on pharma work. There are a couple of generic manufacturers here that are reasonably large by New Zealand standards; there's a veterinary manufacturing presence, medical devices, and a lot of natural health products, which are regulated as low-risk medicines in Australia. We also do some work in the infant formula sector, where some of the larger players treat their supply chains more like pharmaceutical supply chains.

There are a number of operations across these sectors where we provide compliance and operational consulting—mainly for scale-up, but sometimes for compliance remediation. In relative terms, New Zealand also has quite a lot of startups in these areas, and we get quite a lot of work with these companies. We also work in the pharma sector in Australia, where there are is a considerably larger pharma manufacturing presence.

At the end of the day, we really need to get down and deal with management of real and tolerable risk to make medicine supply sustainable

New Wayz has managed to grow through these past 20 years, initially fortuitously. When my business partner left, I would look at his role and say if I'm going to make a serious go of this consulting, I am going to have to keep up with what he's doing in the corporate world. So I used to try to benchmark what he was doing, to keep pace. I started alone, but I now have eight staff; one person has been with me for 16 years and two others for over 10 years.

Who are some of the people who have influenced you throughout your career?

Early on, people who influenced me were Nick Haycocks, Chris Woods, and Simon Shelley, through Glaxo. Also, I met Steve Williams, who did an audit at Glaxo when we were having issues in our laboratory, and he's sort of been a role model for me during my consulting career. Steve cofounded a large consulting company in Australia—one of the oldest, in fact. He also was active in ISPE as one of the architects of the CPIP [Certified Pharmaceutical Industry Professional] program and he had a run on the international board of directors. Outwardly we looked like we were competitors in business, but we weren't. We respected each other's patch and had a common interest in ISPE.

Is he still a competitor?

Actually, a couple of years ago, Steve and I were part a small group that decided to start a business together in Australia. That business is the Centre for Biopharmaceutical Excellence (CBE Asia Pacific). It's an Australian venture—I am the only New Zealand partner.

What's evolved is quite complimentary. New Wayz continues to operate as Maurice with eight people in tow, and CBE is six Maurices, each with different experience and skills. I'm a generalist in New Zealand, but when I go to Australia or into the Asia-Pacific region, I can focus on what I'm really good at, which is process understanding and validation. I don't need to do compliance because Steve is that guy, and I don't need to be an operations specialist, because there's another guy for that. It fits quite well and it's nice working in small teams like this on projects. New Wayz is still focused on New Zealand and CBE is focused outward.

How do you keep up with it all?

I love the industry and I really thrive on the technical challenges. This is an industry that doesn't suffer fools. So when people are interested in finding a solution to a problem, they put resources into it. You're given technical challenges and you're also given the opportunity to look at them properly, plus the context of doing good for patients. It's all good, right?

How do you see your job being good for patients?

My role in New Zealand is about cost and getting the right balance of quality. What happens is that companies recruit from overseas because we don't have a massive pool of experienced people. Those people often bring big systems that aren't quite the right fit for a smaller organization—they're too complicated. Also, experienced people tend to stay in place for a very long time. The company can get to a state I call "vanilla," which is an opportunity for the likes of me to assist to bring about change. But change in a regulated organization is not often easy. If you were to embark on a cost-out program, there could be resistance because the perception

ISPE is revered in Asia and has an opportunity to influence the regulatory landscape without lobbying

is quality takes precedence over cost. Yet that isn't quite right: It's about cost in the context of quality. It is very difficult to move an organization that is steeped in compliance, so you need someone who's credible to be able to say, "Guys, you can do this," or "Guys, you've been doing this the wrong way." That is an important role as cost reduction assists to keeps the cost of medicine down. So that's one aspect. Also, keeping costs down keeps business local, as it's competitive. The second aspect is from my kids' perspective: They are patients, and it's good to be contributing to make sure local manufacturers make decent medicines.

Does the notion of sustainability factor into the work that you do?

Yes, although I probably don't think of it in the context of the environment. To some extent that is what is interesting in Asia. The value proposition in places like Asia is quite different from the one in the United States. The industry is at a sustainable level in Singapore, Japan, and Australia. But we are really struggling in India, and we're doing all right in China, but not as well as I think we could. It comes down to the value proposition.

What do you think it should be?

A colleague of mine has a saying: Do you want a $1 tablet or a 10-cent tablet? Just think about that for a minute. When you go to the United States, you want to make a $1 tablet and, if possible, take it to $1.50 or even $2, if it demonstrates quality. In a place like Thailand they already make a 10-cent tablet. If you turn it into a $1 tablet it will be better for the patient, but fewer patients will be able to access it. So the governments and populations of those countries don't see the value of going toward the $1 tablet, yet we don't want to sustain the 10-cent tablet either. And fundamentally that is the problem that industry has in Asia: How do we drive those quality and safety initiatives without driving the cost of medicine out of the reach of patients?

When I look at China, it seems to me like a market that is going to divide into companies that supply overseas and those that don't. There'll be companies making $1 tablets and companies making 10-cent tablets, and the government may be happy with the 10-cent tablets. Because their risk tolerance is different from that of Europe or North America.

In my opinion there needs to be a paradigm shift in the way we think about quality of drugs, and in a very cynical way it comes down to tolerance of this risk. We want the highest standards possible, so we'll make things compliant to a point where we don't take a risk, but that builds cost. At the end of the day, we really need to get down and deal with management of real and tolerable risk to make medicine supply sustainable.

That's the nub of the problem for industry and ISPE in Asia: recognizing the differences, the diversity, and understanding that we may not want to do it their way, but it may be what's right for that country.

I imagine it's a tough lesson to learn. The pharmaceutical industry is traditional, conservative.

You can't ignore two billion people and you can't ignore their demands. ISPE can be part of that conversation, that paradigm shift. I have seen trainloads of people traveling to Hong Kong from China to obtain the exact same medicine they can find at home, and pay more for it. Why? They believe the medicine in China is counterfeit. I believe this will happen more across Asia as standards of living improve. The shame is that some of those medicines with the bad names were genuine.

How can ISPE be a part of that conversation?

In Asia, PIC/S is a very big thing. It's viewed as the gold standard. Helping the industry aspire to and achieve these standards will help. If industry in Thailand, for instance, can show that it is compatible with PIC/S, it will go a long way to diffusing what we have seen in China, where the local industry is not trusted. Because of the rapid pace at which these countries have to adopt PIC/S, they don't always get it right. I have seen some odd decisions that distract from or deter improvement. Regulators in emerging markets often won't listen to an individual, but they will listen to ISPE. ISPE is revered in Asia and has an opportunity to influence the regulatory landscape without lobbying. We just have to work out a model to make our knowledge more accessible to industry and regulators in these countries so we can assist to smooth the process.

What's next for you?

I'm really enjoying what I'm doing. CBE has given me opportunities I never had access to before. I'm relishing the challenges, and this has brought new business to New Wayz, which is great. I've become a trainer in process validation and I'm enjoying that, as well as contributing to the PV team and to the RCC [Regulatory Compliance Committee]. I just want to do more of what I have been doing, because it's what I like to do.

—Anna Maria di Giorgio

***Pharmaceutical Engineering* is always beside my bed or in my briefcase, and I read the whole thing from cover to cover, every issue**

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Also in this section

ISPE Hosts 2016 Annual Meeting & Expo in Atlanta

1500 attendees from 30 countries and 185 exhibitors gathered at the Atlanta Marriott Marquis in Atlanta

Fifteen hundred attendees from 30 countries and 185 exhibitors gathered at the Atlanta Marriott Marquis in Atlanta, Georgia, US, from 18–21 September to attend the 2016 ISPE Annual Meeting & Expo.

"Our goal with the ISPE 2016 Annual Meeting was to create a gathering place for the pharmaceutical industry where the knowledge-sharing, networking, and discussion of the convergence of pharmaceuticals, medical devices, and technologies could be spotlighted through thought-provoking keynotes, highly relevant education sessions, and a strong focus on the patient," said Susan Krys, ISPE Vice President of Program Development. "Based on the strongly positive feedback we received from our member and nonmember attendees, I would say that we achieved that!

"In 2017 we plan to build on the momentum of this event, with continued emphasis on innovative technologies and patient therapies," she continued, "and as we will be in San Diego, a stronger focus on biopharmaceuticals."

Opening Remarks

Although committee and board meetings began a day earlier, conference education sessions officially commenced at noon on 18 September. The opening keynote address began with introductions by John Bournas, ISPE CEO and President, and Joseph Famulare, VP, Global Compliance and External Collaboration, Pharma Technical Quality, Genentech, a member of the Roche Group, and outgoing Chair of ISPE's Board of Directors.

Bournas noted that the organization had received a record 255 proposals for the conference, indicating the strength of ISPE's global knowledge base. He discussed the ongoing implementation of ISPE's strategic plan, noting that several topics requested by members—biotechnology and facilities of the future—had become the subject of conferences that would be held later

Joseph Famulare, VP, Global Compliance and External Collaboration, Pharma Technical Quality, Genentech, and outgoing Chair of ISPE's Board of Directors, delivers his opening remarks

this year. (For more information on the Facilities of the Future Conference in November and Biopharmaceutical Manufacturing in December, go to www.ispe.org/events.) He also highlighted new global training partnerships with the Institute of Technology Management at St. Gallen University, Switzerland, and Dublin's National Institute for Bioprocessing Research & Training.

Joseph Jimenez, CEO of Novartis and honorary conference Chair, delivers the first keynote presentation

Day 1 Keynotes

Reimagining medicine

Joseph Jimenez, CEO of Novartis and honorary conference chair, delivered the first day's keynote presentation, "Reimagining Medicine," discussing the future of health care and the industry's need to reimagine both medicine and the technology that produces it. As the world's population gets older, larger, and sicker, he said, the company has developed new business models to meet the medical demands of the future.

"These changes are putting a financial strain on health systems; medical costs are currently on track to double by 2030. This means increased pricing pressure. To succeed, we must reimagine medicine—how we innovate, operate, and bring those medicines to market," Jimenez explained.

Novartis's commitment to innovation has allowed it to produce one of the first targeted therapies for leukemia, the first vaccine to protect all age groups against meningitis, and the first oral therapy for multiple sclerosis. But innovation is just one way the company is reimagining medicine.

The second way, he said, is through technology: Novartis has developed partnerships with Google, MIT, and others to bring biology and technology together. The company is also "reimagining" how they operate to increase capacity, enhance quality, and lower cost.

Jim Spavins honored at GPMLF meeting

At the Global Pharmaceutical Manufacturing Leadership Forum (GPMLF) meeting on Sunday 18 September, Mike Arnold, Business Process Owner for Investigational Products and Senior Director of Strategic Partnerships for Pfizer's Global Clinical Supply Chain, and new Chair of ISPE's Board of Directors, presented Jim Spavins, former Head of Pfizer's Global PTx Pharmaceutical Sciences Group, with an award acknowledging his leadership and contributions to the pharmaceutical industry and marking his retirement after 36 years of service at Pfizer.

Arnold highlighted Spavins's decade of strong and unwavering support of ISPE as a Member of the PQLI, Regulatory Affairs, and Supply Chain Conference Program Committees. "Because of your commitment, several ISPE Committees continue to have Pfizer colleagues as members or committee leaders," he said.

Spavins also led the GPMLF, formerly the International Leadership Forum, from 2010–2011, and spearheaded the design and implementation of the Global Positioning Strategy document, which remains a critical component of the GPMLF strategy today.

Stephen Grupp, MD, PhD, Children's Hospital of Philadelphia, delivers the first day's second keynote presentation

Finally, he said, "We must lead with integrity and ethics. This means changing promotional practices, building new capabilities and tools, and rewarding associates based on our values."

CAR T revolution

The afternoon's second keynote presentation was "The CAR T Revolution in Treating Leukemia," given by Stephen Grupp, MD, PhD, Children's Hospital of Philadelphia.

Dr. Grupp described his groundbreaking work with chimeric antigen receptors (CARs) in treating acute lymphoblastic leukemia, the most common cancer in children. While conventional therapy produces a greater than 80% relapse-free survival in children, those who do relapse face difficult odds. "Only a third of this group goes back into remission." he explained, because their cancers often become therapy resistant.

Dr. Grupp and his team have developed treatments using CARs to redirect the immune system. "We're creating a molecule that doesn't exist in nature," he said. Because the cancer doesn't recognize it, the T cells can attack the cancer effectively.

The results are promising. Tests show that the CARs proliferate and persist in patients' bloodstreams, potentially fighting off future relapses. "We can not only control disease," he explained, "but we can bring patients to remission, even if they have cancer in their brains and spinal fluid.

"That's what we hope to offer to people around the world," he concluded.

Flemming Dahl, Head of Quality, Senior Vice President, Novo Nordisk, discusses "Developing the Workforce of the Future" in the second day's first keynote session

Day 2 Keynotes

The second day of the conference began with two powerful keynote presentations. Both spoke to the importance of pharmaceutical engineering to patients.

Workforce of the future

ISPE CEO and President John Bournas opened the session by introducing Flemming Dahl, Head of Quality, Senior Vice President at Novo Nordisk, who discussed "Developing the Workforce of the Future, Today."

Novo Nordisk is focused on three main treatment areas: diabetes, hemophilia, and growth disorders. The company employs 41,000 people and spends $2 billion on R&D annually. It produces about half of the world's insulin, which treats close to 27 million patients.

"Our key contribution," Dahl said, "is to discover and develop innovative biological medicines and make them accessible to patients throughout the world."

But developing a drug takes time and money. Only one in ten thousand ideas makes it to market. The average development timeline for a commercialized drug is around 10 to 15 years at a cost of approximately $1.3 billion.

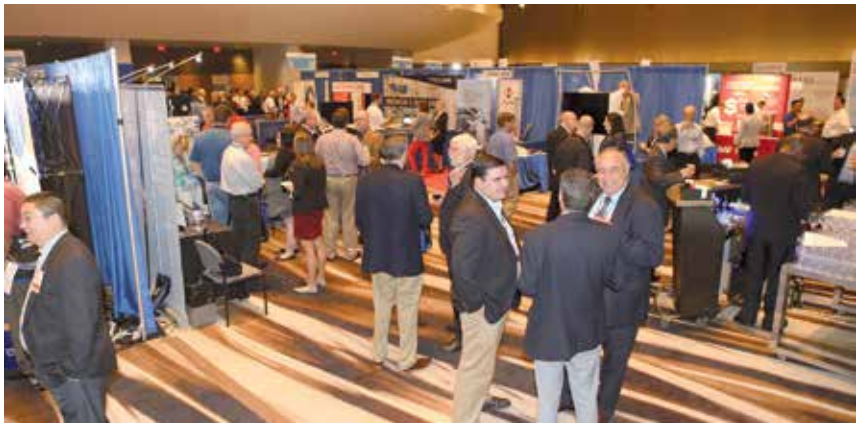
Innovation can help reduce those costs, however. By implementing continuous improvements for its drug Victoza—minimizing wasted time, optimizing steps, and procedures—the company optimized capacity 250%, with yield maximized more than 50%.

Another innovation is Novo Nordisk's oral semaglutide—the first protein-based medicine in a tablet. "Biologics in a tablet—that's the dream for a company like ours," Flemming said.

Despite these successes, however, a dearth of talent means that Novo Nordisk needs engineers of all kinds: IT/automation, mechanical, chemical, and quality. This is a problem across other industrial sectors as well. The two biggest reasons are a lack of available applicants and a lack of technical competence. As a result, Novo Nordisk is looking for people who can share knowledge and work across disciplines. The industry needs a way to develop and share experience, as well.

This is where ISPE can be influential, he said. The organization can bring political attention to the need for engineers, and stimulate positive public discussion around the field of engineering. Flemming urged attendees to "Lead by example; it's not enough to be an expert in your area. You have to be able to share your knowledge and work in other disciplines, as well."

Finally, he said, ISPE should work to build pride within the profession. "Stand up and be proud of what you do. It's a fantastic time to be an engineer."



Following the second day's last keynote presentation, Mike Arnold gave cancer survivor Gavin Pierson a jacket bearing his name, the ISPE logo, and the title of "Young Professional." Back row, left to right: John Bournas, ISPE CEO and President; Steve Pierson, Gavin's father; Nicole Pierson, Gavin's mother; Mike Arnold, new ISPE Board Chair. Front: Gavin Pierson.

Gavin's story

Mike Arnold, Business Process Owner for Investigational Products and Senior Director of Strategic Partnerships for Pfizer's Global Clinical Supply Chain and new Chair of ISPE's Board, introduced keynote speaker Nicole Pierson, mother of a 10-year-old brain tumor survivor.

"I know you don't always get to see patients," she told the crowd, "but we're thankful for the work you do."

At age 5, her son Gavin developed a rapidly growing brain tumor. The diagnosis, she said, "changed our lives forever."

The original treatment plan of chemotherapy followed by surgery and radiation was halted after two months when it failed to slow the tumor's growth. During the next year, Gavin's parents and doctors fought to keep him alive. They applied for a clinical trial, but the prognosis seemed hopeless.

Gavin's tumor, which he nicknamed "Joe Bully," began to flatten his brainstem "like a pancake," his mother said. Despite the grim prognosis, Nicole said, "I just couldn't stop fighting for him."

Gavin endured five craniotomies in a desperate bid to stay alive. Despite this, he continued to decline, and the Piersons learned that their son had only months to live. Nicole applied to Pfizer's compassionate use program for the company's anti-tumor drug palbociclib (IBRANCE). A blood test confirmed that his tumor had the protein required to be admitted to the program and treatment with the drug. In addition, they found a minimally invasive laser ablation treatment that could treat his tumor.

"We went from nothing to two options," Nicole recalled. "We began to hope that Gavin would get to celebrate his seventh birthday."

Gavin was the first pediatric patient to take palbociclib. "He called the medication 'Joe Bully medicine,'" his mother said. "He'd take the pill and say 'Joe Bully, you're going down!'"

And down Joe Bully went. The drug stopped the tumor from growing and gave Gavin time to recover from his multiple surgeries. By his seventh birthday he no longer needed a wheelchair.

He also had laser ablation therapy to decrease, and eventually eliminate the tumor. Now in remission, "he has had to fight neuro deficits from chemo," Nicole explained. "but despite that, he's become a purple belt in karate.

"There are days when were still scared," she admitted. "We don't know if it will come back. But we have a different perspective on life now. We treat every day as a blessing."

Nicole showed the audience a photo of the bottles that the drug came in, arranged into the word "hope." She had saved them all. "I can't throw them away," she said. "Every time I picked them up, it was like a bottle of hope."

As she concluded, she told her listeners, "I hope something I said will inspire you to continue the work you do. Thank you, Pfizer, for giving us hope when we had none. Thank you, ISPE, for inviting me and letting me share our story."

As the audience stood to applaud, Mike Arnold welcomed Gavin onstage to give him a gift: a jacket bearing his name, the ISPE logo, and the title of "Young Professional."

For more information on Pfizer's compassionate use policy and Gavin's story, see "How to Fight a Bully," *Pharmaceutical Engineering* 36, no. 5 (September/October 2016): 20–21.

Day 3

Honors and Awards

The annual Membership and Awards Breakfast held on 20 September honored ISPE groups and members who have demonstrated remarkable dedication and service to the organization during the past year.

Outgoing Chair Joseph Famulare opened the ceremony and called the annual general meeting to order. He began by thanking outgoing directors Jeffrey Biskup, Jennifer Lauria Clark, Britt Petty, and Andy Skibo for their service, introduced the new 2016–2017 board, and acknowledged the past Chairs in attendance.

Famulare next reviewed the 2015 audit result, which showed ISPE gaining strength and steadily rebuilding its revenues. "We've done good work to balance the budget and stabilize the operation," he said. "We're improving both our current revenue streams and actively seeking new ones. We continue to build value and grow the organization."

ISPE remains the global leader in the drug shortages arena, he continued, and the organization's quality metrics initiative leads the way with data-driven approaches. In addition, he said, "our international presence continues to be strong."

Following Joe's remarks, ISPE CEO and President John Bournas announced the 2016 honors and awards.

THE INTERNATIONAL STUDENT POSTER COMPETITION AWARDS recognize outstanding achievement from undergraduate and graduate student members. These research projects are adjudicated at the Affiliate and Chapter levels, with the top selections invited to the Annual Meeting for the final presentation and adjudication.

The 2016 undergraduate winner is Param Bhatter from the University of California–San Diego. The 2016 graduate winner is Sara Sukenik from the University of California–Davis.

THE JOSEPH X. PHILLIPS PROFESSIONAL ACHIEVEMENT AWARD honors an ISPE member who has made a significant contribution to industry. The award is named in honor of Joe Phillips, longtime ISPE supporter and a leader in establishing the Society as an "integrator" of industry and regulators, both during his years of service with the FDA, and later when he became international regulatory affairs advisor to ISPE.

Michael Rutherford, 2016 Joseph X. Phillips Professional Achievement Award recipient. When presented with the award, Rutherford professed himself "totally shocked." He thanked the GAMP organization, whom he called "an awesome group of individuals. The effort they've put in has taken hold and influenced industry."

The 2016 Joseph X. Phillips Professional Achievement Award recipient is Mike Rutherford. Involved with ISPE and GAMP® leadership since 2003, Rutherford currently serves as Chair of the GAMP Global Steering Committee, is past Chair of the GAMP Americas Steering Committee, and has sponsored numerous GAMP Special Interest Groups.

Param Bhatter (center), University of California—San Diego, 2016 undergraduate poster competition winner, with Mike Arnold, new ISPE Board Chair (left) and Joe Famulare, outgoing Board Chair (right).

Sara Sukenik (center), University of California—Davis, 2016 graduate poster competition winner, with Mike Arnold, new ISPE Board Chair (left) and Joe Famulare, outgoing Board Chair (right).

He has played a pivotal role in GAMP's push for improving the industry approach to data integrity. Because of his leadership, he has touched hundreds of companies and countless professionals in his quest to put data integrity at the forefront of the conversation.

Mike's diligent pursuit of regulatory involvement has raised the quality of ISPE's data integrity programs, and the connections he facilitated between industry professionals and regulatory experts have significantly improved the industry's understanding of the issues and the best approaches for mitigating data Integrity complications. He is also highly regarded for his expertise and professionalism, as well as a his strong sense of community, which fosters support and camaraderie among fellow volunteers.

When presented with his award, Mike professed himself "totally shocked." He thanked the GAMP organization, which he called "an awesome group of individuals. The effort they've put in has taken hold and influenced industry."

Bruce Davis, 2016 Richard B. Purdy Distinguished Achievement Award recipient. Davis said that his career in ISPE started when someone asked him to "go and give a talk." Committee seats and the Board of Directors eventually followed. "It grows you, ISPE," he said.

THE RICHARD B. PURDY DISTINGUISHED ACHIEVEMENT AWARD honors an ISPE Member who has made significant long-term contributions to the Society. It is named after one of the Society's founders and most accomplished presidents.

The 2016 Richard B. Purdy Distinguished Achievement Award recipient is Bruce Davis. An ISPE member since 1991, Davis's expertise has been a critical part of the development and delivery of many ISPE products. He has served on countless committees and was a Member of the Board of Directors for nine years, serving as Board Chair from 2007–2008. A key training instructor for

ISPE, he has delivered courses in the US, Europe, Asia, and the Middle East.

Bruce served on the Guidance Documents Committee for many years and participates on many document development teams. Most of all, he is a professional with high integrity who is very kind and generous to everyone with whom he works.

When presented with his award, Bruce said that his career in ISPE started when someone asked him to "go and give a talk." Committee seats and the Board of Directors eventually followed. "It grows you, ISPE," he said.

Maurice Parlane, 2016 Max Seales Yonker Member of the Year Award recipient. Parlane was overcome with surprise at receiving the award. "I really don't know what to say," he exclaimed. "Thank you very much. This is a great Society—it really energizes me."

THE MAX SEALES YONKER MEMBER OF THE YEAR AWARD honors the ISPE Member who has made the most significant contribution to the Society during the past year. It honors a dynamic woman who was an active member, Society leader, and relentless contributor to ISPE and to the industry.

When Maxine Yonker lost her battle with cancer in 2005, it seemed only fitting that her memory be honored with an award that recognizes that same commitment to service. Max's memory reminds us that we are all patients, and that we do vital work to advance the development, production, and delivery of a safe and reliable drug supply.

The 2016 Max Seales Yonker Member of the Year Award is Maurice Parlane. An ISPE member since 1999, Parlane has held leadership roles in the Asia–Pacific Affiliate Council, Australasia Affiliate, Australasia–New Zealand Committee, Board Nominating Committee, and Membership Development Committee. He spoke at last year's ISPE China Annual Meeting, representing the Process Validation Team that spoke with the Chinese FDA. This year he gave two presentations focused on process validation at the ISPE India Annual Meeting.

Passionate about education, Maurice helped deliver the three-day ISPE Process Validation Training course in Singapore, and is working diligently to make this training available elsewhere in the Asia–Pacific Region. He is currently part of the ISPE Process Validation Conference Planning Committee for the October conference and is a member of the ISPE Practical Implementation of the Life Cycle Approach to Process Validation Good Practice Guide writing team. Maurice brings endless energy and enthusiasm to all his ISPE roles, and mentors new ISPE Affiliate leaders as they rise through the ranks.

He was overcome with surprise at receiving the award. "I really don't know what to say," he exclaimed. "Thank you very much. This is a great Society—it really energizes me." (See this issue's profile of Maurice Parlane on page 12.)

THE COMPANY OF THE YEAR AWARD recognizes the outstanding leadership and support provided by a company as reflected by significant active participation in the Society's committees,

Flemming Dahl (center), Head of Quality, Senior Vice President, Novo Nordisk, accepts the 2016 Company of the Year award, with Mike Arnold, new ISPE Board Chair (left) and Joe Famulare, outgoing Board Chair (right).

CoPs, programs and activities, as well as its support of employee participation in ISPE. Owner companies, suppliers, and service providers invest in the Society through employee involvement, sponsorship, and by providing extraordinary leadership. This investment helps foster understanding and advancement of knowledge throughout the industry.

The 2016 Company of the Year is Novo Nordisk. Novo Nordisk has supported ISPE for many years and has increased their participation this year. In addition to members that renew and stay involved in ISPE, the company has greatly increased the number of new members this year. Novo Nordisk members serve as key volunteers in many areas throughout the organization, including committee members, conference speakers, Guidance Document authors, and local Affiliate and Chapter Board Members. Support from Novo Nordisk is far-reaching throughout the global ISPE organization.

Flemming Dahl, Head of Quality, Senior Vice President, accepted the award.

THE COMMITTEE OF THE YEAR AWARD honors an ISPE committee, council, task team, or CoP steering committee for outstanding work in support of Members and the industry. More than 75 committees, councils, CoPs, and other teams

GAMP® Global Steering Committee, 2016 Committee of the Year. Back row, from left: Chris Reid, Arthur Perez, Siôn Wyn, Lorrie L. Vuolo-Schuessler, and Chris Clark. Front row, from left: Michael Rutherford, Heather Watson, and David Selby.

support the Society's mission, and deliver value to the Membership.

The 2016 Committee of the Year is the GAMP Global Steering Committee. GAMP is a truly global group, with steering committees in Europe, North America, Brazil, and Japan. In 2016, GAMP supported conferences and education sessions around the globe. This year, the GAMP Community of Practice celebrates its twenty-fifth anniversary, a significant milestone. GAMP has established itself as the definitive source of industry good practice for computerized system compliance and validation, and the committee continues to deliver programs and products that advance ISPE's mission and support the needs of Membership and industry.

Chair
Michael L. Rutherford

Co-Chair
Chris Clark

Secretary
Heather D. Watson

Past Chair:
Winnie Cappucci

Past Chair
Arthur D. Perez, PhD

Committee Members
Sam Brooks
Marcelo Decanio De Oliveira
Cristiano B. Ferrari
Hirokazu Hasegawa
Paige E. Kane, CPIP
Kevin C. Martin
Christopher J. Reid
David W. Selby, PhD
Eric J. Staib
Lorrie L. Vuolo-Schuessler
Guy A. S. Wingate, PhD
Siôn Wyn

THE AFFILIATE AND CHAPTER EXCELLENCE AWARD recognizes outstanding work of ISPE's 38 international Affiliates and Chapters as reflected by membership development and services, management, industry and society support, and innovation.

Because this year's Awards Committee had an unusually difficult job in selecting the best of the best in this category, they opted to recognize two outstanding teams. The 2016 Affiliate and Chapter Excellence Awards recipients are the Belgium Affiliate and the Turkey Affiliate.

The Belgium Affiliate has done outstanding work this year, particularly in membership development and Young Professional (YP) support. The Affiliate, which hosts membership recruitment and retention activities throughout the year, has the highest retention and recruitment rates in Europe. Its mission is to be an open community that discovers and builds YPs' future in the pharmaceutical industry. To further develop the future generation of leaders, the Affiliate established a YP Board and invites a YP to participate in each monthly Board meeting; YPs also participate in Board subcommittees.

The Turkey Affiliate has done a tremendous job in developing relationships with local regulatory agencies. The Affiliate met with the Turkish Medicines and Medical Devices Agency, and has been officially added to the agency's distribution list. The Affiliate also develops students through outreach programs, career days, and scholarships, and has supported the development of pharmaceutical manufacturing curricula at Istanbul University and Kadirga Vocational School. In 2015, the Affiliate celebrated its tenth anniversary and was featured on a broadcast of Bloomberg News.

One annual award—the **ROGER F. SHERWOOD ARTICLE OF THE YEAR AWARD**, which recognizes writing that provides real value to the industry—was absent from this year's proceedings. Bournas noted that due to the timing of the 2016 Annual Meeting, the award will be announced in January and recognized in the March/April issue of *Pharmaceutical Engineering*.

Members of the Turkey Affiliate, 2016 Affiliate and Chapter Excellence Award co-recipient, with John Bournas, ISPE CEO and President (right)

Jef De Clercq (center), Belgium Affiliate Chair, accepts the 2016 Affiliate and Chapter Excellence Award, with Mike Arnold, new ISPE Board Chair (left), and Joe Famulare, outgoing Board Chair (right)

ISPE'S FACILITY OF THE YEAR AWARDS (FOYA) recognize state-of-the-art projects utilizing new, innovative technologies to improve the quality of products, reduce the cost of producing high-quality medicines, and demonstrate advances in project delivery. The program is about much more than just the science and technology of the facilities, however. It recognizes the shared commitment and dedication of individuals working for different companies worldwide to innovate and advance pharmaceutical manufacturing technology for the benefit of all global consumers.

Award winners in the following categories were announced at the 2016 ISPE/FDA/PQRI Quality Manufacturing Conference, held 6–8 June 2016, in Bethesda, Maryland, US:

- Equipment Innovation: Pfizer Inc.
- Facility Integration: Takara Bio Inc
- Operational Excellence: Baxter BioPharma Solutions
- Process Innovation: Genentech, a Member of the Roche Group
- Project Execution: Janssen Vaccines AG
- Sustainability: Ethicon, LLC

Category winners, honorable mentions, and the overall Facility of the Year Award winners are chosen by a team of judges consisting of prominent industry leaders with extensive global experience. Jim Breen, Lead, Biologics Expansion, Janssen Pharmaceuticals, and 2016 FOYA Judging Committee Chair, took the stage to announce the 2016 Facility of the Year overall winner, beginning with a video of the six category winners and three honorable mention winners.

Jim Breen, Lead, Biologics Expansion, Janssen Pharmaceuticals, and 2016 FOYA Judging Committee Chair, announced the 2016 Facility of the Year overall winner

The 2016 FOYA Overall Winner is Genentech, a member of the Roche Group, for their large-scale cell culture biologics drug substance plant 2 (CCP2), located in Vacaville, California.

This project focused on an upgrade to the original CCP2 facility, which had been put into an "idle but keep warm" status in 2010, combined with a fast-track return-to-service (RTS) project. The RTS project and its fast-track timing

The students' view

Craig Johnson

Attending the ISPE 2016 Annual Meeting was perhaps the best decision I made all year. Activities ranged from networking with professionals from all over the globe and learning about recent developments directly from industry leaders, to visiting the impressive Georgia Aquarium or trying the infamous Beverly soda at the Coke Museum. It was truly a time to be had, from both a professional development and an entertainment point of view!

As a student seeking employment in the near future, the networking was what made the trip exceptionally worthwhile. I was able to meet representatives from companies such as CRB, CAI, and NNE Pharmaplan, who were genuinely excited to speak with a student about their footprint in the pharmaceutical industry and how I can become part of their vision. Then there was Novo Nordisk, the Company of the Year, who just so happens to be expanding their manufacturing facilities and hiring engineers such as myself. The FDA was even in attendance—a move that solidified my faith in our continued efforts to provide quality care to the patients on the other end of the process.

However, as previously mentioned, the meeting wasn't all business. The Young Professionals hosted a "bar-cade" night at Game-X, where you could race your peers on leaning motorcycles or even fend off dinosaurs with your competitor in Jurassic Park. And the visit to the aquarium was as much sightseeing as it was partying, with delicious buffets being served, live music playing in the background, and hysteric moments being captured at the green screen photo booth.

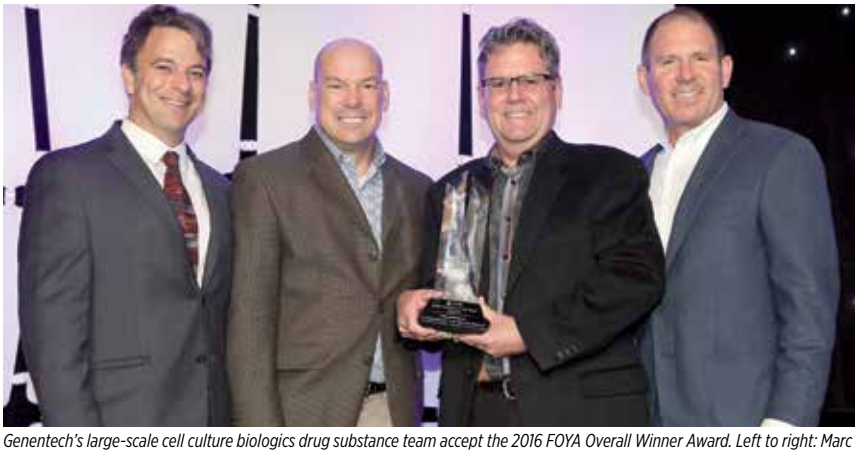
The opportunity provided to me by ISPE-CaSA was invaluable to my professional development, and I cannot stress enough how grateful I am to have been chosen as a representative of my university. I look forward to my continued involvement in the organization, as well as its continued support of the pharmaceutical industry.

Craig Johnson is an undergraduate student majoring in chemical and biomolecular engineering at North Carolina State University, as part of the BTEC program. He is the current Vice President of the NCSU ISPE student chapter.

Tony Le

I had such an amazing time at the ISPE 2016 Annual Meeting! I was able to speak with people from across the globe that I would have never had the opportunity to speak to otherwise. Listening to the experience and passion of the keynote and guest speakers was truly a humbling experience. I hope to be able to contribute half as much to the pharmaceutical industry as they continue to do. I was very fortunate to have been chosen by ISPE–CaSA for sponsorship to attend the meeting. Without the sponsorship, I would have lost out on this opportunity and I will always be grateful for that.

Tony Le is a second-year graduate student in pharmacology and biotechnology/bioprocessing at Campbell University, Blues Creek, NC.



Genentech's large-scale cell culture biologics drug substance team accept the 2016 FOYA Overall Winner Award. Left to right: Marc Lampron, Regional Engineering Americas Vacaville Program Lead; Ed Fitzgerald, Regional Engineering Americas PTB Program Lead; Chris Schreil, Senior Principal Engineer/Project Advisor and Project Team Lead; and Gary Schoenhouse PE, Head of Global Engineering Americas.

Genentech's large-scale cell culture biologics drug substance plant 2 in Vacaville, California, 2016 FOYA Overall Winner

was driven by a need to support product supply of two significant oncology products for which market demand has tripled in recent years. By late 2013, the market had changed and the supply demand of Roche biologic products inventory was forecasted to reach critically low levels. As a result, the decision was made to fast track the restart of the CCP2 plant with RTS required by late 2015.

Revamping the existing CCP2 facility to support new process technology instead of building anew resulted in significant ($50 million) savings in capital. The project was completed two months ahead of schedule, ensuring patient product supply.

Gary Schoenhouse PE, Head of Global Engineering Americas, and Chris Schreil, Senior Principal Engineer/Project Advisor and project team lead accepted the award.

Passing the Torch

Following the awards ceremony, Joe Famulare symbolically handed the chairman's gavel to new ISPE Board of Directors Chair Mike Arnold, who accepted it with a smile and announced: "We have a lot of good stuff to do."

Looking ahead, Arnold said, "I see both opportunities and challenges. Opportunities abound; two are leveraging our Chapters and Affiliates, and our YPs. Challenges are a complex and competitive environment. We have to be flexible and forward thinking to address these challenges. I'm convinced that the answers to these challenges are in this room."

The new Chair also identified four areas of focus: transparency, diversity, collaboration, and strengthening our core. These will be the foundation for four new board committees:

Voice of the Customer: Take members' pulse on issues, concerns, and level of customer satisfaction. Get information back from members—the customers—to allow us to be more effective. As part of this effort, the Board will also conduct annual self-assessments.

Business Development: Identify and assess opportunities for partnerships, collaborations, and new ISPE business focus areas.

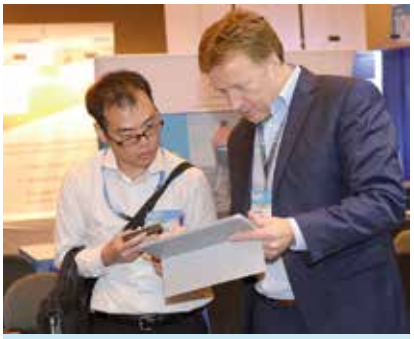
Operations Review: Assess current high-level processes associated with business decisions, and ensure effective and sustainable processes are in place.

China Strategy: Assess opportunities for developing ISPE business in China, and determine how best to leverage this market.

"Let me be clear," Mike said, "ISPE is alive and well. We are heading in the right direction. We have tremendous strengths and opportunities, and I want to take advantage of that. My commitment to you is that we will listen, facilitate sound business decisions, and be as transparent as possible."

The session closed with a video highlighting San Diego, California, site of the next ISPE Annual Meeting, 29 October to 1 November 2017. ■

—Amy R. Loerch



We had an app for that

ISPE debuted a robust mobile event app at the 2016 ISPE Annual Meeting & Expo in Atlanta. Sponsored by NNE Pharmaplan, it provided a variety of new and enhanced knowledge sharing and networking opportunities for attendees. Through the app, attendees could search for and learn more about speakers, exhibitors, tracks, sessions, and featured programming like the special sessions focused on Women in Pharma. They also used it to rate sessions, make their own conference schedule, locate exhibitors and events using interactive maps, connect to social media platforms like Twitter and Facebook, and create a profile to enhance networking opportunities with other attendees. The app was used extensively and proved an effective way to connect and update attendees. ISPE will use the mobile app again at the 2017 Aseptic and Quality Manufacturing Conferences and 2017 Annual Meeting in San Diego. ■

Women in Pharma Debuts at 2016 Annual Meeting

Leaders Agree: Women Must Make Choices, Take Chances

ISPE presented the first in a series of planned annual events entitled, "Women in Pharma" on Monday 19 September. Key female pharmaceutical industry executives shared their stories at the morning session, focusing on the challenges and opportunities each embraced as they progressed though their careers.

The session was led by the session's two Co-Chairs: current ISPE Executive Board Member Frances Zipp, President & CEO, Lachman Consultant Services, US, and ISPE Board of Directors Past Chair Charlotte Enghave Fruergaard, PhD, Partner, Process Technology Consulting, NNE Pharmaplan, Denmark.

Panelists were:

- Lou Kennedy, CEO and Owner, Nephron Pharmaceuticals Corporation, US
- Georgia Keresty, PhD, Global Head, Pharmaceutical Development & Manufacturing Sciences, Janssen Pharmaceutical Companies of Johnson & Johnson, US
- Lori Kim, Director of Global Systems and Standards, AbbVie Operations Central Services, US
- Robin Kumoluyi, Vice President, Quality Systems and Services, Johnson & Johnson, US
- Mary Oates, PhD, Vice President, EHS and Global Quality Operations, Pfizer, Inc., US
- Alice Redmond, PhD, Vice President, European Operations, Commissioning Agents Inc., Ireland
- Carmen Shepard, JD, Global Head of Policy, Regulatory Counsel, and Operations Auditing, Mylan, US
- Jana Spes, Vice President, Technical Operations GSO, Apotex Inc., Canada
- Ingrid Zambrana, Director, Atlanta FDA District Office, Southeast Region, FDA Office of Regulatory Affairs, US

The bottom line: Add value. Work hard. Stand on your own merits.

Dr. Fruergaard's opening remarks referred to the emotional keynote presentation made earlier that morning by Nicole Pierson, whose fierce and tireless determination, coupled with Pfizer's compassionate use program, brought lifesaving therapy to her son, who was dying from an inoperable and incurable brain tumor. "I'm in ISPE because of stories like that," she told the audience.

She turned the podium over to Fran Zipp, who opened with a quotation from Florence Nightingale: "I attribute my success to this: I never gave or took any excuse." In building a career, Zipp said, "there are sacrifices. We've all made them. But opportunities don't happen, you create them."

Zipp introduced the panelists, all highly successful women with different experiences, from different companies.

Lou Kennedy began in sales and now owns a pharmaceutical company. Seventy-five percent of her department heads are female. "We probably only have three men on our sales force. Although men might be faster closers, women get the job done and handle all the details," she said.

Georgia Keresty encouraged her listeners take control of their careers: "You must make some decisions and there are difficult tradeoffs you have to consider. Do you want to be a professional of breadth, or a professional of depth? You


Joanne Barrick


Jennifer Lauria Clark


Charlotte Enghave Fruergaard


Christa Myers


Stephanie Thatcher


Frances Zipp

have to make those choices." Asked about this in a later Q&A session, Georgia noted that it's OK to develop depth instead of breadth and not aspire to management roles. Not every choice has to lead to the top.

A well-rounded background and the willingness to "go for the next new thing" helped Lori Kim get where she is now. A mentor was also a big help in balancing what's critical to career and family. "Don't be afraid to take new challenges," she told the audience.

Robin Kumoluyi's keys to success, she said, were "hard work, taking chances, asking for what you want, and using your network." After a move to Puerto Rico, she told attendees, "I was scared to death. I was in Puerto Rico alone, on my own. But I was in my element, managing QA processes." You do have to make choices, and take chances, she added.

A series of what Mary Oates initially deemed significant challenges turned into incredible opportunities for growth, learning, and success. "My career has been purpose-driven," she said, "and my purpose is to add value and to learn. When challenges arose, I saw them as opportunities to fulfill my purpose. Rather than focusing on career advancement, I focused on adding as much value as possible in the role I had at the time."

"Look for where you can make a difference, and don't be afraid to change."

—Alice Redmond, Commissioning Agents Inc., Ireland

Growing up in Ireland, Alice Redmond said her "stubborn streak" spurred her to insist that girls needed to learn higher-level mathematics and physics. "I knew what I wanted," she recalled. With an engineering degree in biotech, her career has taken her all over the world. "Look for where you can make a difference," she said. "And don't be afraid to change."

Carmen Shepard said her career was "about adding value, and about learning, but mostly figuring out what I like to do best, and how I can bring my energy to something." She also shared it was important to "Make sure you work in an environment that allows you to find your potential."

"Every journey is personal," said Jana Spes. "You'll succeed in your own way. Find your leadership strength and philosophy, and be resilient." She attributes her success to "Closing the experience gap, learning new skills all the time, and taking radical steps when needed."

Ingrid Zambrana said she "found a passion to improve the quality of life" in the US Army. She sums up her approach to work in three key words: "Focus, faithful, and fearless. I navigated through a lot of unknowns. I asked questions and sought assistance. At the end of the day, you choose your opportunity."

The bottom line: Add value. Work hard. Stand on your own merits. Look for opportunities to bond with others. Recognize how far you've come. Celebrate every win, no matter how small. ■

—Amy R. Loerch

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President & CEO, Lachman Consultant Services

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Executive Director, Strategic Development
Commissioning Agents, Inc.

Christa B. Myers
Senior Pharmaceutical Engineering Specialist, CRB

Stephanie K. Thatcher
Principal, ORCAS Project Controls

Women in Pharma: Even Better Than Expected

Frances M. Zipp

When we were planning the Women in Pharma track for this year's Annual Meeting we feared that the audience might be somewhat sparse. Because ISPE's membership of pharmaceutical engineers and other professionals in the manufacturing sphere of the pharmaceutical industry is predominantly male, we weren't sure what kind of reception the session would receive.

Another message was that both men and women have the same needs and face the same challenges in the workplace

Our fears were unfounded. Not only were the sessions well attended and well received, there were a great number of men in the room, and they participated in the breakout session that followed the panel discussion with just as much passion and fervor as their female colleagues. In addition, panelists and participants represented the spectrum of professional accomplishment, from C-suite level executives on the podium to junior new hires in the audience.

A recurring theme was that good leadership is gender-neutral. Good leaders use both feminine and masculine communication styles in their interpersonal interactions, empower their employees, and have an eye toward cultural sensitivity in the workplace. It was evident from the stories told by panelists in the first part of the session that a person's leadership skills and potential drives his or her career growth.

Another message was that both men and women have the same needs and face the same challenges in the workplace. Both struggle to balance work/life commitments, regardless of marital and/or reproductive status. Both need a strong network that includes peers, coaches, and mentors, as appropriate for the different stages of their careers. Both need to embrace challenges and change, focus on what is important to them, and be authentic to themselves in the workplace.

Discussions generated during the breakout sessions continued after the gathering formally concluded. During my closing remarks I proposed setting up a network for mentoring and discussions, and was gratified to see participants lingering in the room, continuing their conversations and exchanging business cards.

It was clear from many participants' comments—most notably by members of the Board of Directors—that Women in Pharma is a topic that will continue to be supported by ISPE. One comment, in fact, was that the Planning Committee will try to structure next year's Annual Meeting to avoid conflicts with education sessions. If that's the case, we expect even more attendees at the Women in Pharma track at the 2017 ISPE Annual Meeting. See you in San Diego! ■

Fran Zipp is President & CEO of Lachman Consultant Services, and a Member of ISPE's International Board of Directors

Fund-Raiser

Throughout the conference, the Women in Pharma team sold "ISPE Women in Pharma" buttons for $5 donations, with proceeds going toward a scholarship at the University of Georgia (UGA). Donations of $20 or more also included an entry in a drawing for a weekend stay at the River's End Restaurant and Inn in Jenner, California, donated by ORCAS Project Controls. The lucky prize winner was Padraig O Se, Regional Manager, John Sisk & Son Holdings Ltd.

One hundred percent of funds raised will be awarded by UGA's Department of Pharmaceutical and Biomedical Sciences to women pursuing degrees in pharmaceutical sciences, biomedical sciences, pharmaceutical regulatory affairs, or an engineering discipline with an interest in a pharmaceutical manufacturing. The monies may be utilized for student memberships to ISPE, registration fees to attend an ISPE-associated national or chapter events—including associated transportation and lodging fees, purchase of an ISPE Guidance Document in support of their degree/education, and/or attendance at ISPE training courses. UGA was chosen because of its proximity to the 2016 ISPE Annual Meeting and the institution's strong industrial pharmacy program.

Plans for next year's Women in Pharma events are already in the making; the team hopes to make them even more successful. ■

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Chong Hock Sia Wins Singapore Affiliate's Special Award

At the ISPE Singapore Affiliate's annual dinner on 25 August 2016, Chong Hock Sia was presented with the Affiliate's Special Award in recognition of his service to the local pharmaceutical industry, his leadership in the Association of Southeast Asian Nations (ASEAN), and his contributions to ISPE over the years. Sia is Director and Senior Consultant for the country's Health Sciences Authority.

Chong Hock Sia (left) accepts the Singapore Affiliate's Special Award from Bob Tribe, ISPE Advisor on Asia Pacific Regulatory Affairs, at the affiliate's annual dinner on 25 August 2016.

ASEAN MRA

A key objective of the ASEAN Economic Community is to develop ASEAN into a highly competitive region with a single market and production base that is fully integrated into the global economy. As Chair of the ASEAN Joint Sectoral Committee on GMP Inspection, Sia helped develop the ASEAN sectoral mutual recognition arrangement (MRA) on good manufacturing practice (GMP) inspection for manufacturers of medicinal products, which was signed by the economic ministers of all 10 ASEAN member states in 2009.

Under the MRA all ASEAN member states are obliged to recognize and accept the inspection reports and certificates issued by each listed (accepted) ASEAN inspection services without duplicating GMP inspection in each other's territory. Singapore Health Sciences Authority, Malaysia National Pharmaceutical Control Bureau, and Indonesia National Agency for Drug and Food Control were the first listed ASEAN inspection services. The Food and Drug Administration (FDA) of Thailand became the fourth on 13 March 2015. The following conversation between Sia and the Singapore Affiliate has been adapted from the fourth edition of the ISPE Singapore eNewsletter, published 15 October 2016. Reprinted with permission.

Your leadership in the development of the ASEAN mutual recognition arrangement (MRA) on GMP inspection has been impressive and will benefit regulatory authorities and pharmaceutical manufacturers in the region for years to come. What are some of the key benefits of the ASEAN MRA on GMP Inspection?

The benefits of the MRA include avoiding duplicate GMP inspections within ASEAN; saving time, money, and resources for both regulators and the industry; facilitating pharmaceutical trade within ASEAN; and improving ASEAN patients' access to medicinal products. As the Pharmaceutical Inspection Co-Operation Scheme (PIC/S) inspection framework had been adopted by ASEAN as the benchmark, ASEAN pharmaceutical manufacturers will become more export-oriented and globalized in their business outlook.

Are there any further developments planned for the MRA?

The scope of the MRA is currently restricted to medicinal products in finished dosage forms. In coming years this will be extended to cover active pharmaceutical ingredients (APIs) and biologics. In addition, there are at present four listed inspection services—Singapore, Malaysia, Indonesia, and Thailand. These ASEAN member states operate a PIC/S-equivalent GMP inspection system and accept each other's GMP certificates without duplication of inspections. FDA Philippines has applied to be a listed inspection service, pending review by a panel of experts. Other ASEAN inspectorates also plan to become listed inspection services.

What do you think is the key priority for pharmaceutical inspectorates and manufacturers in the ASEAN region?

One priority is to make GMP inspection systems PIC/S equivalent. This may be done through the PIC/S accession process or by becoming an ASEAN listed inspection service. ASEAN member states are legally obliged to accept the GMP certificates granted by listed inspection services. Other priorities for ASEAN inspectors and manufacturers alike include paying greater attention to GMP compliance of API manufacturers, good distribution practice, and supply chain integrity, as well as the issues of adulteration, contamination, and falsified medicines.

You have been a great supporter of ISPE over the years, especially through your contribution of technical articles to ISPE's *Pharmaceutical Engineering* magazine. Are you planning any more articles for publication?

Over the past few years I have cowritten several articles for *Pharmaceutical Engineering*, covering topics such as GMPs, APIs, pharmaceutical excipients, quality assurance, and supply chain integrity for traditional and herbal medicines, as well as ASEAN GMP harmonization and training of inspectors. Future articles may discuss the challenges faced by regulators around the world in balancing pre- and post-market controls for various categories of health products, analyzing

The ASEAN MRA on GMP inspection will benefit regulatory authorities and pharmaceutical manufacturers in the region for years to come

the competency of inspectors, and GMP compliance of manufacturers in various jurisdictions.

What are your thoughts on the issues raised at the ISPE 2016 Singapore Conference panel discussion?

The industry is wondering whether inspectors will be able to cope with the onslaught of emerging disciplines such as information technology, computerized systems, biotechnology, and issues such as supply chain and data integrity. On the other hand, inspectors would like to see a consistently GMP-compliant industry, and hope to avoid regulatory inspections based on "inspectors' intelligence." I am of the view that more can be done to foster greater inspector–manufacturer collaboration for a win-win-win outcome—i.e., for the regulator, the industry and the patient/consumer.

How do you think ISPE can help both regulators and manufacturers in the region?

As a not-for-profit international professional society with a good global reputation, ISPE can offer its collective expertise to train inspectors and manufacturing personnel, working in tandem with potential funding organizations. Speaking from experience, I admit that the latter is more easily said than done.

Anything else that you'd like to share with our readers?

I would like to sign off by saying that *Pharmaceutical Engineering* is the journal for pharmaceutical professionals, especially those involved in manufacturing, quality control and inspection! ■

ISPE Guidance Documents Now Available

ISPE Good Practice Guide: Controlled Temperature Chamber Mapping and Monitoring

A controlled temperature chamber is defined as a system, unit, equipment, or room in which the environmental conditions (usually temperature) of a chamber are controlled/maintained/regulated to meet specific user requirements.

This ISPE Good Practice Guide provides industry good practice for the temperature mapping of controlled temperature chambers, along with development of test acceptance criteria and a risk-based approach to practices for periodic review of system performance. The approach described is consistent with that explained in the ISPE Good Practice Guide on Cold Chain Management.

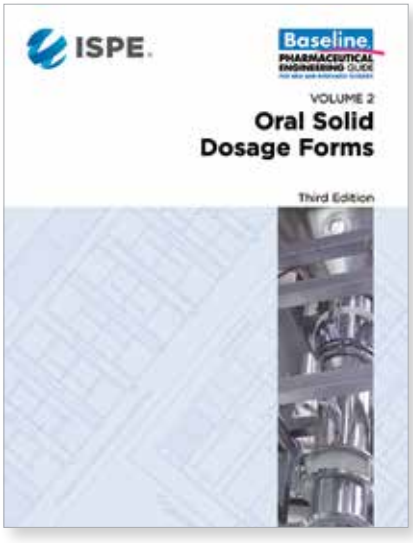
Guidance is provided on controlled temperature chambers used to store raw material, work in progress, or finished product, and which operate under current good manufacturing practices.

ISPE Baseline® Guide: Oral Solid Dosage Forms (3rd Edition)

Technical content within this ISPE Baseline® Guide covers pharmaceutical facilities for the manufacture of oral solid dosage (OSD) forms, including tablets, capsules, and general powders and focuses on compliance with the current regulatory expectations. It may also be applied to pilot and clinical supply facilities and is intended to supplement GEP with suggested approaches to good manufacturing practice.

This ISPE Baseline® Guide is intended for use by industry professionals for the planning, design, engineering, construction, commissioning, qualification, and operation of both new and renovated pharmaceutical OSD facilities. It is also to be used to develop technically sound and compliant solutions while offering flexibility to meet specific facility and project needs.

This ISPE Baseline® Guide offers a tool for consistent framework for regulatory interpretation, while still allowing a flexible, innovative, and compliant approach to facility design, construction, commissioning, and qualification. This approach is designed to allow manufacturers to better serve their customers by helping to reduce costs and improve product quality. Additionally, this ISPE Baseline® Guide provides an overview of potential new technologies, which are being applied selectively in the industry. ■



ISPE Training Institute Courses: February and March 2017

1–3 February 2017

Practical Implementation of Process Validation Lifecycle Approach (T46)

Do you need a practical understanding of PV principles and expectations in the US and EU?

This three-day course includes a blend of concepts and details; related practice application scenarios/exercises to define the requirements for preparation, planning, and execution of validation/process validation; and how to maintain a state of control. It explores the three stages of the validation product life cycle, including process design, equipment and utility qualification, and establishing and implementing process performance qualification (US) or process validation (EU) requirements, as well as putting in place an ongoing/continued process verification program. The course is applicable to all sectors of the pharmaceutical industry—small and large molecules, innovators, and generics.

23–24 February 2017

Science- and Risk-Based Commissioning and Qualification—Applying the ISPE Good Practice Guide: Applied Risk Management for Commissioning and Qualification (T40)

Are your equipment and facility "fit for use" as defined by current global regulatory authorities?

Guidance on the transition of an organization's approach to C&Q to one that incorporates a science- and risk-based approach is the basis for our training course. The class provides a detailed review of the principles and activities that constitute an efficient and acceptable approach to demonstrating facility and equipment fitness: improving the ability to meet documented process requirements, controlling risks within the manufacturing process, producing high quality products, and consistent operation to meet product user requirements. Additional emphasis will be placed on a review of ICH documents Q8(R2), Q9, and Q10, as well as ASTM E2500.

27–28 March 2017

Risk-Based Verification of Facilities, Systems and Equipment Workshop (T48)

Do you have the tools to integrate the new C&Q program into quality assurance and engineering management systems?

Our interactive course shows you how to implement a sustainable approach to a risk-based C&Q program, integrate the new C&Q program into existing quality systems, and define the organizational capabilities for new program support. Templates will be developed to facilitate the translation of the scientific knowledge about the product and process into documented specification, design, and verification of facilities, systems, and equipment while applying the principles of ASTM E2500-07 and ICH documents Q8(R2), Q9, and Q10.

Please visit **www.ispe.org/training** to see all of our courses. ■

Appointments

Zoraida Rodriguez, Member Services Coordinator

Zoraida Rodriguez joins ISPE's Member Services Department with 10 years' solid customer service experience in working with companies such as USAA, Citigroup, and the General Insurance company. A systematic and detail-oriented person with problem-solving skills, she also speaks fluent Spanish. Zoraida earned a bachelor's degree in business administration and an MBA, both from the University of Phoenix. "I am so thankful for the opportunity to serve our members in my role as a Member Services Coordinator," she says. "I look forward to assisting our members and collaborating with the staff at ISPE."

Christy Troiano, Director of Sales

A 14-year health care–industry veteran, Christy Troiano is ISPE's new Director of Sales. As head of the sales team, she oversees sales of tabletops, booths, and sponsorships for ISPE events, and plays a role in business development. In her previous position as director of sales for SPARGO, a full-service event-management company in Fairfax, Virginia, she supported the production of trade shows, conferences, and seminars. Other assignments included senior molecular diagnostic specialist at Predictive Biosciences, selling molecular diagnostic testing to facilities, and sales at Sanofi-Aventis Pharmaceuticals. Christy earned a bachelor's degree in business administration/marketing from Bloomsburg University, Bloomsburg, Pennsylvania, and an MBA, marketing concentration, from Lehigh University, Bethlehem, Pennsylvania. ■

UPCOMING EVENTS

2016 EVENTS

ISPE Biopharmaceutical Manufacturing Conference
5 – 7 December | San Francisco, CA

2017 EVENTS

ISPE Aseptic Conference
7 – 8 March | Reston, VA

ISPE Europe Annual Conference
3 – 6 April | Barcelona, Spain

ISPE Quality Culture Conference
25 – 26 April | Bethesda, MD

Data Integrity Workshop
4 June | Arlington, VA

ISPE/FDA Quality Manufacturing Conference
5 – 7 June | Arlington, VA

ISPE Process Validation/Process Validation Statistics Conferences
12 – 15 September | Bethesda, MD

ISPE Europe Conference on Biotechnology
26 – 27 September | Dublin, Ireland

ISPE Annual Meeting & Expo
29 October – 1 November | San Diego, CA

ISPE Biopharmaceutical Manufacturing Conference
4 – 6 December | San Francisco, CA

www.ISPE.org/Events

FDA Microbiological Policy from the Podium: Formal Guidance Is Overdue

Susan Berlam

Susan Berlam is Senior Director, Global Chemistry, Manufacture & Controls, Pfizer Worldwide Research & Development. She received her BS in pharmacy from the University of Rhode Island and MS in regulatory affairs from Temple University, Philadelphia, Pennsylvania. A registered pharmacist in Rhode Island, she has 32 years of industry experience, working initially in drug product development, sterile drug product manufacturing, and quality assurance. Over the last 11 years she has worked in regulatory CMC leading a team responsible for the registration of numerous NDA and ANDA products worldwide. She has been an ISPE Member since 2007.

In recent years, the US Food and Drug Administration (FDA) has taken greater interest in the control of several microbiological aspects of drug products. The agency has shared its concerns in the form of published articles, podium presentations, and formal information requests during the review of New Drug Applications (NDAs). It has not, however, developed a guideline reflecting the position it appears to have adopted.

While regulatory expectations regarding microbiological purity of pharmaceutical products have continue to evolve, the absence of FDA guidance is generating confusion and inconsistency. In addition, the putative FDA position would benefit from statutory adherence to Code of Federal Regulations (CFR), Title 21, Section 10.115: "Good Guidance Practices," which stipulates the agency's policies and procedures for developing, issuing, and using guidance documents to communicate FDA regulatory expectations.

Two specific regulatory expectations for which the FDA has been issuing industry commitments are 1) establishing in-use hold times for unpreserved sterile products following preparation for administration and 2) detection and control of *Burkholderia cepacia* complex (BCC) in nonsterile aqueous drug products.

In 2009, FDA review microbiologist John Metcalfe summarized the requisite information an applicant should provide in an NDA to justify in-use hold times and conditions for aseptic products.[1] At the American Association of Pharmaceutical Scientists Chemistry, Manufacturing, and Controls Focus Group face-to-face meeting on 4 June 2015, the FDA stated that adherence to the Metcalfe approach was expected and that the agency does not intend to publish any additional guidance on this topic.[2] This message was reiterated at the FDA Small Business and Industry Assistance Regulatory Education for Industry conference held 27–28 September 2016.[3]

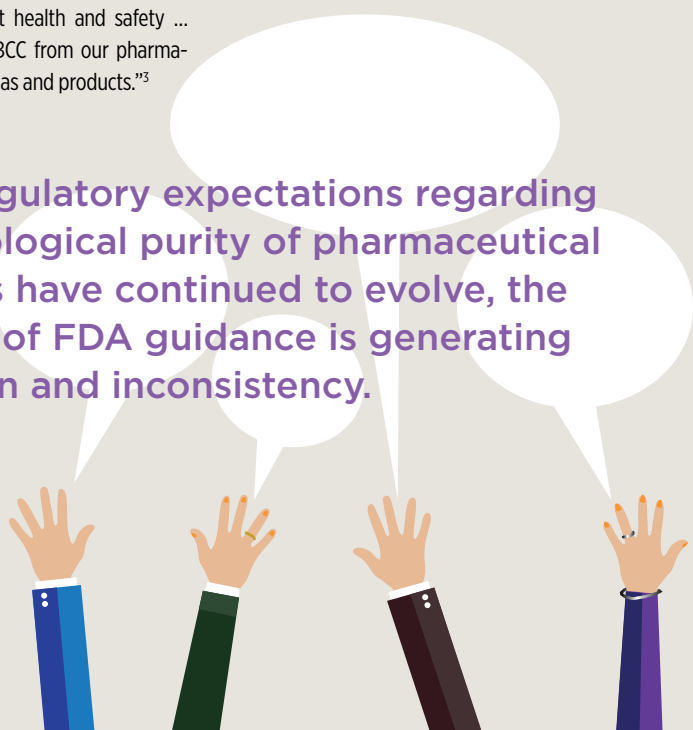
In a follow-up conversation, when asked why this topic was not part of a guidance document, Metcalfe indicated that the regulatory expectation is well established and therefore a formal guidance is not needed. Representatives from other companies, however, have indicated that this expectation is not widely known. On several occasions sponsors have been surprised by the agency's request during marketing application review.

The FDA has also emphasized the need to demonstrate control of BCC in nonsterile aqueous drug products. In 2011, the *PDA Journal of Pharmaceutical Science and Technology* published "*Burkholderia cepacia*: This Decision Is Overdue." The authors, among them FDA representatives, contended that "BCC organisms pose a clear and present danger to patient health and safety … now is the time remove BCC from our pharmaceutical manufacturing areas and products."[3]

BCC contamination has been implicated in drug product recalls for a variety of drug product types—including oral liquids and topical preparations—over the past several years. As a result, the FDA has increased its vigilance regarding BCC control. In 2016, the FDA stated in three presentations at its July and September SBIA Regulatory Education for Industry conferences[3,5,6] that BCC should be controlled in all aqueous drug products.

From these podium presentations, it doesn't appear that the FDA has any appetite to consider GMP controls and/or alternative control strategies based on science and risk. Instead, the agency believes that control of BCC should be included in the release specification for all aqueous nonsterile products.

While regulatory expectations regarding microbiological purity of pharmaceutical products have continued to evolve, the absence of FDA guidance is generating confusion and inconsistency.



FDA presenters admitted that no compendial requirement or standard test method was available to test and control this organism. In addition, they acknowledged the technical difficulties required to develop an appropriately specific method for this organism. Metcalfe confirmed that control of BCC would be the focus of an FDA white paper that will be published by the end of 2016. He indicated, however, that there were no plans to address this topic in a formal guidance document.

The FDA is clearly concerned with emerging sources of microbial contamination and their potential effect on patient safety. The agency's obligation to bring these concerns to the industry is unequivocal. The industry believes, however, that the FDA should develop appropriate regulatory guidance to encourage consistent understanding and adherence. In accordance with 21 CFR Sec. 10.115(e), the FDA should adopt guidance documents to communicate new agency policy or a new regulatory approach.

When the agency uses alternative, informal mechanisms to communicate current regulatory expectations to the industry, product manufacturers, patients, and the public receive mixed messages. "Podium policy" and obscure publications that disseminate microbiological regulatory expectations are ineffective and frequently lead to inconsistent and nonscientific justifiable application and interpretation. Issuing a draft guideline that articulates FDA concerns and recommendations for subsequent dialog is in the best interest of the industry and patients. ■

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Have a point of view you would like to share? Let yourself be heard! Send your submission to amdigiorgio@ispe.org

Medreich Limited's Cutting-Edge Automation System is a First in India

Producing nine billion tablets and capsules a year is almost always a time- and resource-intensive process. Manufacturing employees must often spend time moving raw materials to manufacturing or taking packaged materials to storage instead of focusing on their core responsibilities. To resolve these issues, India's Medreich Limited adopted a unique and innovative approach to material storage and retrieval at its new facility in Bangalore.

Formed in 1976, Medreich is a fully integrated pharmaceutical company with an established global presence. Its client base spans 55 countries and includes a who's who of multinational pharmaceutical firms. The company manufactures and markets products for therapeutic categories that include cardiovascular, diabetic, antifungal, penicillin, respiratory, and many others.

The company has seven manufacturing facilities in Bangalore and one in Hyderabad. Two sites are dedicated to β-lactam (amoxicillin) formulations, one to cephalosporin. The others, including Unit VII, Medreich's recently completed Bangalore facility, are dedicated to general (nonpenicillin) dosage formulations. Once full production goes online in late 2016, Unit VII will be capable of producing nine billion tablets and capsules annually.

Changing Environment

Recently acquired by Japan's Meiji Holdings Co., Ltd., Medreich has become an important player in the Indian pharmaceutical industry, working with many of the world's best-known companies to serve markets in Europe, Australia, New Zealand, and Africa. As Mr. R. Kedareshwar, Executive Vice President, Engineering & Projects explains, when their existing facilities reached full capacity the company knew they needed to make a change.

"Our present manufacturing requirements for tablets and capsules are being met," he explained, "but as the market is growing and as our business is growing in the coming years, we will need to expand and consolidate."

In addition, both the regulatory agency and the company's customers had begun to demand "zero-defect" quality processes and products. Medreich knew that manufacturers that could meet these expectations would be more sought after in the industry.

Medreich Limited

Project: Medreich Unit VII

Location: Bangalore, India

Project Mission: Build an OSD manufacturing and packaging facility to produce and pack nine billion tablets and capsules per year.

Mr. R. Kedareshwar

In May 2012, with these new requirements in mind, Kedareshwar and the Medreich team members began to explore the feasibility of a greenfield project for a new facility that met the following requirements:

- Entire project to be handled by the Medreich in-house team
- Best possible automation and material handling
- Design for large capacities in three shifts to maximize use of assets
- 100% skilled staff to reduce the risk of even a small lapse or failure
- Vertical materials flow to save on expensive land requirements

Small Footprint

The company had to optimize its land use. "Land is a very precious item in Bangalore," says Kedareshwar, "so we had to use it in an optimal way. It was a major challenge to design a plant with a small footprint."

The new manufacturing facility was designed and built on a mere 3,685 square meters, with enough room left over to build an additional manufacturing facility in the future. Operations are spread over four independent levels, each with four connecting points where materials must be either delivered or picked up: raw material entry, primary material entry, secondary material entry, and packaged goods exiting the facility. In addition, materials are received in the warehouse at three locations and dispatched at two; there are also locations for rejected material delivery and/or retesting. In all, there are 24 locations involving material movement.

In a typical factory setup, Kedareshwar explains, material movement is resource intensive. "It is quite challenging for a manufacturing person to move materials from the warehouse to manufacturing or from manufacturing to the warehouse. In the manufacturing area, the team usually spends a lot of time in supportive activities like arranging the raw materials and taking packaged goods from manufacturing to storage. Our aim was to minimize the time required for these supportive activities so that personnel can focus on the manufacturing operations and improve the quality of the product or concentrate on other aspects of the manufacturing process."

Medreich Limited adopted a unique and innovative approach to material storage and retrieval at its new facility in Bangalore

Front view of administrative block

Automated Storage and Retrieval System

With these challenges in mind, the Medreich team decided to connect all locations in the new facility's manufacturing and warehouse areas via a fully integrated automated storage and retrieval system (ASRS). "ASRS are available in several manufacturing facilities, but in this plant we connected the system into our manufacturing operations with a network of conveyors and automated lifts," says Kedareshwar.

"When a person in the manufacturing area makes a request on a computer, the material will be picked up from the warehouse and delivered to that particular location and that particular floor. That gives a great relief to the manufacturing personnel from the supportive activities." This is especially helpful during evening or night shifts, when fewer staff may be available and moving materials across the plant becomes more challenging.

Integrated granulation line

More Efficient Labeling

To ensure optimal functioning and reduce the amount of time spent on support activities, the Medreich team also devised a more efficient and effective labeling scheme for all materials moving through the facility.

In most pharmaceutical manufacturing plants, colored labels are applied to containers depending on where the material is to be moved (e.g., quarantine, approved, rejected). "These operations can be quite complex when you're talking about nine billion capsules and tablets, which demands 400 pallets of transfer each day," says Kedareshwar. "They are also prone to errors when you have to apply labels, remove labels, and change labels. If any mistake happens, it is disastrous. So we removed all of these labels and use only one universal label. Once the material moves into the warehouse, the label is not changed; only a barcode is added and tracked. The status of the material is then always known on the system."

Interior view of warehouse ASRS area

The decision to integrate the ASRS in both the warehouse and manufacturing areas was not only a logistical challenge, but a software challenge as well. Distinct software packages—SAP, software for the weighing machines, in-boarding documents from the vendor—had to be combined and integrated so that each program could communicate with the others and provide users with complete product information at all times.

Quality control lab

Noting that Medreich left room for an additional facility on the available land, Kedareshwar confirms that he could certainly envision using ASRS in the new facility.

Regulatory Approval

A major challenge for Kedareshwar and his team was receiving approval from the Indian regulatory authorities, who had to be convinced that straying from the traditional labeling and segregated storage methods would provide superior results.

"We are removing the present labeling system and are going to a single white-colored label with the barcode," says Kedareshwar. "It was a challenge for us to get it accepted by the Indian regulatory authorities, but after explaining the entire system and having seen all the verification systems, they were quite convinced. They have gone through the system and they approved the facility. This was a major challenge for us, because we are going away from the conventional system in India, where there are very few automated storage systems."

The Unit VII project was finished on budget in the stipulated time of 24 months. The facility and product validations were completed successfully, with necessary approvals from the state government of Karnataka, Drugs Control Department. Initial validation batches showed that the process was efficient and effective, and that the facility's intended objectives had been met.

Perspective

Looking back on the project, Kedareshwar is proud of how employees have reacted, and pleased with the efficiency of the facility. "Employee morale is quite high because they have the opportunity to work in the most modern plant with a very high level of automation," he says. "If we were to do things in the regular way, we would have to employ at least 80 to 100 people in the warehouse operations, but with this type of operation our staff will be reduced to a maximum of 20 people.

"The major thing is that we avoided errors due to manual handling, which is always a major concern in the pharmaceutical industry. That is totally eliminated because the entire material transfer is tracked by the barcode label. And that is a major point for us: At nine billion capsules and tablets, to operate error free is a very challenging job." ■

—Mike McGrath

LETZNER
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My Letter to 40-Year-Old Me

Ten years in the future

Dear Robert,

It's great to see that you are still having a lot of fun and living life to its fullest. I hope that whenever things get out of hand you remember that you will always be able to get through it. Remember all those people you met at ISPE, who are always thriving, full of energy, and being part of the change to deliver faster and better quality medicines to the people who need them the most.

Wow! It's amazing to see how the European Medicines Agency was able to work with all its stakeholders to implement serialization successfully across all of its countries. Ten years ago it was hard to believe this would happen, since many countries in Europe were going through sociopolitical challenges. But this proves what people can achieve when they work together to provide the best for the patient.

In 2026 the world is even more interconnected and challenges seem even bigger than they did 10 years ago

It's also nice to see that topics like facility of the future, workforce of the future, and data integrity are now part of daily life in pharmaceutical manufacturing.

Brody Stara

I'm glad to see that ISPE training has evolved to provide full immersive virtual reality and augmented reality scenarios for GMP inspections. This is necessary, because although we managed to simplify inspections through mutual recognition agreements and the work of the International Conference on Harmonisation, the laws have become increasingly complex. We can use simulations to study data integrity issues in manufacturing, too, with courses for all levels of the workforce, from the shop floor to management.

I'm really proud that industry innovations have drastically reduced the amount of paper we generate when working in GMP. Electronic documentation is now widely accepted during inspections and audits. It's also amazing to see that personalized medicine is a given, through full automation integration and single-use technology.

When I first joined ISPE Young Professionals more than 10 years ago, we made it our mission to do everything possible to deliver faster and better quality medicines. After my time as the Global YP Chair, two amazing young professionals Brody Stara (Amgen, Boston, USA) and Caroline Rocks (Mylan, Ireland) took over. Thanks to their work, it is now possible for young professionals across the world to collaborate on a daily basis, building their leadership skills to be the force of change in their generation.

Caroline Rocks

Robert, in 2026 the world is even more interconnected and challenges seem even bigger than they did 10 years ago. I recommend you continue to work on the challenges you see arising in your industry. Try to do the impossible, and don't worry—you will always win or learn something new.

Have fun.
Robert

Note: The idea for this column came from Richard Branson, founder of Virgin Group, who wrote letters to "10-Year-Old Me," "25-Year-Old Me," "50-Year-Old Me," and "65-Year-Old Me" on his personal blog.

New in 2017

Many thanks to Robert Landertinger for his perspective, thoughts, and contributions to Pharmaceutical Engineering over the past year.

In 2017, "YP State of Mind" will be penned by the Committee's two new Chairs: Brody Stara, Engineer at Amgen, and Caroline Rocks, Senior Process Engineer at Mylan Ireland. Watch for their first column in the January–February issue.

—ISPE Publications Team

Robert W. Landertinger Forero is Chair of the ISPE Young Professionals Committee and a core team member of the Drug Shortages Initiative team. Fluent in 5 languages (German, Portuguese, Spanish, French and English) Robert is an invited speaker in countries like Mexico, Ireland, China, the USA, and Germany. He has written for or been covered by *Pharmaceutical Engineering*, *BioPharma-Reporter*, and other publications.

Meet Young Professional Caroline Rocks

It's a question debated by many young professionals: Is it better to build a career by growing through the ranks with a single employer, or is working for several organizations a faster route to career advancement?

Irish young professional Caroline Rocks, 32, chose the latter route. Given the experience and success she's achieved, it's difficult to argue with her choice. A senior process engineer for Mylan Global Strategic Manufacturing as well as a university lecturer, she is also a founding member of the ISPE Ireland Young Professionals Committee, recently completing her term as Chair. In September of this year she was named Co-Chair of ISPE International Young Professionals.

Caroline first considered a career in the pharmaceutical industry when her chemistry teacher told her that biotechnology was the next frontier in science and engineering. "Her advice definitely influenced my decision to go into this industry, and in hindsight she was more than right," says Caroline.

Early Career

She began a four-year bachelor's degree in chemical engineering at University College Dublin, where she earned first-class honors and a summer internship at Pfizer's Grange Castle biotech campus in Dublin. "That was the first time I got to see process equipment and cleanrooms," she explains. "The facility was brand new and state of the art and I really loved it."

After completing her degree in 2006, Caroline accepted a position as a junior process engineer at Jacobs, a consulting firm. There she joined a team of architects and engineers designing new pharmaceutical facilities and modifying existing ones. During her four-year stint at Jacobs, she became involved in two larger projects, one at Wyeth (now Pfizer) and another at Genzyme.

The Genzyme project, a new fill-finish facility for biologics, motivated Caroline to get her master's degree in biopharmaceutical engineering.

Caroline Rocks

"I wanted to become an SME specifically in the field of biopharmaceuticals," she says.

She completed her master's degree part-time at University College Dublin in 2010, once again earning first-class honors.

Another Side of the Industry

After four years of consulting, Caroline moved to the client side in 2010 and began to work directly for manufacturing companies. "Looking back, it was a bit of a risk. Ireland was in a recession, but at the time I was really keen to diversify my experience and see another side of the business," she says.

Over the next four years, she worked for Rottapharm-Madaus (now Meda), Pfizer, APC, and Bristol-Myers Squibb before taking her current position at Mylan.

"I was really fortunate, because by undertaking contract work I gained a lot of exposure in a short amount of time at facilities of varying scale, age, and process types," she explained. "I know it is often debated whether it's a good thing or a bad thing to show lots of job changes on your CV, but I was convinced that it was a good thing to do while I was a junior engineer and still in my twenties.

"I was keen to learn from lots of different people, lots of companies, and lots of facilities and product," she continued. "It was the best way for me to fast-track my development and figure out what I wanted to do long-term in my career. But before I turned 30, I decided it was time to grow within one company, so I applied for a job with Mylan, and I'm still with them today. I now work on projects in Mylan's worldwide portfolio, working in different regions and cultures. This has greatly expanded my professional and personal experience."

Helping ISPE Ireland Grow

Caroline joined ISPE after attending a young professionals' seminar in 2013. "I didn't know about ISPE when I first graduated out of college," she says. "My manager at Jacobs was a long-time committee member for the Ireland Affiliate, and they were organizing their first YP-focused event. He asked me to be one of the speakers because it was a boot camp on commissioning and qualification and I was working in that area at the time."

ISPE International YP Chair Robert Landertinger was also in attendance. "He spoke about the benefits of ISPE and encouraged us to start a YP group in Ireland," she says. "He put me in touch with three other people and we became the four founding members of the Ireland YPs."

With Caroline as its first Chair, the Ireland YP committee has grown from four to 20 members, representing 16 companies, and has held multiple events across Ireland. "This year we are implementing a strategy to reach out to students in Ireland so that they can get the benefits of being part of ISPE before even starting their career," she says.

Looking Ahead

Caroline intends to continue expanding her experiences within the industry. "I've been involved in the product life cycle from concept engineering to CQV," she says, "but there's a whole other part of that cycle from clinical phase all the way to commercialization that I am interested in seeing. This is the major goal I have over the next few years."

Caroline intends to continue lecturing, and says she wants to stay involved in ISPE, as well. "I finished up as Ireland YP Chair this year and I am now the Co-Chair of the International YPs. In 2017, Ireland will host the ISPE biotech conference for the first time, so I look forward to being involved in some way as well," she concludes. ■

—Mike McGrath

Making the Connection

David G. Smith

David G. Smith is Principle Recruiting Partner for Biogen's manufacturing, manufacturing sciences and quality organizations in the United Sates.

Here's a question I get often:

I've been trying to connect with industry professionals to arrange informational interviews, but I seem to be striking out. What might I be doing wrong?

I commend you for trying to gain a better understanding of your career path. Informational interviews can provide critical information for modeling your job search and career development. Your challenge is a common one, however. Before reaching out to a potential networking contact, I suggest that you keep the following points in mind:

Keep the time short

Valuable networking contacts tend to have very full schedules, and they guard their time closely. Offering to buy lunch off-site might seem like a nice gesture, but it would require your contact to take as much as two hours out of their day to travel, park, and drive back—on top of the meeting time. Make the time commitment you request as small as possible. You might suggest finding time to talk at an event you are both already scheduled to attend, or ask if they would be willing to meet for coffee or on the way to work. Video meetings (i.e., FaceTime, Skype) could be a good alternative if you can't find time to meet in person.

Try to be introduced

A recommendation or introduction from a trusted colleague can go a long way toward opening a door. Before making contact, see if you are connected in some way to the individual you want to meet. Verify the relationship and ensure that the introduction will come from someone that the contact would know, respect, and trust.

Talk to the right person

Do your research before you request a meeting with someone you don't know. Review their LinkedIn profile to ensure they can provide the advice you seek. See if their biography is posted on the company website or with organizations to which they belong. See if you have any interests in common, and note that in your request.

Reciprocate their generosity

Networking is a two-way street. To increase your chance of getting something you want, you should be able to offer something in return. Many candidates underestimate the value of what they could offer a potential contact. Since industry professionals are busy, many might find value in the latest news about his or her area of expertise, advance notice of an upcoming industry talk/event, or even a recap of an event they were unable to attend.

Use a proven template

Like many people in the industry, I often receive requests for career assistance. Here are a couple of creative examples that led to some good conversations:

Hi David,
I see you are a fellow member of ISPE. I am on our Affiliate's Young Professionals committee, and I would like to invite you to attend [event title] which will take place at [date, time, location]. We are expecting a great discussion, and given my research, I know the membership would appreciate the opportunity to learn more about you and your organization. I have attached our advertisement for the event, and I'd be glad to help you register and provide answers to any questions you may have. Would you have a few minutes to discuss by phone soon? I would be happy to accommodate your busy schedule.
I look forward to hearing from you.

Sincerely,
John Doe

Hi David,
I am a senior engineering student at [university name]. I am finishing my senior design project, which focuses on next-generation bioreactor design. Given your role with [name] company, I thought you might be interested in the results of our project. I have attached a brief overview for your review. Would you be willing to allow me to present and discuss our process and results from our work? Please let me know what day and time would be convenient for you, and I will make arrangements to work around your schedule and preferred location.

All the best,
Jane Doe

If you don't hear back right away, don't give up—follow up

Follow up, and be pleasantly persistent

If you don't hear back right away, don't give up—follow up. Sometimes this is more important than the initial request; it's an opportunity to show that the meeting is truly important to you. After a week, send a second message and ask politely if your contact has had a chance to read your previous email. Limit your follow-ups to a one per week until you've heard a response. Don't assume they're not interested. You never know what might be preventing their response, and it's your responsibility to continue to follow up as politely and as enthusiastically as possible. ■

I hope you find these tips helpful. Send me your career questions at david.g.smith@biogen.com. I look forward to answering them in a future column.

ISPE's Australasia Affiliate: Dealing with Geographic Isolation

The pharmaceutical industry in Australia and New Zealand is in an interesting position. On the one hand, both countries are somewhat isolated, yet on the other hand, they are on the doorstep of the lucrative Asian markets. Those challenges and benefits are reflected in ISPE's Australasia Affiliate, which covers both Australia and New Zealand. While serving such a broad geographic area presents many challenges, the Affiliate enters its twentieth year with a lot of optimism.

Dr. Benjamin Sauer

The Australia and New Zealand pharmaceutical industries comprise a full range of organizations, from biomedical research, biotechnology firms, originator and generic medicines companies to service-related segments like wholesaling and distribution. This includes solid oral dose, parenteral injectables, creams, emulsions and suspensions, vet pharma, and radiopharmaceuticals.

"We have a number of multinational pharmaceutical companies, some with existing manufacturing, like AstraZeneca, Pfizer, and GSK, and some with distribution supply, like Merck, Boston Group, and others," explains Benjamin Sauer, Vice President of the ISPE Australasia Affiliate and National Operations Manager, Global Medical Solutions, Australia. "There are a lot of small- to medium-tier and smaller niche manufacturers as well."

In Australia alone, pharmaceutical exports reached $3.9 billion in 2012–2013, making it one of Australia's major high-tech industries; overall turnover for the pharmaceutical sector represented $23.4 billion in 2012–2013.[1-3]

With a combined population of close to 28 million people—23.2 million in Australia and 4.5 million in New Zealand—it is an attractive region both as a domestic market for pharmaceuticals and as a source for expertise. In Australia, the industry employed approximately 16,500 people in manufacturing and spent $404 million on pharmaceutical manufacturing R&D in 2011–2012. Sales of complementary medicines are worth around $2 billion a year.[4]

ISPE's History in Australasia

ISPE's introduction to Australasia came in 1994 with a joint regulatory conference of US Food and Drug Administration and Australia's Therapeutic Goods Administration speakers held in Australia's capital, Canberra. The event was arranged by ISPE International along with local members, including one of the Affiliate's first Directors, Bruce Moon.

This first meeting generated a lot of interest, and periodic meetings continued while arrangements were made to establish a legal entity in Australia that also met ISPE International's requirements for an Affiliate under the International Charter.

The International Society for Pharmaceutical Engineering (Australasian Division) Limited was officially registered in Australia in 1997. The original charter envisaged chapters in Australia and New Zealand. Bruce Moon was a key figure in the operation of the Affiliate, particularly in the early years. As membership coordinator, he regularly attended Annual Meetings in the United States. Moon played a very active role with the Affiliate until his retirement in 2006. In 2007, he was recognized for his service to ISPE with the Richard D. Purdy Distinguished Achievement Award.

While Membership levels have remained relatively steady through the years, typically running in the 300–400 range, Sauer acknowledges that the Affiliate has seen two significant periods of contraction. The first was in 2008–2009, when a series of pharma company mergers and consolidations was accompanied by significant downsizing and site closures in Australia and New Zealand. The second resulted from the global financial crisis. Current membership sits just shy of 300 members.

As envisioned in the original charter, the Affiliate now has five Chapters, each centered near the larger cities:

- New South Wales (Sydney)
- Victoria (Melbourne)
- Queensland (Brisbane)
- South Australia (Adelaide)
- New Zealand

These regions are home to many pharmaceutical companies. "Both Sydney and Melbourne have very high-density big pharma," says Sauer. "South Australia has got Pfizer and other large companies and Brisbane is developing, so there are a lot of new companies there." New Zealand also features many of the world's better-known pharma companies.

In Australia alone, pharmaceutical exports reached $3.9 billion in 2012–2013, making it one of Australia's major high-tech industries

In addition to the five Chapters, the Affiliate also sponsors Student Chapters at University of Adelaide and previously at Swinburne University, located in Melbourne.

Geographic Challenges

"Coming back from the Annual Meeting, it was good to hear the challenges that the other Affiliates and Chapters are having. Some of them are similar and some are different," says Sauer. "For us, our challenges are our isolation from everyone else and our broad geographic reach."

Indeed, travel to locations in the Asia–Pacific region such as Singapore requires an eight-hour flight. Flights from Sydney to London, England, or to New York take more than 22 hours and require at least one stop. The time zone differences make things difficult, as well. Sydney, for example, is three hours ahead of Singapore, 10 hours ahead of Europe, and 15 hours ahead of eastern North America.

Even within the Affiliate's own region, distance is a challenge. From the east to west in Australia—Sydney to Perth—is a five-hour flight and a three-hour time difference. The longest distance, from Auckland, New Zealand, to Perth requires a seven-hour flight with a five-hour time difference.

"Comparatively, a place like Boston, where they have a huge amount of members and a close proximity, engaging customers and delivering content can be a little bit easier," says Sauer. "We obviously have those challenges with our broad geographic reach to ensure that we get our customers value. Even trying to get presenters can be challenging, but I think we do that quite well."

Sauer explains that over the last 12 months, the vast majority of the Affiliate's programs were held in Sydney and Melbourne (three to four events each), with two events held in New Zealand, and one event each in Adelaide and Brisbane.

"We are not-for-profit and we're proud of that," says Sauer. The last four years were challenging, he notes, but revenue is now improving. This

Maurice Parlane, 2016 Max Seales Yonker Member of the Year Award recipient

The Australasia Affiliate congratulates Past President Maurice Parlane on being named the 2016 Max Seales Yonker Member of the Year Award winner.

"Maurice has clearly had a lot of impact in his local New Zealand industry and in Australia, but his influence and passion has reached into AsiaPac and as far as the United States."

—Benjamin Sauer, Vice-President, ISPE Australasia Affiliate

allows the Affiliate to provide content and networking opportunities for its Members. "But we need to have some funds to support those events," he continues. "If you have a look at the two-day highly technical events that we run, they cost us between $60,000 and $70,000 apiece. For a smaller affiliate, that is fairly significant and a high risk. So, it takes a highly engaged volunteer to run it."

Indeed, as Sauer confirms, volunteer engagement is shared by Affiliates and Chapters around the world. "It is hard for us to meet face-to-face because our Board Members are all over Australia, and as a not-for-profit, we don't want to spend too much on travel expenses. We do meet face-to-face once a year and have monthly teleconference board meetings."

Key Contacts

Officers

President: Nenad Firez, AMEC Foster Wheeler

Vice-President: Benjamin Sauer, Global Medical Solutions

Treasurer: Tracy Clemmer, Protek Consultants

Secretary: Helen Atkinson, SeerPharma

Past President: Maurice Parlane, New Wayz Consulting

Directors

Shane Bourne, Seqirus Australia

Brett Cole, Biosafety Pty Ltd

Jason Fletcher, CSL Behring

Paul Fletcher, Centre for Biopharmaceutical Excellence

Mark Richards, AstraZenca

Rajesh Shiv, CSL Behring

Romit Singh, Device Technologies

Affiliate Manager

Mandy Bromilow

In addition to the five chapters, the Affiliate also sponsors Student Chapters at University of Adelaide and previously at Swinburne University

Reasons for Optimism

Despite the challenges the Affiliate faces, Sauer is quite confident that they are heading in the right direction. "We may have had a bit of a quiet period, but I think that has definitely changed," he says. "We have already forecast our events for the next year, which is something that we've never done in my time on the Board. We have engaged the customers with surveys, found out what kind of content they want, and are now ensuring that we bring that content with enough notice to give opportunity for people to come. We also recently started providing newsletters and white papers as well."

For 2017, the Affiliate has planned six events, with many being held in multiple locations. The Affiliate is also hoping to leverage stronger relationships with other ISPE Affiliates and Chapters, such as Singapore or Boston. "With the Singapore Affiliate, it is more using our group's weight to attract high-quality speakers," says Sauer. "And with the Boston Chapter, we'd like to leverage some of their online or remote content. We want to get a road show going in the next month or two with a test group to see how it would work. If it goes well, we could run it with the local networking social events as well."

Sauer acknowledges that event revenue is improving as well. "In the last two years we have started to engage sponsors more and have exhibitions at our higher-cost events to help share that risk a little bit better."

Finally, Sauer says the Affiliate plans to focus more on its Student Chapters. "There are only a handful of members at the moment, but we plan to engage them, give them discounted opportunities, and make sure that they know that we're running events to try to keep them engaged," he says. "There are a few universities, and Adelaide is one of them, with relevant content, so we want to ensure that we engage those students and give them the opportunity to network with their peers and maintain their interest in the industry and ISPE." ■

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2017 ISPE Conference on Excellence in Quality Culture and Performance

Powerful Tools to Shape Quality Excellence

The influence of an organization's quality culture in delivering the outcomes that matter to the patient has emerged as a key enabler from the recent public discourse on measuring performance and quality metrics.

Cultural excellence requires that all employees be passionate about eliminating mistakes by making quality their driving principle. This goes beyond following the content of quality policies and procedures to create an environment focused on continuous improvement and learning.

By examining the powerful force that culture exerts on day-to-day operations within organizations, ISPE's Quality Culture Team have established that although for many the concept of quality culture remains abstract, the behavioral impact is very real indeed.

ISPE are therefore delighted to announce the 2017 ISPE Conference on Excellence in Quality Culture and Performance to be held in Bethesda, Maryland, 25–26 April 2017. The conference will coincide with the publication of the ISPE Cultural Excellence report, a collection of practical powerful tools that outlines a comprehensive behavior-based approach to improving quality culture as a means of delivering enhanced quality outcomes.

At the conference you will learn from industry peers through case studies and the sharing of best practice:

- How to implement the practical approaches and tools compiled in the Cultural Excellence report
- How industry leaders can contribute to and help shape quality culture
- Which best practices enable a collective mindset to drive toward improving quality
- Gemba's key role in coaching and mentoring the desired attitudes and behaviors
- How to use a practical new tool to target and measure behavior that matter
- Which best practices are required for effective management oversight and review
- What critical enablers are necessary to build and sustain a culture of excellence

Mark your calendars now—more information will be shared via www.ispe.org/events and the iSPEAK blog as it becomes available.

PHARMACEUTICAL ENGINEERING®

Quarterly Report

QUALITY CULTURE

November-December 2016

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In this section

Introduction

Nuala Calnan, PhD

In the January/February 2016 edition of *Pharmaceutical Engineering*, the ISPE Quality Culture Team presented its "Six Dimensions of Cultural Excellence" framework in an article entitled "Cultural Excellence: Ensuring that 'Culture of Quality' Is More Than Just a Slogan."[1] During a presentation at ISPE's recent Annual Meeting in Atlanta, Georgia, Team Co-Lead Nuala Calnan, PhD, confirmed ISPE's commitment to publish a comprehensive report on cultural excellence in 2017.

The report will share insights on quality culture improvement across the six dimensions and outline work this team has undertaken to develop a series of approaches, practices, and tools to support industry implementation of this framework, as well as promote behavioral change to benefit the patient. In addition, ISPE will host the 2017 ISPE Conference on Excellence in Quality Culture and Performance: Powerful Tools to Shape Quality Excellence from 25–26 April 2017 in Bethesda, Maryland. Information will be shared via www.ispe.org/events and the iSPEAK blog as it becomes available.

In this Quarterly Report on Quality Culture, three of the six Dimensions of Cultural Excellence subteam leads share some of their work in advance of the final report. This section includes articles from the Leadership & Vision, Gemba Walks, and Leading Quality Indicators subteams.

Finally, quality culture improvement has emerged within the context of the industry discussions arising from the FDA's draft guidance and proposed metrics set. This quarterly report announces an exciting new research program on pharmaceutical manufacturing quality metrics that FDA has embarked upon with the Pharmaceutical Operational Excellence Benchmarking team at St. Gallen University, Switzerland, under the leadership of Professor Thomas Friedli.

ISPE plans to publish a comprehensive report on cultural excellence in 2017

Shaping Excellence

How Leader Actions and Behaviors Influence Quality Culture

Erika Ballman

In ISPE's Six Dimensions of Cultural Excellence framework, the first dimension addresses leadership and vision, and explores the leader's role in defining, achieving, and sustaining cultural excellence in pharmaceutical manufacturing.

In this article, Erika Ballman, lead of the Leadership & Vision subteam, describes the process her team used to find shared leadership traits, behaviors, and actions attributable to positive culture. This year the team embarked on a series of groundbreaking "Shaping Excellence" interviews with senior quality leaders from across the pharmaceutical and medical technology industries. A summary of the team's findings was first introduced at the 2016 ISPE/FDA/PQRI Quality Manufacturing Conference in June 2016. Here, a more comprehensive range of leader insights are shared.

The Importance of Quality Culture

The degree to which quality is embedded in an organization's culture can mean the difference between success and failure.[1]

—François Sallans, Johnson & Johnson

The relationship between corporate quality culture and operational excellence continues to be actively explored. Indeed, ISPE's Quality Metrics Pilot Program Wave 2 findings, presented in June 2016, indicate a statistically significant correlation between the quality culture survey results and the performance metrics of right first time, deviation recurrence rate, and recalls.[2]

It is logical that companies benefit when they emphasize excellence in the way their work is performed, but is a corporate culture of excellence or "quality culture" substantive enough to be communicated or measurable in a way that can be improved? Moreover, how do industry leaders contribute to and help shape quality culture? Are there best practices that can assist and enable a collective mindset to drive toward improving quality?

The ISPE Quality Culture team, co-led by Matt Pearson, Senior Director, Genentech, a member of the Roche Group, and Nuala Calnan, PhD, Dublin Institute of Technology, asks these questions in an ongoing effort to develop practical approaches, practices, and tools the pharmaceutical industry can use to assess and improve cultural excellence. The Quality Culture team's road map is the cultural excellence framework, which consists of six dimensions that are integrated yet studied independently for their impact on quality culture (Figure 1).[3]

Figure 1: The six dimensions of cultural excellence

"Shaping Excellence" Interviews

The role of leadership in fostering and developing a vision of quality forms the starting point of the Six Dimensions framework.[3]

—Nuala Calnan, Dublin Institute of Technology

The Leadership & Vision (L&V) subteam focuses on establishing and engendering a vision of quality through leader-led behavior.

Consisting of ISPE members from different pharmaceutical companies and sectors, the L&V subteam developed an ambitious research concept to explore best practice leader-led behavior and ask valued leaders to comment on cultural excellence to find commonalities. Through one-on-one interviews, intended to be conversational and informal, industry-respected leaders shared what they believe are the most important actions and behaviors can leaders take to shape quality culture.

Over several weeks in spring 2016, 19 industry leaders representing various industry sectors and geographical regions were interviewed, guided by questions developed by the L&V subteam. These leaders also represented executive levels (vice president, global head, senior director) of corporate leadership, collectively contributing hundreds of years of shared industry leadership experience. These interviews gave the L&V subteam key insights into shared thoughts and unique perspectives, and produced a research data set that included over 18 hours of audio files with more than 125 transcript pages.

Figure 2 outlines the demographics of the leaders and their organizations.

Defining a Culture of Excellence

Leaders were first asked: "How do you define a culture of excellence? What do you look for? What do you measure?"

There is a bottom-up and a top-down connection. It comes very much from the behaviors, that the behaviors are correct. There is strong support from senior management, but at the same time there is a high level of engagement at the shop floor level.

—Joseph P. Murphy, Roche Ireland Ltd.

Employee and employer have a mutually beneficial relationship that allows the individual to feel like he or she is performing and contributing at their best. It is a win-win situation.

—Allen Napetian, Genentech, a member of the Roche Group

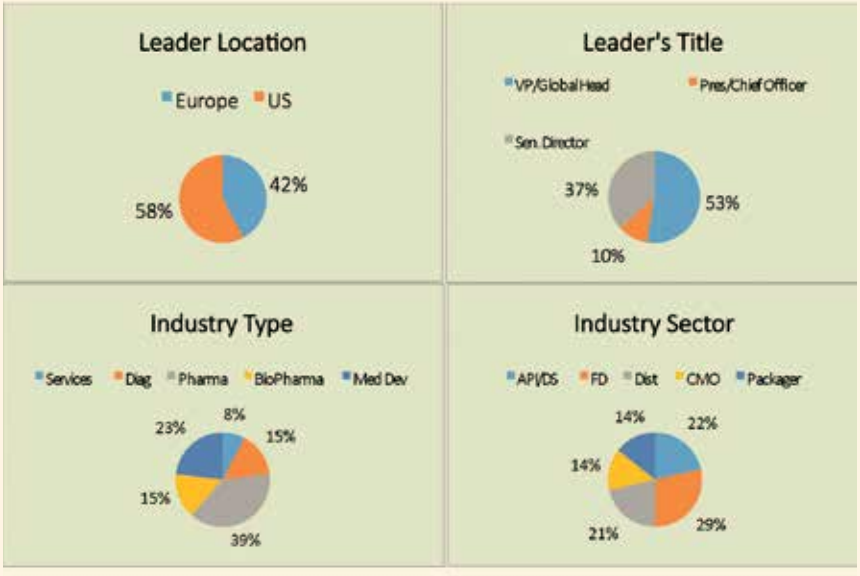
The organization's purpose and the principles govern not only the work we do but how we engage with each other. In terms of a culture of excellence, I look for clarity in principles and purpose, and I look for it to drive the work and shape the experiences that we have.

—Mike Vallender, Emergent BioSolutions

Clear themes emerged in response to these opening questions related to the organizational environment, leaders, and employees:

- The organization has a sense of purpose in which employees are elevated beyond themselves.
- Leaders and employees are engaged and have the right mindset about product quality, service, and patient safety.
- An emphasis on quality drives predictable and improved outcomes, and not solely compliance expectations.
- Leaders articulate clear goals and model their expectations.
- Employees understand the organization's purpose, goals, and expectations and are self-motivated to reach them.

Figure 2. Leader demographics (n = 19)



A clear vision enables those in the organization to see how their roles fit into a bigger picture so they can work in alignment with the overall corporate goals

- The organization promotes continuous improvement and constant learning through words and actions.
- Leaders and employees demonstrate behaviors that enable and drive business success.
- Employees recognize the importance and value of their work product.
- When problems arise, there is a focus on problem-solving, not finger-pointing.

A corporate culture espousing these ideals would prove equally beneficial for companies, regulators, employees, and patients, but how can it be achieved? Furthermore, how can it be sustained? We examined the industry leaders' responses to determine how we might shape this type of culture.

Leader 5Vs

When considering the role of the leader in influencing culture, it is critically important to focus on behavior and actions. Interviewed leaders acknowledged the key role these two elements have in the site and company culture.

There was no mention of external forces—no "silver bullet" solutions—but an implicit and internal attitude, shaped by the leaders' focus and demonstrated commitment to excellence. While leaders must set the tone and vision and provide enabling tools, there was broad agreement that cultural excellence cannot be achieved without an engaged and motivated workforce. It is not sustained, however, without the support of leadership and an ongoing investment in people, improvements, facilities, new capabilities, and quality and business systems.

Figure 3: 5Vs of leader influence

It emerged that leading with "head, heart, and hands" requires connections between technical ability, emotional intelligence, and principle-based values. Based on the findings and insights gained, the team created a well-rounded leader model entitled the "Leader 5Vs" (Figure 3) that are associated with positive leader influence on quality culture.

The 5V categories are:

- **Vision:** Strategy, unifying goals, game plan, company mantra or credo, the desired state
- **Values:** Guiding principles, ethical conduct and expectation, humility, empathy, patient focus
- **Voice:** Passion, credibility, authenticity, and clarity, as well as the ability to articulate the vision, and inspire and motivate others
- **Vigilance:** Ability to drive accountability, determination, grit, focus, discipline, and follow-through
- **Visibility:** Leader presence, what he/she gives priority/time to, what he/she reacts and responds to

On vision

To be effective, the vision is to be communicated, understood, and acted upon by every employee and external business partner, including suppliers and contractors.[1]

—François Sallans

The Johnson & Johnson credo[4] is a renowned example of vision, as it is the foundation on which all decisions and actions regarding quality are made within the company. Another example of a strong vision is from Emergent BioSolutions: "Protect and enhance 50 million lives by 2025." This communicates the importance the company places on patient safety.

A clear vision enables those in the organization to see how their roles fit into a bigger picture so they can work in alignment with the overall corporate goals. A vision that acknowledges quality also enables everyone in the organization to see its importance.

Every action we take should be aligned with and in support of our vision. If there is misalignment, we have to be willing to have the courage to challenge whether we've strayed from our vision or whether it is no longer relevant. Employees will see right through this, and engagement will suffer.

—Allen Napetian

Vision is a critical element of leadership. It is a cornerstone, providing the foundation for the team to build upon. It's important that vision be built in collaboration, allowing all team members to see themselves in it and understand its genesis. It is a critical element in establishing direction from which long-term strategy and planning can be constructed.

—John Pinion, Ultragenyx

Best practices related to vision identified during the leader interviews include:

- Keep the vision consistent: It is detrimental to shift messages too often; it becomes confusing and unclear in the organization.
- Have the determination to ride the cycle of change. Celebrate gains, and work through the setbacks. There will always be those who are resistant to change or see no reason for it.
- Seek ways to share the vision with the organization often; the right message cannot be overcommunicated.
- Ensure that the vision regarding the company's commitment to quality is readily available and can be communicated to all employees by all leaders in the organization.

Leaders must also vigilantly monitor and display key performance metrics to hold the organization accountable to its continuous improvement goals

On values

A common refrain from the interviewed leaders was the central role of integrity. Quality is often described as "doing the right thing when no one is looking"; the personal integrity of both leaders and employees is essential to achieving and maintaining a culture of excellence.

Leader values or "soft skills" such as humility, empathy, and the ability to listen were thought to be highly connected to higher levels of employee engagement, a necessary enabler to a positive culture. Leaders confirmed the importance of modeling desired behaviors and "walking the talk" as it relates to quality systems and standards. This requires that day-to-day decisions be congruent with corporate values.

It's about people. It's how you make them feel. Are you making them feel inspired? Motivated? Full of purpose? Or are you making them feel ignored, small? You've got to define the mission and you've got to have a vision, but it's people who give you your authority as a leader in the first place, so take care of them.

—Chris Bell, Emergent BioSolutions

Courage was also commonly mentioned in leader interviews as an important value. Leaders within organizations must display the courage to make tough calls, innovate, push the envelope, challenge effectively, and break old paradigms. Leaders should also promote an environment that is open to change—where ideas that may help improve site quality are welcomed.

The majority of leaders interviewed believe they have a "speak-up" culture where concerns can be raised and employees feel comfortable doing so. This is viewed as ideal for enabling cultural excellence. Many of the leaders' companies provide anonymous call-in phone lines that allow employees to share concerns confidentially about quality or safety, for example. Some leaders, however, acknowledged that there is danger in assuming the culture is speak-up without verifying this through the employees, metrics, and results.

There's a danger in saying "Of course everyone feels free to speak up." It becomes important for senior leaders to go out, be visible, where the work is being done. If there is a sense of seeing and hearing things for the first time, it's probably an indication that this is not as ingrained in the culture as it should be.

—Conrad Mutschler, Perrigo

On voice

You need messages that are understandable so that everyone can articulate them in his/her own words. This begins with routine and consistent cascades of communication ... a source of information that is understandable and can be interpreted across different leaders and leadership styles.

—Allen Napetian

When a leader articulates a vision, his/her voice and body language must be viewed by the organization as credible and trustworthy. If the leader doesn't believe in the stated vision, however, it can have an unintended opposite effect. The leader must speak authentically to influence the desired behavior most effectively.

On vigilance

Vigilance is necessary to stay the course, put in the hard work, and endure the ups and downs of leading an organization through a journey of cultural improvement. Remaining consistent to the vision is essential.

Leaders must also vigilantly monitor and display key performance metrics to hold the organization accountable to its continuous improvement goals. If you don't measure it, you can't improve it, so understanding the key metrics that drive quality improvement is critical.

Leaders discussed their use of site scorecards, risk-assessment heat maps, and standing management overview meetings, in which quality metrics are periodically reviewed and discussed, often across various operating sites and multiple functional areas.

Leading quality indicators most commonly measured at the leaders' companies are:

- Measurements of process robustness (process capability)
- Corrective and preventive action (CAPA) effectiveness
- CAPA ratio of proactive-to-reactive actions
- Preventive maintenance
- Internal-audit findings and their risk criticality
- Total cost of quality, measured as ratio of prevention vs. remediation cost

More unique considerations for leading quality indicators include measurement of organizational learning, such as the number of green belt and yellow belt certified employees or candidates, as well as other training-related and learning-based metrics.

The majority of leaders interviewed believe they have a "speak-up" culture where concerns can be raised and employees feel comfortable doing so

Most leaders acknowledged, however, that they are most responsive to lagging quality indicators related to the severity of nonconformances and deviations, consumer complaints, and recalls or adverse events. Many indicated a common desire to move their organizations further toward the use of leading quality indicators, like those mentioned, for proactive review and discussion.

Know exactly what it is your organization is doing, what they're experiencing, how they feel about the culture, and what their feedback is and let that drive some of the tactical work that you do to change culture versus taking an "off the shelf" approach ... once you start down the path, continue to get feedback from people. Is this the right thing? Does it resonate with you? That's difficult to do because it requires the leader to be a lot more visible, a lot more engaging than is comfortable to many.

—Mike Vallender

You've got to provide timely feedback. To do that, you've got to be a first-class noticer (to paraphrase Warren Bennis). Pay close attention to how words and behaviors are making people feel in the context of the culture you want. Don't let something slide more than once without giving feedback, and encourage others to do the same.

—Chris Bell

Every meeting, discussion, or email is a potential opportunity to develop our leaders. If we see a behavior or an action that does not model the leadership we are pursuing, we need to take full advantage by responding.

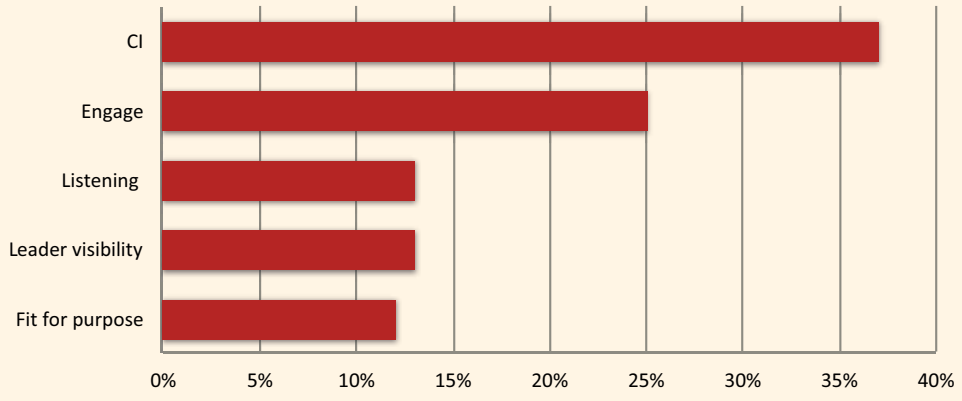
—Steve Steffes, Perrigo

Leader vigilance also involves the periodic monitoring of down-line leaders and the overall organization assessing and reassessing the state of the culture. A commonly used tool is the employee engagement survey, usually conducted every one to two years. This allows employees to share confidential feedback on the organization and leadership. Leaders suggested that conducting this survey over multiple years to see changes and improvements is of most value in "reading" for culture or cultural changes.

On visibility

Quality culture scores related to leadership (coaching, daily dialogue, and management presence on the shop floor) were also demonstrated in the "ISPE Quality Metrics Initiative: Pilot Program Wave 2 Report" as those with the highest correlation to external quality outcomes, emphasizing the importance of leader presence.[2]

Figure 4: Gemba purpose in leader organizations



All interviewed leaders indicated that their companies conduct some level of Gemba activity on the shop floor. The leaders themselves often participate in site walk-throughs, providing an opportunity to interact with employees, front-line supervisors, and area leaders. Gemba was most commonly viewed as a continuous improvement (CI) tool or philosophy (Figure 4).

According to the ISPE Quality Metrics Pilot Program Wave 2 data, the highest range in quality-culture scores were from the "leadership categories" in the areas of Dialog and Gemba, as defined below:[2]

Dialog: *We have daily quality metrics reviews and quality issue discussions on the shop floor.*

Gemba: *Management is on the floor several times a day both for planned meetings and also to observe and contribute to the daily activities.*

—ISPE Survey Questions: Leadership Section[2]

This highlights an opportunity for industry leaders to positively affect these areas with greater leader presence and by holding other leaders accountable for reaching higher levels of visibility.

Everywhere you go, you set up listening posts like town hall meetings or roundtable meetings. You have the ability to get to know and relate to the people of the organization.

—Louis Yu, Valeant Pharmaceuticals International

It became clear that employee attitudes and mindsets can be shaped by leader storytelling and quality testimonials. The leaders interviewed indicated that they hold formal and informal quality-based discussions. These are achieved formally with town hall meetings, standing management review meetings, and corporate quality updates; informal methods include employee-management roundtables, one-on-one meetings with leaders, and plant Gemba walk-throughs. These sessions provide leaders with an opportunity to talk about quality and allow employees at all levels to ask questions. Another critical element of these sessions is that they allow leaders to listen to the quality concerns, issues, and ideas raised by employees at all levels of the organization.

Conclusion

The individual leader's actions and behaviors clearly contribute to site and company culture. Our research has shown that there are commonalities among industry leaders related to behavior, actions, and traits that can aid in employee engagement and the attainment of goals, as well as facilitate a corporate culture of excellence.

For those leading and driving cultural transformation programs, key points to consider include:

- Share a vision that includes the importance of quality frequently and broadly within the organization.
- Demonstrate decision-making and behaviors that align with the stated quality vision and value excellence above sole focus on regulatory compliance.
- Shape employee experiences and mindsets through formal and informal quality discussions where site metrics are reviewed and quality issues can be raised.
- Use Gemba as a best practice activity for the shop floor, laboratories, or other functional areas. Consider Gemba guidelines or checklists to aid the walk-through.
- Develop key site metrics and implement leading quality metrics and proactive measurements to drive continuous improvement.
- Provide structural enablers to support organizational improvement and inspire an environment of continual learning.

Crucially, leaders can challenge their organizations to drive for excellence and create a culture where all benefit. ■

Acknowledgments

The author wishes to acknowledge the esteemed industry leaders who participated in and inspired the work of "Shaping Excellence" as well as ISPE L&V subteam members Kent Brown (Novartis), Thomas Hajduk (Boehringer Ingelheim Germany), Katie Izdebski (Emergent BioSolutions), Ann-Marie Mernin (Johnson & Johnson), and Andrew Mens (Johnson & Johnson).

Gemba Walks in the Pharmaceutical Industry: Best Practices and Recommendations from Real-Life Experiences

Margit Schwalbe-Fehl, PhD

Within ISPE's "Six Dimensions of Cultural Excellence" framework, the third dimension focuses on Gemba and its close links to the leadership dimension as a key engagement and communication tool.

In this article Margit Schwalbe-Fehl, lead of the Gemba Walks subteam, shares insights and best practice recommendations based on real-life Gemba experiences and lessons learned from ISPE member companies.

The Japanese term *Gemba* means "actual place." Jim Womack, author of *Gemba Walks*, expands this definition to call Gemba the place in an organization "where humans create value."[1] Gemba is a well-defined element of lean concepts and, as such, an accepted operational excellence tool in many industries that have adopted lean principles. The well-known Toyota production system has used Gemba walks for decades. Within the pharmaceutical industry, however, the concept of Gemba has not yet been widely implemented.

The concept is strikingly simple. Womack, the guru of Gemba walks, describes it as: "I just take walks, comment on what I see and give courage to people to try."[1] In the pharmaceutical industry, however, you may hear complaints that supervisors, let alone management, rarely have time to go out on the shop floor or into the laboratories where they could interact with employees and observe what is really going on.

Why Do Gemba Walks?

Gemba walks demonstrate visible commitment from the leadership to all members of the organization. They allow site leadership to spread clear messages using open and honest dialogue and get a real indication of the progress of behavioral change at all levels. They empower employees because their contributions to site results are recognized and their ideas for continuous improvement are heard.

Following an extensive review of practices in this area, it is the view of the Gemba Walks subteam that Gemba walks should replace, or at least substantially reduce, traditional conference-style meetings and hence minimize the production of the many charts and reports created just for such meetings, to communicate progress related to shop floor activities. Because Gemba walks facilitate stand-up style meetings on the shop floor or in the lab, they tend to be much shorter and more efficient than the typical conference-room presentations. Furthermore, decisions are often made more quickly because all participants have all the necessary information right in front of them.

Sharing Gemba Best Practices

The Gemba Walks subteam reviewed a wide range of practices from other industries and from published examples,[2] as well as experiences from ISPE members. The subteam has been ambitious in defining "best" practices, confident, based on the evidence, that the approach has worked well in all manufacturing industries, and there is no reason why it cannot be used effectively in the pharmaceutical industry.

This confidence was confirmed by listening to the leaders' voices in the interviews the Leadership and Vision subteam performed. These validated our thinking that once Gemba walks are implemented, the organization quickly recognizes their benefits (Figure 1).

Our starting point in outlining these Gemba best practices commenced by defining what a Gemba walk is and what it is not, within the context of the pharmaceutical industry (Table A). Understanding these distinctions is a key success factor for your Gemba program.

Understanding Gemba Walks

Our examination of successful programs showed that before implementing Gemba walks it pays to communicate both the purpose and overall approach to all levels of the organization by explaining the "why," the "who," and the "when."

Training Gemba walkers by practicing a few Gemba walks should be considered in the implementation phase to ensure that Gemba walks are effective and provide value to the organization from the beginning. This training can be supported by tools such as a set of prompts or questions that help start the dialogue on the shop floor, in the warehouse, or in the labs. An example of such questions is provided in Table B. It is also useful to provide Gemba walkers with layout plans and to create checklists of what to look for.

It cannot be emphasized enough how crucial it is to create a positive atmosphere during a Gemba walk to make people feel at ease as much as possible. You will still most likely experience some initial shyness from employees in bringing up really sticky points, especially if the culture of the site has previously not rewarded this behavior, but do not let this discourage you from continuing.

Make the mental shift of asking "Why is this happening?" instead of "Who did it?" to extract valuable existing knowledge from people on the floor.

Gemba walks demonstrate visible commitment from the leadership to all members of the organization

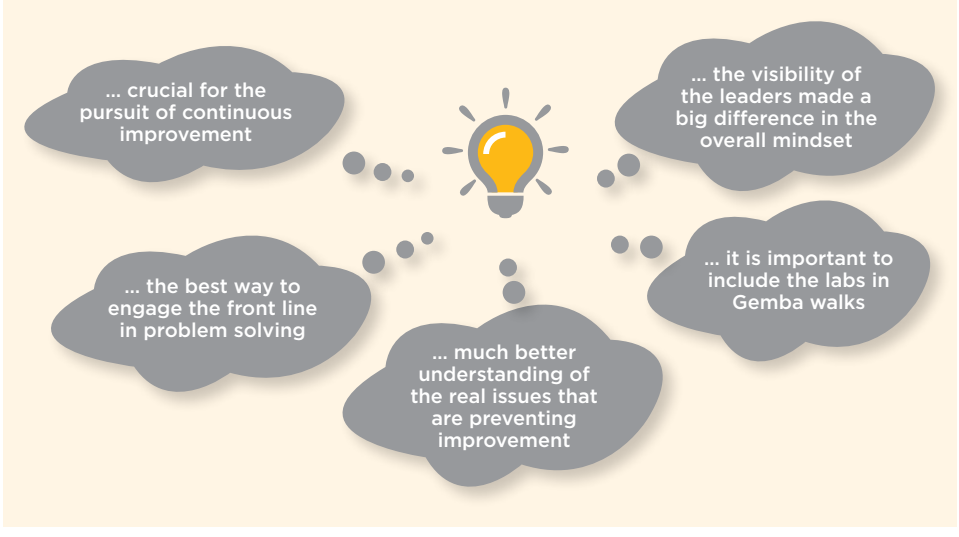
Make your Gemba walks about recognition, not auditing, by adopting the simple but important rule of "4 to 1": Express four recognitions for every action identified.

It is also critical to create a Gemba walk schedule that covers all areas to be visited. Best practice recommends creating an annual schedule so that the walks are a priority on everyone's itineraries. Consider, especially in the beginning, implementing a metric to measure participation and adherence to schedules; once Gemba walks have been ingrained in the site culture, such a metric may be modified to measure the effectiveness of Gemba walks by measuring the number of completed improvements, for example.

An often-cited benchmark goal within the automotive industry, regarding the amount of time managers should aim to spend on the shop floor, is 60%. We recognize that many pharmaceutical manufacturing sites are still a far cry from this benchmark; nevertheless, we have included it within our best practice recommendations for Gemba walk frequencies. These schedule recommendations, as described in Table C, may initially represent a stretch target, but in our opinion they are manageable in the longer term.

Naturally, the biggest impact for the organization will come from a program of regular Gemba walks by supervisors, team leaders, and site leadership. This level of visibility is absolutely fundamental for success as employees appreciate seeing supervisors and managers making decisions on the floor.

Figure 1: Feedback from leaders' interviews



You may be surprised to learn that we also recommend Gemba walks for internal customers (e.g., purchasing, supply chain planners) and site-support functions (e.g., human resources, finance). We believe that both the visited areas and Gemba walkers benefit significantly from the insights and discussions generated during these walks. Operators and lab analysts gain insight into the bigger picture of site performance, such as the expectations of external customers that the other functions have to deal with, and internal customers start to understand some of the constraints, real or perceived, that the visited areas may be challenged with.

Table A: Gemba walks

A Gemba walk is:

- An enabler for cultural change in management style and philosophy
- A role-modeling opportunity for leaders
- Empowerment of operators and analysts
- An enabler for continuous improvement through problem solving on the shop floor with the people who experience the problems
- An opportunity to find the root cause of issues, spot waste and quality risks, and for leaders to remove obstacles
- A coaching/mentoring opportunity to build and/or enhance capabilities and behaviors and recognize and reinforce desired behaviors
- An enabler for communication of site priorities/challenges and how the unit's performance contributes to the overall success of the site
- An opportunity to learn from the shop floor; encourages informed decision-making for leaders
- An opportunity for the operators to demonstrate their pride and excellence in their jobs

A Gemba walk is not:

- An audit (neither quality/compliance nor environmental health and safety)
- A general complaint/venting session
- A debate to defend individual viewpoints without facts
- A troubleshooting exercise in which participants focus exclusively on areas with (technical) issues

Gemba is a well-defined element of lean concepts and, as such, an accepted operational excellence tool in many industries that have adopted lean principles

Indeed, it was repeatedly reported to our team that some of the quick wins when implementing Gemba walks were observed from involving internal customers (including planners or raw materials buyers) in Gemba walks at labs or on the shop floor. Gaining an understanding of how current established practices can affect the work downstream often led to a quick removal of obstacles, resulting in enhanced performance. Also, communication breakdowns between functions could be identified and resolved earlier.

We saw again and again how developing a better understanding of current working processes led to a quick resolution of some major pain points. On the positive side, moreover, going to the "real place" provided an excellent opportunity to recognize contributions and achievements of individuals or teams in person.

Table B: Example of a Gemba walk pocket guide

Gemba guide (A): Leader "self-ask" questions	Gemba guide (B): Leader "coaching" questions
1. What is the PROCESS? Look for: Steps that add value, flow between steps, standardization of tasks	**1. What is the standard?** Hopefully it will be clear at a visual glance. Helps check understanding of the standard.
2. What is NORMAL/ABNORMAL? Look for: Standard work, expected state, variation to the expected state	**2. How do we develop a standard?** Used where a standard is ambiguous or lacking.
3. What is WORKING WELL? Look for: Standards being followed, ideas being generated, lessons shared	**3. How clear is the standard to those doing the work?** Reveal the depth to which standards have been put to use.
4. What is NOT BEING FOLLOWED? Look for: Checklists not populated, equipment in poor condition, poor housekeeping, variation to standard work	**4. How clear is the standard to those not doing the work?** Leaders should require that they can understand the status of safety, quality, and on-time output in less than five seconds each
5. What is BROKEN? Look for: Equipment requiring repair, safety hazards, status of line clearance controls	**5. How well are we performing against the standard?** The variation in responses can reveal a lot about how well people understand their standards.
6. What is NOT UNDERSTOOD? Look for: Variation to standard, poorly constructed procedures, understanding of team priorities	**6. Why are we not performing to the standard?** This is a golden opportunity for a leader to practice the five why questioning. Fight the urge to give the answer!
7. What is CREATING WASTE? Look for: Any forms of waste—transport, inventory, motion, waiting, overproduction, overprocessing, defects	**7. What can we do to improve the current condition?** This question can be used as a catch-all in any situation, any condition, any gemba.
8. What is CREATING STRAIN? Look for: Poor workstation design, inadequate environmental and/or ergonomic design factors, overburdening of activities	**8. How can we make the abnormal condition more immediately visual?** Often the reason problems persist is because they go undetected.
9. What is CREATING UNEVENNESS? Look for: Uneven production schedules, variation in staffing levels, process interruptions	**9. Why do you think I asked you these questions?** The true learning happens when people practice for themselves how to look at and assess their process through a different lens.
10. What is NOT VISIBLE ENOUGH? Look for: Signals to problems, performance indicators, management presence, communication of team priorities, standards	**10. What other questions would you have liked me to have asked?** The main use of this question is for the leader's learning.

Gaining an understanding of how current established practices can affect the work downstream often led to a quick removal of obstacles, resulting in enhanced performance

Table C: Recommended frequency for Gemba walks by management group

Gemba walkers	Best practice frequency	Minimum recommended frequency
First line supervisors	Each shift, multiple times	Each shift
▪ Team leaders of individual units in manufacturing/packaging ▪ QC team leaders in different labs (e.g., raw materials, spectroscopy)	Daily covering different shifts	2 per week
▪ Head of manufacturing for manufacturing area ▪ Head of packaging for packaging areas ▪ Head of quality control for labs	1 per day	1 per week
Site leadership team	1 per day	1 per month
▪ Site internal customers ▪ Manufacturing/packaging supervisors ▪ Lab managers ▪ Supply chain team leaders ▪ Manufacturing/packaging and lab managers ▪ Lab supervisors ▪ Manufacturing/packaging team leaders	1 per quarter	1 per year
Site support (e.g. human resources, finance)	2 per year	1 per year

Table D: Example of a Gemba walk action tracker

Date	Action description	Stakeholder	Action owner	Target date	Status	Comments

As a general principle, Gemba walks should be conducted at varying times during the workday and at every shift to get maximum exposure to the shop floor and laboratory. Site management showing up during the late shift in the lab or on the shop floor in the early morning provides an excellent opportunity to show respect to all personnel and at the same time understand how practices might differ from one shift to another. Other good Gemba walking times are during shift huddles, or mid-morning and mid-afternoon, when initial shift start-up activities are over.

As the key purpose of Gemba is to identify continuous improvement opportunities, it is critical to record commitments and agreed actions. One of the easiest ways to do this is to display agreed actions on visual boards in the area. These can be either manual or electronic, whatever works best for the site in question. The record should reflect the agreed action, the responsible person(s), and due dates. Progress or closure should then be reviewed at follow-up Gemba walks. For longer-term actions, the responsible person should provide updates or status reports.

An example of how the recording could be organized is provided in Table D. Remember, though, that compliance-related actions identified during the Gemba walk must be tracked via the site's deviation/corrective action and preventive action (CAPA) system. Similarly, if an agreed action affects good manufacturing practice (GMP) processes or systems, formal site change control must be initiated.

For further illustration of some key principles and learnings from real-life implementations of Gemba, the Gemba Walks subteam has also developed a case study from a global pharmaceutical manufacturing site and a summary of the lessons learned from implementing Gemba in labs (see pages 62–65). We hope that these encourage more pharmaceutical manufacturing sites to implement Gemba walks in their quest for a culture of excellence.

Conclusions

Gemba is a key concept to enhance the culture of excellence of a site by creating visible management commitment and engaging employees at all levels of the organization. Gemba walks enhance communication of priorities, objectives, and desired behaviors, and foster dialogue and understanding between management and employees. They also provide the opportunity to engage internal customers in the Gemba walks, to allow both sides to better understand the drivers and restrictions in the daily work, and to see the "bigger picture" in an organization.

Gemba walks enhance communication of priorities, objectives, and desired behaviors, and foster dialogue and understanding between management and employees

Implementing Gemba as an isolated tool is certainly not enough to drive cultural change; it does, however, offer the most immediate and direct intervention that a site can implement and hence the boldest move to make a visible cultural change. ■

Acknowledgments

I would like to thank the members of the ISPE Quality Culture Gemba subteam for many productive discussions and for sharing their experiences and lessons learned: Jose Cardoso de Menezes, University of Lisbon, Portugal; Karen Casey, Johnson & Johnson, Ireland; Joseph Kuntz, Pfizer, USA; Richard Mark, AstraZeneca, Australia; Brianna Peterson, Boehringer Ingelheim, Germany; and Willard Weissman, Sanofi Pasteur, USA.

Special thanks go to Jim Powers at Bridge Associates International LLC, USA, for sharing his insights and lessons learned from many years of implementing Gemba in the laboratories of pharmaceutical and consumer health care manufacturing sites.

Gemba Case Study

A global pharmaceutical site had been working on initiatives to build an integrated quality culture, one that fosters continuous improvement and in which all employees think with a quality mindset. It recently started two new improvement initiatives: one targeted to improvements to the existing management walk-through process and one to implementation of right-to-operate (RTO) metrics. Both were built on the principles of the Gemba walk.

Monthly management walk-throughs were already a part of the site's self-inspection program, but there was room for improvement in the way they were conducted. The walks focused on housekeeping and facility maintenance improvements and were performed by a large group. This could be intimidating for employees who worked in the visited area, and could prevent productive interactions. Site management also felt that the walks duplicated weekly quality assurance and daily operations walk-throughs, and often created scheduling conflicts. While observations from the walk-throughs were categorized, trended, and reported, it was difficult to identify true quality indicators.

The site management team decided to foster a culture of quality by changing the program to provide opportunity for open dialogue and demonstrate management engagement. At the same time, the focus of the walk-throughs became more interactive and topic based.

In addition to these improvements, the site also decided to implement RTO metrics as an extension of existing site metrics. The site defined a set of base metrics that reflected the manufacturing vision, mission, and principles but were shift-specific and adjustable to the needs of specific areas. They were therefore more directly linked to operational excellence outcomes and directly controlled by the supervisors and operators of each shift.

Implementation

The site designed the process to be less formal, to encourage open conversation, and move away from a checklist approach. A topic was proposed each month, along with potential questions to generate conversation. Suggested topics came from the Quality Lead Team and could be derived from different sources, like the site self-inspection program, quality management reviews, or industry hot topics. The walk-throughs were no longer scheduled at specific times; instead, management was encouraged to go any time during their assigned month. Topics proposed for the management walk-throughs were suggested as a starting point, but the walkers could change the topic to allow open dialogue.

After completing the walk-throughs, leaders who participated in the topic-based walk-through led a discussion at the monthly quality lead team meeting to highlight what they observed and any concerns expressed on the floor. Meeting minutes captured the discussion. Follow-up items were tracked via the meeting action tracker or, if warranted, as CAPA items.

RTO metrics were reviewed monthly per shift on the shop floor while the scorecard was displayed on the monitor in the control rooms of the area in which the review occurred. The review was facilitated by the shift supervisors, who explained the metrics results. All shift operators, operations managers, the operations director, and site head participated.

The RTO metrics review became a forum in which employees could interact with their leadership and discuss hurdles or barriers to obtaining operational excellence. At the same time, the review also offered an opportunity to share success stories and provide examples of operational excellence; it also provided a space for conversations around the pulse of the organization, concerns or questions on the floor, or areas where leadership could help reduce or eliminate barriers. The scorecards were made available on a collaboration site so that shifts could see their performance (and that of other shifts) at any time. The meetings were scheduled for 20 minutes per shift, and all follow-ups were tracked by the operations director. Some were entered into a formal tracking system, while others were completed and communicated at the next meeting.

The site management team decided to foster a culture of quality by changing the program to provide opportunity for open dialogue and demonstrate management engagement

The review offered an opportunity to share success stories and provide examples of operational excellence

Tangible Results

The site has seen tangible results with the implementation of both initiatives. The new interactive management walk-throughs have identified a number of continuous improvement opportunities as well as safety enhancements. With the implementation of RTO metrics the site has seen an increase in engagement; "be safe" and "safe start" stories are shared more frequently, while human-error deviations such as entry errors have gone down.

One tangible outcome occurred in API production: A leader was observing manual addition in an area that had recently undergone improvements. The operator voiced a concern that while he had two manual additions, they were being performed differently; they should be treated the same way. As the leader asked questions to better understand the process, he discovered improvements for storing secondary containers for the addition. With the two-way communication, two improvement opportunities were identified that would have been missed in the previous walk-through style.

A continuous improvement from the RTO metrics relates to training—one of the predefined scorecard metrics. Following a discussion at an RTO metrics review, a training representative was added as a participant. The resulting discussion uncovered and corrected a barrier that was causing this metric to be missed. The training metric is now consistently on target to meet the expectation for operational excellence.

Both initiatives were very well received by all involved parties. Leadership finds the walk-throughs informative, and operations personnel like having the opportunity to share their concerns. It took time to get past viewing the RTO metrics as a "scoring" exercise instead of an opportunity for improvement and greater interaction; in the meantime, the approach is well accepted and valued as a means to share success and remove barriers to continuous improvement.

The site intentionally kept the programs simple and adjustable to the needs of individual areas and allowed some flexibility in implementation. Based on the learnings from these two initiatives, the site believes that the better the programs are tailored to the working style of the site, the easier they are to implement and the more successful the outcome. ■

Implementing Gemba Walks in Laboratories: Lessons Learned

Implementation

Sites can implement Gemba in their laboratories successfully whether they have prior experience or not. It is possible to implement Gemba in the labs only (using the labs as pilots for Gemba implementation, for example), although the site will benefit more when Gemba becomes part of the site culture and the approach is implemented throughout all operational areas (such as manufacturing, packaging, and warehouse).

Up-front training and communicating the "why" and "how" of Gemba will make the implementation much more effective. The most important factors are:

- Teach Gemba walkers the dos and don'ts of Gemba, including best practices
- Plan detailed implementation steps
- Do a first practical exercise in Gemba walking
- Train ice-breakers
- For the visited areas, create awareness of who is coming and how often; detail objectives and opportunities

It is often debated how formal a Gemba program should be. In the beginning, implementing Gemba walks through a formal program helps emphasize the cultural change of getting people out of their offices and demonstrating management commitment to a published schedule. This perpetuates the desired behavior by allowing people to observe management making decisions right on the shop floor. If the desired culture change has been achieved, Gemba will be part of the site's DNA and questions will surface more readily.

Up-front training and communicating the "why" and "how" of Gemba will make the implementation much more effective

In the labs, Gemba walks can be performed either along the path of a product sample from receipt through release of results, or in one particular area, such as a raw materials lab. A mixture of approaches normally works best to ensure that the walkers understand all facets of lab work.

Surprises

Even the first training Gemba walks often created an "aha" moment, especially for organizations that did not do Gembas before. For many customers—even for some site management—the Gemba walk was their first time in the labs. They were often not aware of the knowledge and competencies in their labs. In these situations, Gemba walks provided much-needed understanding of an analyst's complex and difficult job, and the many steps involved in a single analysis, such as time needed to prepare samples and instruments, requirements for data assessment, and level of rigor around the data. Gemba walks also addressed the lack of familiarity with basic processes for chemistry and microbiology analysis.

One of the most frequent quick wins after implementing Gemba walks was the removal of artificial complications in planning and prioritization (and repeated reprioritization). They could often be resolved relatively easily through some basic enhancements in communication between the supply chain and the labs. Many sites found examples where testing was supposed to have been stopped years prior but was still being performed due to a lack of communication.

Expect that people in the visited area will be shy at first, especially if they have never experienced direct interaction with site management

The overall learning was that once people talk and understand the drivers behind their customers' actions, it is relatively easy to improve the overall outcome for the site.

Challenges

The hardest part of Gemba is tracking commitments agreed upon during the walk, especially when they are owned by more than one part of the organization. Best results occur when sites capture commitments on visual boards, lab leaders own communication about the progress, analysts are empowered to address such issues that have previously been discussed, and actions are agreed upon. This requires understanding that making the change is a collective responsibility.

Culture Shifts and Tangible Results

The successful implementation of Gemba walks in labs has resulted in building trust and seeing the excitement in the eyes of the analysts that people are interested in their work. The analysts appreciate their contributions as part of the overall site performance, which leads to robust engagement of untapped hearts and minds. By enhancing the understanding of how practices in supply chain and operations have an effect on work done in the lab, tangible improvements in meeting schedules and improving the lab output quality were achieved. The visible interest in how lab results are used has led to a significantly better quality of work and reduction in stress.

The most consistent tangible results were:

1. Enhanced planning between supply chain and labs for raw material orders/testing and finished goods testing
2. Adjustments in key performance indicators to drive overall results instead of departmental objectives: Replacing the key performance indicator of lab cycle time, for example, by adhering to a lab schedule, resulted in better planning accuracy for operations, fewer schedule changes, and less wasted time
3. Artificial barriers affecting workflow, inventory, and timing were removed
4. A better quality of work, with fewer deviations and out-of-spec results
5. Lower lab personnel absentee rates

Cautions

Expect that people in the visited area will be shy at first, especially if they have never experienced direct interaction with site management. This should not be interpreted as a sign that Gemba walks are not working. Be patient and willing to create an atmosphere that is positive and makes people feel at ease.

Gemba walks are meant to replace conference-room meetings, so make sure to stop routine meetings that would replicate meetings in the labs. Don't add Gemba on top of old practices. Don't convert Gemba walks into audits. It may be tempting to "save" time by trying to do both at the same time, but that is the surest way to kill the benefit of Gemba walks. Gembas are also meant to be short; don't overcomplicate the process or extend them to become hour-long meeting substitutes.

Leaders might be uncomfortable in the laboratory at first; some may not have a laboratory background, and may not understand the operation and its complexities. In these cases, the solution is to ask a lot of questions during the first walks and let analysts explain what they do and why they do it. Being interested in their work is the best door opener.

Continuous Improvement

Sites should undertake the following best practices, based on years of experience with Gemba walks in labs:

- Always ask yourself if the Gemba walks add value. If not, why? Find opportunities for adjustments.
- Measure Gemba performance with simple metrics, such as adherence to schedule and the number of continuous improvement opportunities implemented as a result.
- Measure tangible results from continuous improvement opportunities. ■

One of the most frequent quick wins after implementing Gemba walks was the removal of artificial complications in planning and prioritization

Leading Indicators of Quality: Pinpointing Behaviors and Measuring Results

Nuala Calnan, PhD

The fourth dimension of ISPE's "Six Dimensions of Cultural Excellence" framework focuses on those elements related to the monitoring and surveillance of key "triggers" and the design and development of leading quality indicators (LQIs).

In this article Nuala Calnan, PhD, head of the LQI subteam, shares key insights on the inherent links between culture and behavior, and outlines the role of leading measures of quality in driving desired patient-focused behaviors. This article shows how Leslie Braksick's IMPACT tool can be adapted for use in pharmaceutical manufacturing for the design of meaningful measures that pinpoint specific desired behaviors to promote a culture that enshrines prevention rather than cure.

Understanding Behavior as a Derivative of Culture

Culture as a concept is thus an abstraction, but its behavioral and attitudinal consequences are very concrete indeed.[7]

—Edgar H. Schein

An article published in *Pharmaceutical Engineering* earlier this year[2] introduced the work of Edgar H. Schein, one of the world's leading authorities on organizational culture and leadership. The article included his definition of culture: "how we perceive, think about, and feel about things."[7]

Schein formally links behavior to culture by indicating that behavior is a *derivative* of the prevailing organizational culture. This link provides a concrete means to understand and interpret the powerful force that culture exerts on day-to-day operations within organizations and offers a focus for action for those within the pharmaceutical industry seeking to improve their quality culture.

Viewing the relationship between behavior and culture as an abstract-to-concrete continuum is particularly helpful when designing practical improvement strategies. Schein cautions against evaluating cultures in an absolute or superficial way, however, such as good vs. bad or strong vs. weak. This is sound advice that the pharmaceutical industry should heed if it is to avoid the trap of substituting mere lip service for development of a strong quality culture. Too often this manifests as a traditional culture of compliance with an overemphasis on "doing things right" instead of enabling the workforce to do the right thing.

This is the foundation for ISPE's Six Dimensions of Cultural Excellence Framework (Figure 1), which supports a transformational journey toward a culture of patient-focused excellence by sharing approaches, practices, and tools. Such a transformation requires the identification and selection of "desired" behaviors to be "hardwired into new habits so that employees become assets to, and champions of, the transformation effort."[6]

The need for a transformation from a compliance-led to an excellence-led culture is further supported by the findings of a 2014 survey of 60 multinational organizations undertaken by CEB (formally known as the Corporate Executive Board) entitled *Creating a Culture of Quality*, which proposed that organizations must find a new approach to quality, "one that moves beyond the traditional 'total quality management' tools of the past quarter century."[8] The CEB survey notes that specific actions are needed to shift from a rules-based quality environment to a true culture of quality and concludes that employees must become passionate about eliminating mistakes by *learning* to apply their skills and make decisions in complex situations while *reflecting* more deeply on the potential risks and consequences of their day-today actions.

Figure 1: The six dimensions of cultural excellence

Moving from the abstract to the concrete, we now examine how this "learning" can be targeted to pinpoint the desired behaviors and inhibit those that are undesirable. In their contribution to the book *Leading Pharmaceutical Operational Excellence*, Morse et al. reference Leslie Wilk Braksick in their change-management model.[6]

Braksick's work is founded on the principles of behavioral science presented in her book *Unlock Behavior, Unleash Profits: Developing Leadership Behavior that Drives Profitability in Your Organization*. In his foreword to the book, W.R.K. Innes acknowledges the power and complexity of behavioral science when he proposes that behavior is probably "the most powerful, and yet least understood aspect of leadership" and can be "as complex as the human condition itself." Reassuringly, Innes also says that "like any complex system, human behavior is driven by a few simple principles."[1] This article outlines these "few simple principles" that can help reinforce good behavior in your teams.

The ABCs of Behavioral Science

Great execution depends on—behavior.[1]

—Leslie Wilk Braksick

The "ABC" model of behavioral science outlined by Braksick (Figure 2) holds that **A**ntecedents lead to **B**ehaviors, which lead to **C**onsequences. Antecedents are events that precede behaviors; they trigger what people say and do. They enable behaviors; they do not, however, motivate behaviors. In fact, consequences motivate behaviors by either reinforcing or discouraging them (i.e., consequences determine whether desired or unwanted behaviors occur and recur). Therefore, the sequence is as follows:

- Antecedents trigger behaviors
- Behaviors are followed by consequences, which, in turn, determine whether behaviors will recur

The significance of this work becomes evident when the actual effects are examined. Braksick holds that antecedents only exert approximately 20% of the influence on what we do or say, whereas consequences exert 80% of the influence on behaviors. However, Braksick maintains that leaders, especially those in corporate settings, have an overreliance on antecedents to foster new behaviors, and typically, when they fail to deliver "they just pile on more antecedents: issue memos, pep talks, training manuals and restate [their] expectations."[1]

Based on their work at Boston Consulting Group, Morse et al. note that managers "persist in spending 80% or more of their time trying to manage by working on As, leaving Cs largely unmanaged."[6] Braksick advises a combined approach to achieve maximum impact, stating that while an antecedent alone will produce small, often temporary changes in behavior, and a consequence alone will produce modest, lasting changes in behavior, antecedents backed up by consequences will produce the greatest effect on changes in behavior.

The Rules of Four

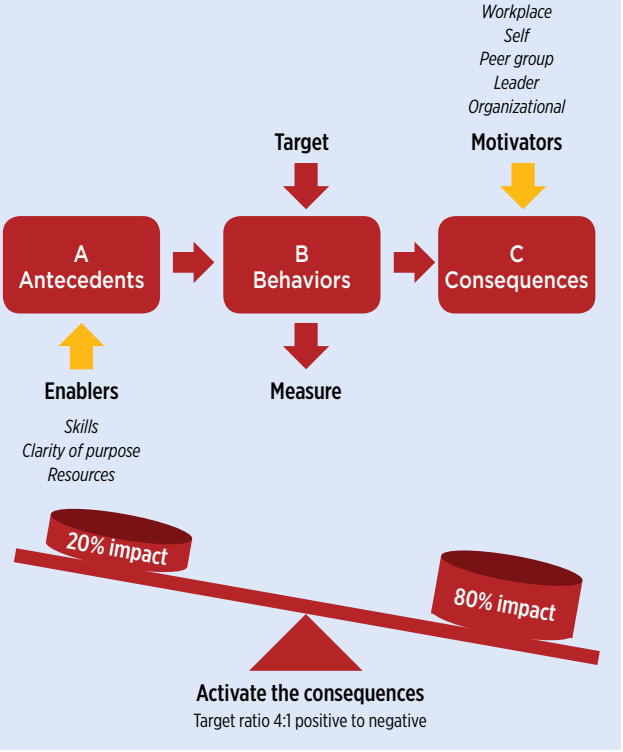
The "consequences rule" defined by Braksick states that consequences have a "4x greater impact on behavior than antecedents." Put simply, this means that consequences are the real motivators (or demotivators) and antecedents are simply the enablers.[1] Research undertaken by Losada and Heaphy in 2004 concludes that peak performance is achieved at a 4:1 ratio of positive to negative consequences.[5]

These rules raise two challenges for pharmaceutical companies that must be considered when targeting desired behaviors within a new learning culture. The traditional culture of compliance has relied heavily on rules-based antecedents to determine behaviors, such as documenting requirements in standard operating procedures and focusing on skills and task training. Within this environment, consequences tend to be those associated with nonachievement of desired behaviors and are largely negative (such as sanctions based on deviations, or retraining for failures attributed to "human error").

Employing the ABC model and the rules of four to drive real change in the elements of daily work that have the biggest effect on patient safety—i.e., the behaviors of all those involved in the supply of high-quality medicines—requires a new way of thinking about how consequences are designed and used.

Accepting that consequences have four times greater impact than antecedents will require a phase shift in the amount of time spent designing and managing them, from leaving them "largely unmanaged" to investing significant time in designing appropriate and motivating strategic consequences. Furthermore, for each desired behavior identified, the 4:1 ratio of positive to negative consequences should also be applied for lasting performance outcomes. The behavior tools provided by Braksick's model

Figure 2: The ABCs of behavioral science



Adapted from Braksick (2007) and N. Morse, et al. (2013)

are simple, but changing minds and attitudes to emphasize *reinforcement* instead of *enforcement* may prove more complex.

Linking Culture, Attitudes, and Behavior: The LQI Model

Industry-based research undertaken by the author coupled with industry engagement through the ISPE Quality Metrics task team and Quality Culture subteam have enabled an inside view of many quality culture and quality metrics programs across a diverse range of companies both within Ireland and internationally. The majority of quality metric dashboards in use remain heavily focused on lagging, historical metrics; very few are oriented toward proactive, leading measures of quality performance.

It is useful to look at the differences between leading and lagging indicators; LNS Research provides these simple definitions:[3]

- A *leading indicator* can be defined simply as a performance measurement that occurs before a process begins
- A *lagging indicator* is the opposite; it is a measurement that indicates results

Leading indicators often measure behaviors and are predictive; lagging indicators tend to be historical measurements of results that nevertheless offer opportunities for reflection and analysis. Since behaviors are typically precursors of results, Goodwin advises that "it's important for manufacturers to optimize the use of leading indicators where possible to nip potential problems in the bud, upstream from the undesired results."

Management reviews of historical, lagging metrics for both the business and the patient are of questionable value, as Gotts states: "Using metrics that measure past events is like driving while looking through the rear window. It's easy not to see an opportunity or threat on the road ahead until you're upon it."[4]

Based on the truism "What gets measured gets done," the "numbers" selected matter. They convey the choice of organizational culture—the rules-based culture of compliance or a learning-based culture of excellence. They influence and reflect prevalent attitudes and mindsets within the organization—i.e., "how we perceive, think about, and feel about things." Most importantly, they can provide concrete means to employ the ABCs, and to construct meaningful combinations of antecedents and consequences to positively reinforce the desired behaviors.

Pinpointing Behaviors, Measuring Results

Having established that the choice of metrics provides an opportunity to positively influence behaviors (and therefore benefit the patient), this author adapted Braksick's IMPACT model for use in the pharmaceutical industry as a quality metrics tool to design behavior-based LQIs, sometimes referred to as leading behavioral indicators (LBIs). The aim is not to prove the superiority of forward-looking metrics over historical ones

Table A: A worked example of the IMPACT tool for designing behavior-based LQIs

Identify goal	Select the measure to deliver goal	Pinpoint the behaviors	Activate the consequences	Transfer knowledge and skills to sustain change	LQIs
Consistent delivery of high-quality medicinal products	Increase the number of batches which are right first time to X%	Promote and actively coach for enhanced attention to detail where "quality is everyone's job." Encourage a speak-up culture where concerns, issues or suggestions are surfaced in a timely manner in a neutral, constructive forum. Commence proactive daily multidisciplinary interim batch issues reviews.	Organize team briefings on the specific consequences for the business and the patient for rejected or delayed batch approvals. Review outcomes from recent rejected/delayed batches with the team. "Celebrate"/acknowledge each RFT batch by senior leadership and local management during gemba walks. Use of visual management boards for motivation on progress toward goal. Acknowledge improvement efforts by team members in team/public areas/ newsletters. Motivate the team through team awards (e.g., movie tickets, team lunches)	Learning teams use root cause analysis (RCA) tools to proactively identify and document solutions to issues raised. Lessons learned are documented and shared with wider workforce. Lunch and learn sessions are arranged to facilitate Q&A between different improvement teams. Create "improvement" case studies in a shared area on the intranet.	**Leading:** Measure and report on attendance at the multidisciplinary meetings. No. of employee / team RFT improvement suggestions implemented (by period) No. of "good catches" identified at interim batch reviews (by batch) No. of successful root cause analysis exercises completed by the team (by period) **Trended lagging:** % RFT batch approvals/ investigation free lots % RFT batch records (paperwork completion)

but to find an appropriate combination of reflection and prediction to help organizations become more proactive than reactive with regard to their quality performance.

At any given time, each organization will need to focus on different behaviors to motivate specific areas of performance improvement or, conversely, address recurring quality failures. Therefore, no set of universal metrics is recommended. Rather, the tool is provided to enable the design and redesign of customized LQIs/LBIs as part of the overall journey toward excellence.

The LQI design tool, which forms one element of a broader LQI framework developed by the author, was influenced by a successful collaboration with the Pharmaceutical Operational Excellence (OPEX) Benchmarking team based at the University of St. Gallen, Switzerland. The collaboration provided insights into the benefits of designing measurement tools that have a balanced approach to reviewing qualitative progress on a series of enablers as well as measuring quantitative results in the form of metrics.

The tool below describes only the design of the quantitative measures or results.

Designing Measures for IMPACT

The IMPACT model requires the following steps in selecting and designing LBIs:

1. **I**dentify the desired quality-improvement goal.
2. Establish the appropriate **M**easure to deliver the goal.
3. **P**inpoint the "desired" behavior to deliver the goal.
4. **A**ctivate the **C**onsequences to motivate the delivery of the goal.
5. **T**ransfer the knowledge across the organization to sustain the performance improvement.

Table A shows a pharmaceutical industry example of this tool, focused on promoting right-first-time (RFT) behaviors. For best results and buy-in, these measures should be defined and agreed upon in conjunction with the team responsible for delivering the identified goal.

The strength of the tool comes not only from pinpointing the behaviors that matter but from actively designing positive consequences that are meaningful to the team, bearing in mind the optimum 4:1 ratio of positive to negative consequences that are deemed most effective in motivating behavior in the longer term.

Finally, the tool also addresses an often neglected aspect of change management: sustaining the change. By identifying feedback elements of knowledge transfer (the "T" in IMPACT) at the beginning, teams can sustain and share the know-how gained in solving the problems under examination. Another key attribute and critical motivating factor in successfully scaling up excellence can be getting team members involved in what Sutton and Rao call spreading their "splendid deeds from the few to the many." [9]

Summary

Designing behavior-based leading indicators of quality is one concrete way that organizations can influence the shift from a compliance-led culture to an excellence-led culture of quality. The key to success lies in activating the consequences that can motivate the desired behaviors that matter to your business and your patients.

Acknowledgments

The author wishes to acknowledge the involvement of the ISPE LQI subteam members over the past 18 months: Stuart du Kamp (Septodont) Jose Torres (Alkermes), Christian Maender (University of St. Gallen), Cheryl Wellman (G&W Laboratories), Anne Sofie Østerdal (Novo Nordisk), Tim Kozo (Johnson & Johnson), and Mani Krishnan (Pall). ■

Announcing FDA's Pharmaceutical Manufacturing Quality Metrics Research

Thomas Friedli, PhD, Prabir Basu, PhD, and Nuala Calnan, PhD

In the world of pharmaceutical production, it is universally understood that a robust quality system provides key elements of assurance and oversight for manufacturing processes: It ensures that patients are provided with medications that are safe, effective, and reliably produced at a high level of quality.

Despite recent advances in the manufacturing sector, however, quality issues continue to arise that can result in recalls, withdrawals, or harm to patients. Quality issues have also been linked to the rise in critical drug shortages.[1] Regulatory agencies currently assess the risk profile of manufacturing sites based primarily on their compliance history, as seen in warning letters and field reports, in conjunction with records on product recalls, and market-based quality problems. These are not necessarily the most informative measures and, by their nature, provide historical or lagging data or signal detection.

More relevant data relating to the state of quality, provided in advance, would better inform the risk factors that might predict quality problems and future drug shortages. This could become a valuable source of information for risk-based assessments and inspection scheduling of pharmaceutical manufacturing operations around the world.

The US Food and Drug Administration's (FDA) approach to quality oversight has evolved in recent years. The new Office of Pharmaceutical Quality (OPQ) has made it a priority to establish a more sound basis for ensuring that pharmaceutical products meet high quality standards throughout their life cycle. The FDA draft guidance proposed a set of standardized manufacturing quality metrics. The establishment and collection of these metrics could provide various stakeholders—from industry to regulators—with greater insight into the state of quality at a given manufacturing facility and allow stakeholders to better anticipate and address quality issues and their associated risks while simultaneously reducing unnecessary regulatory burden.

More relevant data relating to the state of quality, provided in advance, would better inform the risk factors that might predict quality problems and future drug shortages

As part of this initiative, the FDA has recently awarded a research grant* to Switzerland's University of St. Gallen to help establish the scientific basis for such metrics and integrate quality in its ongoing operational-excellence (OPEX) efforts.

OPEX Program

The Institute of Technology Management at the University of St. Gallen (ITEM-HSG) is a global academic leader in establishing solid and meaningful OPEX programs. For more than a decade it has worked hand in hand with the pharmaceutical industry to develop widely accepted global programs. These programs have positioned ITEM-HSG at the forefront of promoting, measuring, and monitoring operational excellence in the pharmaceutical industry.

St. Gallen has been responsible for the largest independent benchmarking project in the pharmaceutical industry since 2004, with 334 global manufacturing sites contributing key performance indicators (KPIs), in addition to providing rich qualitative data on organizational enablers for excellence. The institute's experience in metrics tool development and access to this global industry data set, coupled with experienced independent data analysis resources, uniquely position the St. Gallen OPEX project team to contribute significantly to the FDA/OPQ initiative on quality metrics.

Key Objective

In support of the OPQ's commitment to transform the assessment of drug quality from a qualitative to a quantitative or semi-quantitative expertise-based assessment, the key objective of this project is to evaluate potential quality metrics candidates, including those suggested in the FDA's June 2015 draft guidance,[2] and propose how they may be utilized to monitor the status of product and facility quality across the inventory of FDA-regulated sites. The proposed quality metrics will facilitate the effectiveness of current manufacturing controls, improve delivery of key quality outcomes in manufacturing operations, and seek to establish significant correlations to the underlying quality culture of an organization.

* Grant #1UO1FD005675-01: "FDA Pharmaceutical Manufacturing Quality Metrics Research"

FDA has recently awarded a research grant to Switzerland's University of St. Gallen to help establish the scientific basis for such metrics and integrate quality in its ongoing operational-excellence efforts

Based on St. Gallen's extensive global OPEX database and nearly 15 years' experience in research and collaboration with the pharmaceutical industry, the research team will evaluate and propose meaningful, measurable, and reportable potential quality metrics candidates, including quantitative and quality culture–related indicators.

Research Approach

The St. Gallen OPEX model is a comprehensive excellence model able to map site performance from an overall system perspective. It comprises factors related to quality as well as cost- and time-related KPIs, and evaluates dozens of enablers that affect these KPIs. This well-established pharmaceutical program can show, based on data, that the very foundation of superior overall excellence is quality.

The research strategy will be executed in five stages:

Stage 1. The current FDA metrics concepts contained in the "Request for Quality Metrics – Guidance for Industry"[2] will be examined in detail, and the underlying research assumptions will inform further work. For the Stage 1 hypothesis evaluation, the research team will rely on existing data from the St. Gallen global OPEX database.

Stage 2. Researchers will develop a set of quality metrics suitable for overall system performance. Quality will be built in at its very foundation. The system will be described from supplier inputs to final delivery and will also comprise maintenance-related data, enablers, cultural indicators, and classical operational performance figures. This stage will be summarized and evaluated using a gap analysis procedure between the proposed St. Gallen metric sets and the FDA guideline metrics. The main objective is to determine if the limited set of KPIs given in the draft guidance can display a comparable base for an overall system-based evaluation, such as the St. Gallen model.

Stage 3. Based on the gap analysis and Stage 1 outcomes, the research team will propose possible modifications of the set of metrics and examine potential implementation challenges.

Stage 4. The team will use its industry access to check the practicability of the proposed metrics. Implementation hurdles and issues will be discussed and documented, based on case study research. Interaction with industry, however, will commence at the beginning of the project and continue throughout.

Stage 5. The team will create an overall research report to document progress and results and conclude findings. Intermediate and final results will be discussed in open public meetings with the FDA and industry in the United States, Europe, and Singapore.

Collaboration

St. Gallen will collaborate on this project in Ireland with Nuala Calnan, PhD, at the Dublin Institute of Technology (DIT), and in the United States with Prabir Basu, PhD, former Executive Director of the National Institute for Pharmaceutical Technology and Education. ■

The key objective of this project is to evaluate potential quality metrics candidates, including those suggested in the FDA's June 2015 draft guidance

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About the Authors

Erika Ballman is the Quality and Regulatory Site Manager for Albemarle Corporation in South Haven, Michigan. She currently heads quality operations for the Charlotte, North Carolina–based company's API manufacturing site. During her 17 years in the pharmaceutical industry Ballman has held technical and quality leadership roles with Baxter BioScience and Perrigo Company. Erika earned a BS in chemistry from Michigan State University, East Lansing, Michigan, in 1998. An ISPE member since 2003, she has been a contributor to the ISPE Quality Metrics Team and Member of the ISPE Quality Culture Core Team since its formation in 2013. Erika currently leads the ISPE Leadership & Vision subteam of the Quality Culture Core Team.

Prabir Basu, PhD, is an independent consultant advising on pharmaceutical manufacturing and cGMP issues. He has been collaborating with University of St Gallen on research in operational excellence (OPEX) in pharmaceutical manufacturing since 2006. Dr. Basu has over 20 years' experience in pharmaceutical development and pharmaceutical manufacturing. As a former (2004–2011) President and Executive Director of the National Institute of Technology and Education, Prabir has extensive experience working with the FDA. A fellow of the American Institute of Chemical Engineering, Prabir has coedited three books and coauthored over 50 journal and conference papers. He has been an ISPE Member since 2004.

Nuala Calnan, PhD, is an adjunct Research Fellow with the Pharmaceutical Regulatory Science Team at the Dublin Institute of Technology, Ireland. With over 20 years' experience in the pharmaceutical industry, Dr. Calnan's research and industry consultancy focuses on the integration of knowledge excellence, operational excellence, and cultural excellence in delivering enhanced quality outcomes for the patient. She is currently a member of the St. Gallen University–led team who were awarded a one-year FDA research grant to examine the role of quality metrics in determining risk-based inspection planning. An ISPE Member since 1997, Nuala also co-leads the Quality Culture Team and the ISPE/PQLI Task Team on Knowledge Management.

Thomas Friedli is a Professor for Production Management at St. Gallen University, Switzerland, whose main research interests are managing operational excellence, global production management, and management of industrial services. Responsible for the university's OPEX Benchmarking in the Pharmaceutical Industry (the largest independent Benchmarking in this field) Professor Friedli leads a team of 14 researchers who develop new management solutions for manufacturing companies. He also is the editor, author, or coauthor of 13 books and various articles. He has been an ISPE Member since 2014.

Margit Schwalbe-Fehl, PhD, is a Managing Partner of Bridge Associates International LLC, a consulting firm specializing in quality and manufacturing excellence. She works with clients in Europe and the US to implement robust and effective quality management systems, developing quality strategies and supporting organizational development activities. Prior to her career in consulting, during her more than 25 years in the pharmaceutical industry, Dr. Schwalbe-Fehl held positions with increasing levels of responsibility in the field of quality at major global pharmaceutical companies. An ISPE member since 2007, she holds a diploma in chemistry and a PhD in analytical chemistry from Johannes Gutenberg University in Mainz, Germany.

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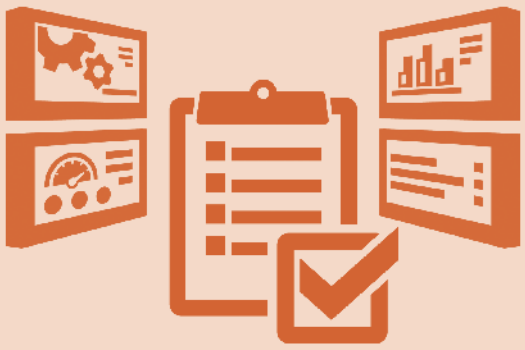

Current Challenges in Implementing Quality Risk Management

James Vesper and Keven O'Donnell

The views expressed in this paper are those of the authors and should not be taken to represent the views of the Health Products Regulatory Authority

Since quality risk management (QRM) was formally introduced to the pharmaceutical industry in 2005 with the publication of the International Conference on Harmonisation (ICH) Q9 guideline on quality risk management,[1] pharmaceutical firms have adopted and implemented its concepts, tools, and methods in different ways and at different rates.

As a consultant/trainer and an inspector at a national regulatory agency, we have independently visited or inspected a variety of companies in North America, Europe, the Middle East, and Asia; we have listened to presentations at technical conferences; and talked with QRM practitioners. Through these experiences, we have observed several recurring themes that appear to be common industry challenges. This paper identifies and discusses seven of them; they are given with the intent of stimulating a discussion on the implementation and use of QRM and the difficulties that are currently seen.

1. Using formal QRM on everything

Management will sometimes ask that a formal QRM process—i.e., using recognized tools like failure mode effects analysis (FMEA) or fault-tree analysis (FTA)—be performed on issues ranging from the critical to the trivial. This broad misapplication of the QRM process has caught the attention of good manufacturing practice (GMP) inspectors who now see formal QRM reports addressing issues that in the past would have been decided simply on the basis of key GMP requirements that were well understood by management.[2] Using a risk-assessment tool to "justify" the release of a batch of product following a serious contamination incident, for instance, without reprocessing or reworking that batch now appears to be occurring more frequently than in the past, with highly questionable batch release decisions in some cases.

It is often better to focus efforts on root cause analysis and to take appropriate corrective and preventive actions (CAPAs) without overreliance on subjective risk assessments that could lead to the conclusion that the risk is low and that no actual CAPAs are needed. With a solid root cause analysis and a good understanding of the likely impact of a problem issue (on batch quality and to patients) in place, these approaches can often be more timely and effective than moving through all of the QRM phases.

Formal risk assessments sometimes fail to add value or clarity to a situation because risk assessments often only superficially address root cause analysis, resulting in ineffective risk-control actions. In addition, because risk assessments are often performed by busy people, the results are often not as supported by scientific rigor as they should be. This can lead to high levels of subjectivity and uncertainty in outputs and conclusions, which further contribute to risk.

In 2005, the International Conference of Harmonization published ICH Q9, its guideline on quality risk management (QRM), which identified QRM as a foundational component in any modern pharmaceutical industry quality system. As firms have adopted it, regulators and other experts have observed a number of issues that limit QRM's effectiveness as a mechanism to proactively identify and reduce quality risks that may affect the patient. The issues are:

1. Using formal QRM tools in situations where they are not actually needed
2. Using QRM to justify an action instead of as a tool for truly assessing and exploring risks
3. An organization's culture can limit how QRM is applied proactively
4. Misapplying a specific risk-assessment tool as a QRM process
5. Using rating scales that are neither specific nor appropriate to a given situation
6. Not acknowledging when uncertainty (or the lack of important information) is present
7. Neglecting to keep risk assessments current with changes that could affect underlying assumptions and key decisions

Consider, for example, a case involving a potential product contamination incident at an active pharmaceutical ingredient (API) site. At the end of a production campaign, a metal mesh screen used in one of the final steps was found to have broken; a large section of the mesh material was torn from its housing. Some batches from the campaign had already been released and shipped to a drug product manufacturing site, while batches still at the API site were given a "hold" status and placed into quarantine. In response to the problem, several actions were taken:

- A deviation was raised to investigate the issue, coupled with a formal risk assessment exercise (using FMEA) to decide whether to release the remaining batches.
- The risk assessment found that the screen break presented a low risk of batch contamination.

- This conclusion was used to justify the release of the quarantined API batches to a drug product manufacturing site.

Later, during a regulatory inspection, the inspector reviewed the QRM exercise. Significant problems were found, including customer complaints citing metal in the API. This cast considerable doubt on the validity of the QRM outcomes and the resulting batch release decisions. For example:

- Because the empirical evidence gained from the deviation investigation was misinterpreted, scientifically unsound likelihood estimates were made that significantly affected the risk assessment outcomes. The company, for example, maintained that the mesh section had remained intact despite being dislodged, and assigned a low likelihood rating that metal fragments had entered any API material. But the evidence pointed to the contrary—a piece of mesh wire had broken off when the failed screen was examined while being washed.
- There was no documented rationale as to why a piece of 316 stainless steel up to 850µm in length in a tablet represented a hazard with a medium severity rating and not a high severity rating, nor was there a documented clinical assessment of potential contamination and its risk to patients.
- The company relied on controls and risk mitigation assumed to be in place at the drug product manufacturer to detect metal in the formulated tablets, and paid inadequate attention to detecting and removing metal fragments from the API lots of concern while they were still on-site. This was not considered an acceptable approach, as it meant that the risk of releasing contaminated API to the drug product site had not been adequately assessed.

Providing a subjectively derived risk score to a manager who may not know how to interpret it correctly (e.g., a risk score indicating a low likelihood of occurrence but concerning an issue of potential patient impact and harm) may result in a decision that runs counter to GMP principles.

As we noted before, some organizations incorporate formal quality risk management in all such instances, but this is not actually a GMP requirement. Applying formal QRM "for everything" is at variance with ICH Q9 (section 1, page 2), which states, "The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk." Additionally, some quality decisions should be so obvious that conducting an extensive risk assessment to support decision making is not necessary.

The above example showed how an improperly performed risk assessment can adversely affect batch release decision-making. (For a detailed review of inspectional issues in relation to improperly performed risk assessments, see Waldron, Greene, and Calnan.[3])

In this case, one has to ask whether the firm's management should even have requested a formal risk assessment to determine if the API lots in question should be released without reprocessing or reworking them. Even if the intent of such a risk assessment was truly focused on understanding the risks presented by a broken screen, the subjective nature of the risk-scoring approach and the potential implications for patients seem to have been overlooked. Again, from the Q9 guideline (section 1, page 6): "Appropriate use of quality risk management [which in this case, we posit, was inadequately performed] can facilitate but does not obviate industry's obligation to comply with regulatory requirements." In this case, a key regulatory requirement was to not release contaminated API batches to a drug product manufacturing site.

The intent of QRM is to make data-driven and scientifically sound decisions proactively, not to justify an action or a decision that has already been taken

2. Risk assessment to justify a decision, not assess risk

The intent of QRM is to make data-driven and scientifically sound decisions proactively, not to justify an action or a decision that has already been taken. The outcome of a risk assessment may, of course, support an action, but there should be a logical, fact-grounded rationale to defend what is done. Considering risks should be a thoughtful inquiry instead of a biased vindication.

Our experience shows that when risk assessments fall into this category, they sometimes lead to risk treatments that, when challenged by regulatory inspectors during inspections, do not withstand any level of scrutiny. In these cases, decisions are often not aligned with facts or the way that the risk question was explored.

"Change control" is a quality system element used by some organizations in which QRM is used to justify the proposed plan asking "What could go wrong?" and then devising a control strategy for that possibility.

Consider a case where QRM was performed in conjunction with a proposal at a drug product facility to revise (i.e., mainly reduce) calibration frequencies for instruments and other measuring devices at the site.

- In the risk assessment, the proposed reduced calibration frequencies identified two unacceptable risks. These were considered mitigated by three types of currently in-place detection-related controls: daily verification checks, in-process controls, and finished product testing.
- While to some the risk-reduction strategy may have seemed adequate, when the details were examined on inspection, it became evident that many types of instruments and equipment items at the site (including those deemed critical—e.g., pressure transmitters and in-line temperature probes) were not required by procedure to have any kind of daily verification checks performed, and the validity of this type of control for the risk in question was highly questionable.
- It was not clear how the two other types of documented risk-mitigating controls—in-process controls and finished product testing—could lead to the timely detection of process variation due to out-of-calibration instruments and other equipment items.

- Closer examination revealed that the risk-assessment part of the change control could actually assign the same 12-month default calibration frequency to both GMP-critical and GMP-noncritical instruments. There was no documented explanation to justify the practice, even though inspectors often want to know the basis or rationale for a decision.

Given the nature of the deficiencies seen with this application of QRM, it was clear that a true sense of inquiry and objectivity were lacking in the risk-assessment process to evaluate the proposed change; the emphasis seemed more on justifying the change control proposal. While Q9 does use the word "justify" in its guidance (though only twice in Annex II of the guideline), the emphasis of risk assessment in Q9 is more on "evaluate" or "determine," terms that are used multiple times. This points to the importance of analysis over defending a particular position or proposal.

3. Reactive "firefighting" instead of proactive QRM

Some companies take pride in their ability to react quickly to quality incidents. Their organizational culture rewards individuals and teams who show extra effort in solving difficult technical and operational problems. These so-called heroes are fully focused on the mission at hand—solving the problem—and they receive increased recognition and praise in return.

The problem with this model is that the work and effort being highlighted are usually unsustainable in the long term, as they can be very labor intensive. Also, the "we-can-fix-it" attitude often precludes the development of more proactive systems.[5–6] Unfortunately, these organizations do not give the same visibility to those who are the fire preventers—the people who take proactive steps so that the problems do not occur in the first place.

During a month-long holiday shut down, for example, an injectable product manufacturer expanded the scope of work to include digging through a hallway floor and into soil to replace a sewer line. Since the hallway was adjacent to and outside of the graded areas (A/B and C/D), engineering staff felt that no proactive change control was necessary.

Unfortunately, mold and spores made it through the inadequate containment controls and into the aseptic manufacturing area. Multiple failures to bring the area back into production required extensive investigation and remediation, and experts from other corporate sites were brought in to help. When the area finally was back on-stream (four months later than planned), all involved went out for a celebratory dinner paid for by management in recognition of their accomplishment.

If before the digging started someone had asked a simple risk questions such as, "What might go wrong if we go ahead with this plan?" or "To what

hazards might our production facility be exposed?" effective precautions might have been taken. Regrettably, those who proactively ask these "what-if" questions are not always recognized for anticipating unwanted situations.

ICH Q9 (section 1, page 1) is useful in this area: It highlights the proactive nature of QRM: "An effective quality risk management approach can further ensure the high quality of the drug (medicinal) product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing."

4. Equating FMEA with QRM

A 2006 PDA survey[9] found that FMEA was the most widely applied tool for assessing change controls and for adverse event, complaint, or failure investigations at sites. Observations and anecdotal evidence suggest that this is still true. While FMEA is useful and versatile, some organizations consider it a complete QRM tool in itself. This is in part because typical FMEA worksheets include columns for risk treatment items (i.e., risk-reducing actions) and a reassessment of the risk priority numbers (RPNs). This approach essentially leaves out the third and fourth elements: risk communication and risk review. Despite this limitation, many companies still rely on FMEA as their overall approach to QRM.

Formal risk assessments sometimes fail to add value or clarity to a situation because risk assessments often only superficially address root cause analysis, resulting in ineffective risk-control actions

Some firms have not yet seen that hazard identification and risk assessment tools can be used together synergistically. For example, a high-level preliminary risk assessment might be used first, followed by FMEA on particular parts of a drug container's design. FTA—a more detailed deductive tool—would be appropriate in understanding the causes of key failure modes.

QRM does not necessarily need a complicated and complex process to be effective. For example, one company decided to completely redesign the packaging used for many of its products to ensure a common brand livery (identity). Within weeks of the new product pack launch, complaints from pharmacists began to arrive, pointing out the risks of dispensing errors because of the loss of adequate differentiation between the rebranded products (and between strengths of the same products). Had someone adequately considered the simple risk question of "What might go wrong if we implement this packaging design change?" such problems might have been avoided.

Sometimes those assessing risks using an FMEA get so lost in the details that they lose perspective on the larger risk picture. A review of a QRM report for an API process showed that a firm's development engineers had performed a very detailed well-executed FMEA where the highest risks related to charging particular chemicals into the process and maintaining narrow temperature controls. When asked about the five most serious risks in manufacturing the API, however (not just the specific process operations), or what the technical staff worried about at night, the risk-assessment team members could not come up with a response. It was clear that they did not have the bigger risk picture in mind.

Even when considering the flexibility and usefulness of FMEA as a tool only for risk assessment and control, it is still relatively weak in these areas. FMEA in and of itself offers only a superficial approach to root cause analysis for failure modes, and it provides few, if any, strategies for limiting how much subjectivity may be associated with its RPN outputs. Despite several very useful publications on the limitations of FMEA and its RPN-based approach to risk prioritization (see, for example, Schmidt[12]), the industry continues to place a high reliance on FMEA as a primary tool for conducting QRM.

Some FMEA limitations can be overcome by using other tools in a synergistic manner. When identifying the potential root causes of failure modes in an FMEA, for example, a number of other tools can be used, such as Ishakawa (root cause) analysis, the "Five Whys" tool, FTA, and event-tree analysis,[10–11] a tool has found acceptance in the aeronautics industry, but is less used in the current GMP environment.

5. Inappropriate rating scales

Rating scales are critical to accurate and consistent descriptions of hazard likelihood, impact, and detectability. Scale-based values are assigned during risk assessment and then used during risk evaluation when determining which risks are to be addressed and reduced. Experience has shown, however, that creating and using rating scales properly are two of the most challenging aspects when implementing a QRM program.[7]

Firms use a variety of scales for rating occurrence, severity, and detection, with some more reasonable and defendable than others: 1–3, 1–5, or 1–10 are used frequently. Some scales rate severity numerically, as 1, 3, 5, 7, 10, 20, and 40. A rating of 20, for example, means that there may be one fatality due to the drug; 40 may mean that multiple fatalities could be involved. When one firm was asked about its unique rating scale for detectability, they said that it came from an outside consulting firm; no one inside the company could fully explain its logic.

Generally, two different approaches to scale development are used in the industry. The most common is to apply the same scale (particularly the scale for likelihood or probability of occurrence) to all risk assessments, regardless of the nature of the individual situation, product, or process that is assessed. Firms (and some regulatory agencies) like this approach because the risk ratings may then be compared across products, processes, departments, and even sites.

One limitation of this approach is that while the probability of occurrence scale may be entirely appropriate for one manufacturing process or product, it may be entirely out of range for others. Another is that using the same scale in all risk assessments may place too much emphasis on the final RPNs. This is a problem because directly comparing RPNs from a range of risk assessments fails to recognize that RPNs are derived from ordinal number scales; multiplying ordinal numbers to generate RPNs has questionable mathematical validity.

The second approach to using likelihood scales is to use available information, as limited or as imperfect as it may be, to develop a customized scale for a particular risk assessment. A scale could be based on data from 50 small-scale lots of a drug substance produced in the last two years as part of product development work, for example. A 10-point scale based on available data created here could connote much more precision than the actual experience base provides; a three-point scale may be more appropriate in that situation.

If, on the other hand, the process for manufacturing this drug substance was similar to that used for other products at the site (e.g., a common fermentation process, or a particular chemical synthesis pathway), using that knowledge could be very appropriate when developing an occurrence scale. This could result in a much larger experience set.

Several firms that we have recently visited or inspected have developed likelihood and severity scales that use the same ordinal number ranges (1–5) or the same levels (e.g., the levels for severity may range from negligible to serious), but they also have keywords or definitions assigned to each part of the scale that must be considered in a risk-assessment exercise.

In a 1–5 ordinal number severity scale, for example, there may be five degrees of patient-related impacts, a set of keywords describing five different degrees of GMP noncompliance, and other sets of keywords relating to drug availability or hazards affecting critical quality attributes, etc. So instead of simply assigning a severity rating based on the high-level names associated with the available severity levels (e.g. level 2: low severity), the risk-assessment team must consider specific keywords that define each level to arrive at a severity rating for that hazard or failure mode. This helps assign severity ratings in a more consistent and less biased manner.

A similar approach can be taken when customizing likelihood-of-occurrence scales for individual risk assessments. Scales can have keywords and definitions that relate to occurrences per unit of time, such as one event or fewer in five years, one or more events every week, or numbers of batches, numbers of units produced, (e.g., tablets, vials), etc.

In addition to having scales customized for a specific risk-assessment exercise, it is also important for the QRM team to document its rationale for making key decisions, such as the construction of the scale, the selection of a particular category, and the like. This can help support the ratings that are assigned, and can be a useful source of information for those reviewing the risk-assessment exercise in the future.

Some firms have not yet seen that hazard identification and risk assessment tools can be used together synergistically

6. Introducing uncertainty via subjectivity

Risk increases as uncertainty increases. The ISO 31000 standard, published in 2009, defines risk (13, page 9) as the "effect of uncertainty on [achieving one's] objectives." Uncertainty can be due to a number of different factors, such as lack of information about or limited experience with a process or material during the early stages of process development. Uncertainty can also be present when options to detect a particular hazard are lacking or the detection methods are not used. Acknowledging that uncertainty is present or that you do not know something are two of several ways to respond.

Subjectivity in risk assessment work is another important bias that should be addressed.[14]

Subjectivity can be the result of differences in perceptions, stakeholder values and experiences, and other factors. ICH Q9 discusses the difficulty of achieving a shared understanding of the application of risk management because each stakeholder might:

- Perceive different potential harms
- Place a different probability on each harm occurring
- Attribute different severities to each harm

Subjectivity can be compounded by groupthink as part of brainstorming activities—during hazard identification steps, for example, and when probability ratings are being assigned. In addition, a lack of diversity in risk-assessment teams can limit the breadth and effectiveness of risk-assessment exercises.

Subjectivity can have other negative effects, as well. As discussed in ISO 31000,[13] stakeholders form judgments about risks based on differences in values, needs, assumptions, concerns, etc. As a result, it can be difficult to reach agreement on the acceptability of a particular risk, or on the suitability of the course of action proposed to address that risk.

This is not to say that subjectivity should be banished from discussions on risk. Without the critical analysis of alternative viewpoints, groupthink can blind team members to significant risks.

Subjectivity is not just how we perceive and discuss risks—it can also be a consequence of the scoring method used to estimate the risk. In the likelihood-of-occurrence scale shown in Table A, the phrases "very unlikely," "unlikely," and "very possible" are used to indicate "low," "medium," and "high." This represents another way to assess the likelihood of occurrence (instead of the quantity of transactions, also provided for in the table—

Table A: Generic likelihood-of-occurrence scale

Likelihood of occurrence The likelihood of a pump failure (leading to potential oil migration across the diaphragm) occurring within a given time period and per a quantity of transactions.	**Low**	< 0.5% failure rate, meaning no failure occurs within 200 consecutive uses of the pump. (This corresponds to at least 4 years of usage of the pump without a failure, based on 50 pump uses per year.)
	Medium	< 2% failure rate, meaning one failure in every 51-200 pump uses. (This corresponds to a failure occurring within 4 years of pump usage, based on 50 pump uses per year.)
	High	≥ 2% failure rate, meaning one or more pump failures per year.

one per hundred, etc.). If the quantitative aspect of the occurrence scale were not there, however (as is often the case), the scale would provide no guidance to what these phrases mean, especially in the context of the risk-estimation exercise in question, introducing subjectivity into the likelihood-of-occurrence ratings. (Research has found that different people interpret phrases such as these in very different ways—see Budescu, Por, and Broomwell for a useful research study in this regard.[15])

A number of recommendations for addressing the problems of subjectivity and uncertainty during risk-assessment activities are presented in previous publications by the authors.[2, 4, 10] Some useful strategies include:

- Ensure that QRM teams have a facilitator who knows about factors that can influence risk perception, and about these problems that can arise as a result of human heuristics, particularly during brainstorming sessions. This can help achieve more science-based likelihood-of-occurrence estimates and severity ratings for hazards that are not adversely influenced by risk perception factors.
- Ensure that risk-assessment teams are sufficiently diverse can help with failure mode identification activities, and when risk control proposals are being discussed and determined. Inviting someone onto the team with a different point of view to challenge what has been proposed [13] to also be of value.
- Use key words in scales to identify levels of severity, likelihood, and detectability.
- Acknowledge that uncertainty is present during risk analysis. Useful strategies include documenting any pertinent assumptions made during the risk assessment in the risk-assessment report, and the likely range of any risk ratings (or RPNs) considered especially difficult to assess. Addressing such ranges is not unlike the approach used by storm forecasters for tropical storm predictions.
- Realize that you may know more than you think, and source the data to support that knowledge.[11]
- Build good science into all risk assessments by ensuring that validated data, wherever available, are given prominence over the unsupported opinions of those who may speak the loudest in risk-assessment teams. Another simple strategy is to design the risk-assessment tool to ensure the following: Before any probability, severity, or detection ratings are assigned to failure modes or hazards, the current GMP controls that may help prevent, detect, and reduce the potential effects of those failure modes or hazards should be formally documented and assessed.

7. No meaningful risk reviews, or "once and we're done"

Many QRM models include a recurring loop for review and monitoring; often, however, this step is disregarded.[16] When reviewing a risk assessment, the assumptions, decisions, and actions made in the original risk assessment can be compared to the current situation. Ongoing monitoring activities are also important, as they can identify situations or changes that could affect the original risk assessment and the decisions made.

Companies often ask "How frequently should risk-review exercises be performed?" The answer depends on various factors, including, as Q9 (1, p. 5) states, "the level of risk that was originally determined in the risk assessment."

Other useful factors to consider are:

- How much new knowledge and experience has been gained with the process of concern?
- How much uncertainty was associated with the probability estimates and with the identification of failure modes last time?
- How much has the process changed since the original risk assessment was performed?

Some risk reviews may be coupled with annual product reviews (APRs). We think this is a useful strategy and one that can make best use of the extensive data compiled for APRs.

It can also be useful if clear risk-review instructions are prescribed in the risk team report (e.g., "Please review the effectiveness of the detection control for Failure Mode 5, as we relied on that control a lot when assigning the low risk rating there"). Doing this recognizes that the risk team members will usually have good insight into any problems and assumptions that arose, and they should be familiar with how dynamic (or static) the situation was, and is.

Regardless of when the risk reviews are performed, it is important that reviewers have access to the original risk team's key recommendations; these should be documented, together with information on the rationales behind key risk ratings. If there were significant uncertainty in a likelihood-of-occurrence estimate during the original risk-assessment exercise, for example, the team should document the need to reexamine this more carefully during the review exercise, taking into account certain types of information that should, by then, be available to better inform that estimate.

Conclusion

As pharma and biopharma firms continue to apply QRM, many are integrating risk-based thinking into their quality systems and making increased use of risk assessment and related tools. Teams that perform QRM activities are also becoming more competent as they develop knowledge and skills through experience.

At the same time, however, several issues continue to exist across the industry; failing to address these will diminish the value gained from the industry's QRM work.

Some firms use formalized risk assessment tools inappropriately, especially when the GMPs for regulatory expectations indicate the path forward is clear. In other cases, organizations unintentionally reward reactive QRM and "firefighting" over prevention and proactivity, because their cultures are rooted and experienced in managing crises.

Other issues include:

- Poorly defined and irrelevant rating scales are sometimes used in risk-assessment exercises, producing outcomes with high levels of subjectivity.
- Risk-communication and risk-review activities are either not performed or are performed only as an afterthought, providing little added value.
- The rationale for key decisions is lost or not properly documented. As a result, it can be unclear during risk-review activities why the original risk assessment team made the decisions it did.

The underlying intent of QRM is not simply to identify a risk score for a hazard or create a plan to reduce that risk; rather, it is to bring together knowledgeable people from different disciplines with various informed perspectives who can analyze, anticipate, and prevent potential problems. Not only should this help ensure safe, pure, and available medicines for the patients that need them, it should contribute to a richer and more robust understanding of products and processes within the organization. ■

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About the Authors

James Vesper, founder and president of LearningPlus, Inc., has more than 35 years' experience in the pharmaceutical industry. Since 1991 he and his firm have worked with pharma/biopharma, device, and blood products organizations around the world on performance solutions and custom learning events; he has also been a consultant to the World Health Organization's Vaccine Quality Network–Global Learning Opportunities. He has a BS degree in biology from Wheaton College, Wheaton, Illinois, a master's degree public health from the University of Michigan School of Public Health, Ann Arbor, Michigan, and a PhD in education from Murdoch University, Perth, Australia. He has been an ISPE member since 2004.

Kevin O'Donnell is Market Compliance Manager at the Health Products Regulatory Authority in Ireland. In this role he is responsible for a number of compliance-related programs, such as the Quality Defects & Recall program and the agency's Sampling & Analysis activities. Kevin is also a Senior GMP Inspector at the HPRA, and is currently chair of the PIC/S Expert Circle on Quality Risk Management. He earned a BS in chemistry and mathematics from University College Galway, Ireland, in 1991, followed by an MS in pharmaceutical quality assurance in 2002 and a PhD in quality risk management in 2008, both from Dublin Institute of Technology, Dublin, Ireland. Kevin has been an ISPE member since 2004.

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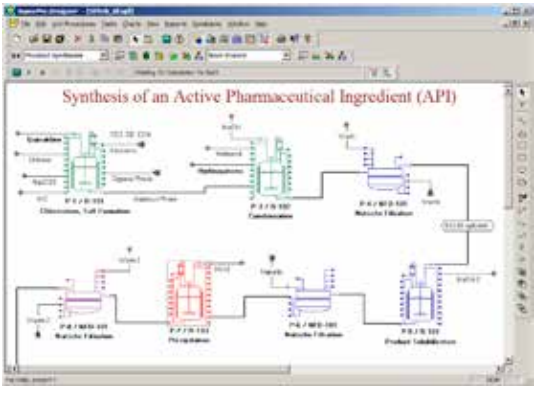

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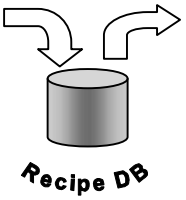

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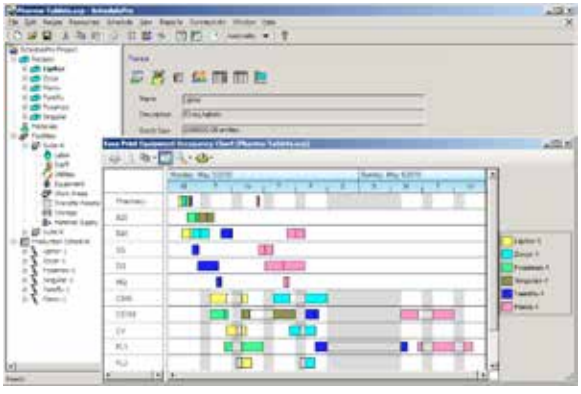

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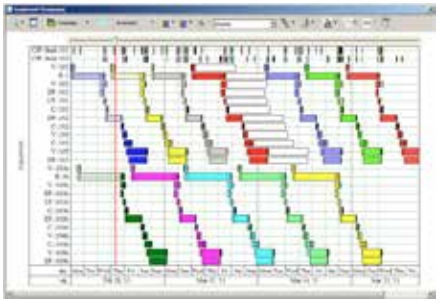

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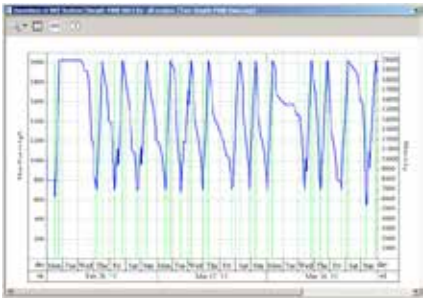
Tracking demand for resources (e.g., labor, materials, utilities, etc.)



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SchedulePro is a versatile production planning, scheduling, and resource management tool. It generates feasible production schedules for multi-product facilities that do not violate constraints related to the limited availability of equipment, labor, utilities, and inventories of materials. It can be used in conjunction with SuperPro (by importing its recipes) or independently (by creating recipes directly in SchedulePro). Any industry that manufactures multiple products by sharing production lines and resources can benefit from the use of SchedulePro. Engineering companies use it as a modeling tool to size shared utilities, determine equipment requirements, reduce cycle times, and debottleneck facilities.

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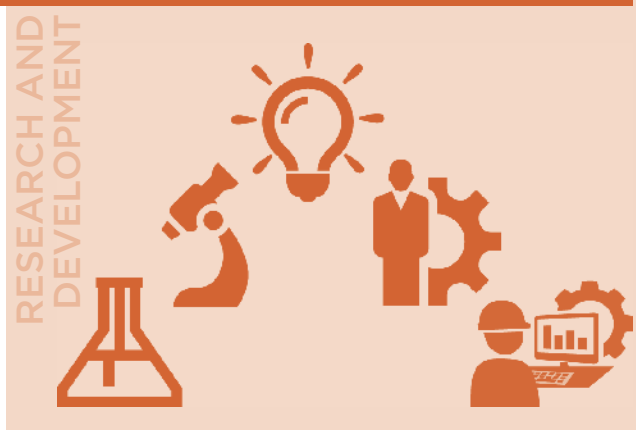


Distribution Quantification of Synthetic Amino Acid Oligomers

Ke Wang, Fangfang Liu, Stéphane Caron, and Kimberly Erland Vukovinsky

A chemical coupling reaction that produces the targeted molecule with a composition p in the final product may be viewed as a discrete stochastic process. Under the assumption that the sequence of solid phase peptide synthesis follows a Bernoulli process, each coupling step is considered as an independently and identically distributed Bernoulli trial, and the theoretical composition of each synthetic amino acid oligomer (peptide) is formulated. The composition calculation is illustrated through a synthetic hexamer (peptide with six amino acids) and a dodecamer (peptide with twelve amino acids) with several postulated scenarios to maximize synthetic efficiency of the desired peptide at the expense of smaller derivatives. This computational evaluation provides guidance for the synthetic strategy and ultimately facilitates the final desired product purification.

The field of synthetic organic chemistry relies on the ability of chemists to identify the best strategy for the synthesis of a molecule, beginning with readily available starting materials. The functional groups, topology, and stereochemistry of the synthetic target—a peptide in this paper—influence how it is deconstructed through this retrosynthetic analysis.[1] One of the most common strategies to maximize synthetic efficiency is to develop a convergent synthesis;[2] this is intrinsically more efficient than a linear reaction sequence as it reduces the length of the longest linear sequence and thus maximizes the utilization factor for each starting material. Figure 1 provides a comparison of a linear and convergent sequences.

An exception to the benefit of the convergent sequence has been the synthesis of peptides. Since the introduction of solid phase synthesis by Merrifield,[3] several protecting groups, solid support, and novel coupling agents have been discovered to facilitate the addition of successive amino acids to a peptide.[4]

The synthesis of the peptide is generally a linear process, where the growing oligomer chain on the solid support reacts with an amino acid to grow the chain by one unit. All excess reagents not attached to the solid support are washed away and the new oligomer proceeds to the next coupling reaction. The desired product is obtained through the final removal of protecting groups and cleavage from the solid support.

This methodology has led to the preparation of elaborate peptides in an automated fashion, and gains much of its power from its repetitive and predictable nature.[5] One drawback of this approach, however, is that the amino acid introduced to the growing chain is often used in large excess to drive reaction completion. While this might not be a concern when using naturally occurring amino acids, it would be preferable to avoid a wasteful excess of costly and difficult-to-prepare unnatural amino acids.

When comparing a linear vs. convergent synthesis, a probabilistic assessment could be used to quantify the compositions of different lengths of peptides after the introduction of multiple amino acids based on the conversion yield. Introduced in this paper are two synthesis examples for a targeted hexamer and a targeted dodecamer, whose composition in the reaction product mixture were calculated under the assumption that an amino acid coupling reaction follows an independent and identically distributed (i.i.d.) Bernoulli distribution.

With this assumption, the distributions of peptides with different lengths can be formulated. As activation and deprotection reactions do not change the composition of the peptide chain being grown, they will not affect the ratio of products of different chain lengths. Several potential scenarios were postulated with the objective of maximizing the ratio of the desired peptides at the expense of smaller derivatives. A general formulation of peptide distribution and product ratio was also proposed. This evaluation provides guidance for the synthetic strategy and ultimately facilitates the final desired product purification.

Hexamer Synthesis

Three hexamer solid phase synthetic strategies are presented in Figure 2. Scheme (a) represents a linear synthesis of growing oligomer to the solid support. The synthesis of hexamer is accomplished in six coupling steps: A monomer is produced after the first amino acid unit coupling to the chosen linker, a dimer after the second coupling, and then the process is repeated to grow the oligomer chain to the desired length. At the end of reaction, the targeted hexamer is obtained through the final removal of protecting groups and cleavage from the solid support.

Scheme (b) describes a convergent two-chain approach where two independent parallel chains are considered with each chain growing to the half-length oligomer described in the linear scheme (a). After three coupling steps, one chain is cleaved from the solid support to be coupled to the other chain. The hexamer synthesis in a convergent two-chain scheme requires seven coupling steps and two cleavages from the solid support. Similarly, a convergent three-chain approach, as displayed in scheme (c), requires eight coupling steps and three cleavages from solid support.

This computational evaluation provides guidance for the synthetic strategy and ultimately facilitates the final desired product purification

Each unit amino acid coupling could be considered as an i.i.d Bernoulli trial with success probability p. With this assumption, the distributions of peptide types (monomer, dimer, trimer, tetramer, pentamer, and hexamer) are mathematically expressed in Table A for all three postulated schemes in Figure 2.

In a linear single-chain scheme, the peptide compositions follow a binomial distribution (n, p) with probability mass function:

$$p(X = x) = \binom{n}{x} p^x (1-p)^{n-x}, for\ x \le n \quad (1)$$

where n is the number of coupling steps (n = 6 for a synthetic hexamer), p is the coupling reaction yield, and X is a random variable representing a peptide with certain length, i.e., X = 1 is monomer, X = 2 is dimer, … , X = 6 is hexamer.

$\binom{n}{x}$ is the binomial coefficient and is equal to:

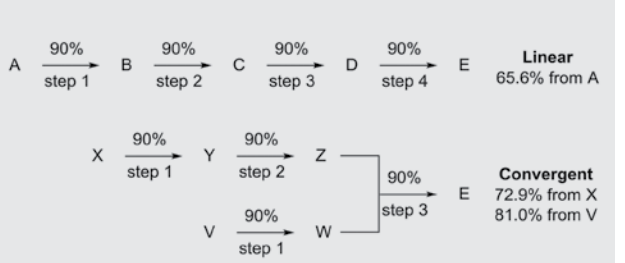
$$\frac{n(n-1)(n-2)\cdots(n-(x-1))}{x(x-1)(x-2)\cdots 1}$$

Substituting the values of n and x into Equation (1) provides the formula for linear synthesis oligomer composition in Table A (column 2).

In a convergent two-chain scheme, each chain produces an oligomer mixture including monomer, dimer, and trimer. The distribution of monomer, dimer, and trimer in each chain also follows a binomial distribution with n = 3. The composition of the oligomers after the last step of the two-chain coupling is calculated via conditional probabilities, dependent on whether the last coupling between the two chains succeeds or not. The oligomer composition is calculated in the following procedure:

- Let X and Y be random variables representing the number of successful coupling after n trials in each chain respectively, both X and Y follow a binomial (n, p) distribution. Given X and Y are independent, X + Y follows a binomial (2n, p) distribution.
- Let W be a random variable representing the last coupling step of two-chain products, W follows a Bernoulli distribution as well, i.e. P(W = 1) = p for the probability of successful coupling reaction.
- Let Z be a random variable representing the type of peptides produced in this process (Z = 1 is monomer, Z = 2 is dimer, … , Z = 6 is hexamer),

Figure 1: Linear vs. convergent sequence



under the assumption that W, X, and Y are independent from each other, the oligomer compositions in the two-chain scheme in Table A (Column 3) are obtained by substituting the values of X, Y, and Z into the following equation (2):

For $j = 1, 2, 3,$

$$\begin{aligned} P(Z=j) &= \sum_{i=0}^{1} P(Z=j|W=i)P(W=i) \\ &= P(Z=j|W=1)\cdot p + P(Z=j|W=0)\cdot(1-p) \\ &= P(X+Y=j|W=1)\cdot p + P(X\ or\ Y=j|W=0)\cdot(1-p) \\ &= \binom{6}{j} p^{j+1}(1-p)^{6-j} + \binom{3}{j} p^{j}(1-p)^{4-j} \end{aligned}$$

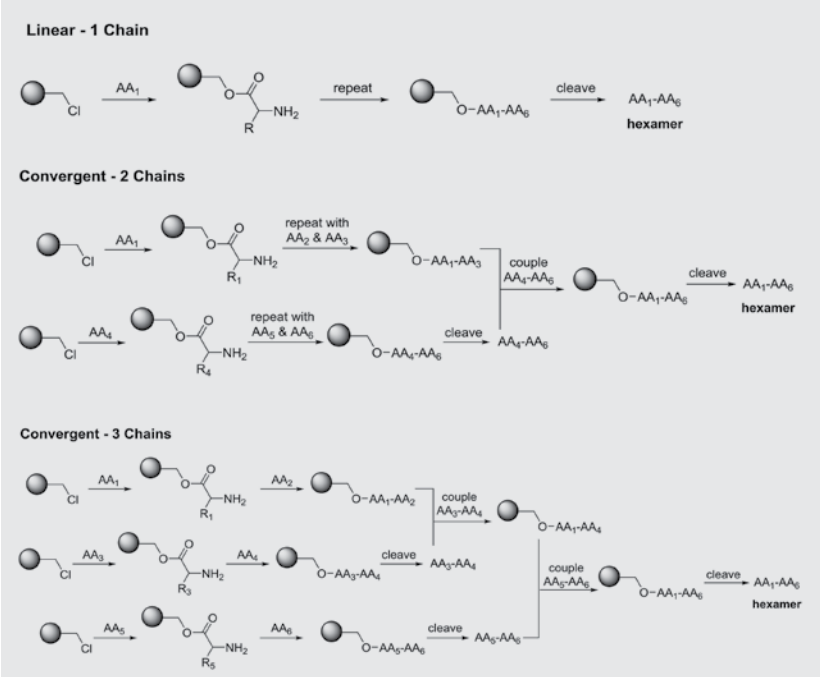
For $j = 4, 5, 6,$

$$\begin{aligned} P(Z=j) &= \sum_{i=0}^{1} P(Z=j|W=i)P(W=i) \\ &= P(Z=j|W=1)\cdot p + P(Z=j|W=0)\cdot(1-p) \\ &= P(X+Y=j|W=1)\cdot p + 0\cdot(1-p) \\ &= \binom{6}{j} p^{j+1}(1-p)^{6-j} \end{aligned} \quad (2)$$

The oligomer compositions in a convergent three-chain scheme in Table A (column 4) are calculated in a similar structure:

- Let X, Y, and Z denote the number of successful couplings after n trials in each chain; X, Y, and Z follow a binomial (n, p) distribution. Given that X, Y, and Z are independent process, X + Y + Z follows a binomial (3n, p) distribution.
- Let W1 be the outcome of coupling chain 1 and chain 2, and W2 be the outcome of the last step coupling of three chains, then W1 and W2 follows Bernoulli distribution with success rate of p.
- Assume X, Y, Z, W1, and W2 are all independent, if S denotes the type of peptide after the coupling of three chains, where S = 1 is monomer, …, S = 6 is hexamer, then the yield of each peptide as shown in Table A can be calculated by substituting the values of X, Y, Z, W1, and W2 into the following equation (3):

Figure 2: Schematic solid phase synthetic routes for a synthetic hexamer through linear single-chain and convergent two- and three-chain



For $s = 1, 2$,

$$
\begin{aligned}
P(S=s) &= \sum_{i=0}^{1}\sum_{j=0}^{1} P(S=s|\,W_1=i, W_2=j)\mathrm{P}(W_1=i, W_2=j) \\
&= P(S=s|W_1=0,W_2=0)\cdot(1-p)^2 + P(S=s|W_1=1,W_2=0)\cdot p(1-p) \\
&+P(S=s|W_1=0,W_2=1)\cdot p(1-p) + P(S=s|W_1=1,W_2=1)\cdot p^2 \\
&= P(X=s|W_1=0,W_2=0)\cdot(1-p)^2 + P(X+Y=s|W_1=1,W_2=0)\cdot p(1-p) \\
&+P(X+Z=s|W_1=0,W_2=1)\cdot p(1-p) + P(X+Y+Z=s|W_1=1,W_2=1)\cdot p^2 \\
&= P(X=s)\cdot(1-p)^2 + P(X+Y=s)\cdot p(1-p) \\
&+P(X+Z=s)\cdot p(1-p) + P(X+Y+Z=s)\cdot p^2 \\
&= \binom{2}{s}p^s(1-p)^{4-s} + 2\cdot\binom{4}{s}p^{s+1}(1-p)^{5-s} + \binom{6}{s}p^{s+2}(1-p)^{6-s}
\end{aligned}
$$

For $s = 3, 4$,

$$
\begin{aligned}
P(S=s) &= \sum_{i=0}^{1}\sum_{j=0}^{1} P(S=s|\,W_1=i, W_2=j)\mathrm{P}(W_1=i, W_2=j) \\
&= P(S=s|W_1=0,W_2=0)\cdot(1-p)^2 + P(S=s|W_1=1,W_2=0)\cdot p(1-p) \\
&+ P(S=s|W_1=0,W_2=1)\cdot p(1-p) + P(S=s|W_1=1,W_2=1)\cdot p^2 \\
&= P(X=s|W_1=0,W_2=0)\cdot(1-p)^2 + P(X+Y=s|W_1=1,W_2=0)\cdot p(1-p) \\
&+ P(X+Z=s|W_1=0,W_2=1)\cdot p(1-p) + P(X+Y+Z=s|W_1=1,W_2=1)\cdot p^2 \\
&= 2P(X+Z=s)\cdot p(1-p) + P(X+Y+Z=s)\cdot p^2 \\
&= 2\cdot\binom{4}{s}p^{s+1}(1-p)^{5-s} + \binom{6}{s}p^{s+2}(1-p)^{6-s}
\end{aligned}
$$

For $s = 5, 6$,

$$
\begin{aligned}
P(S=s) &= \sum_{i=0}^{1}\sum_{j=0}^{1} P(S=s|\,W_1=i, W_2=j)\mathrm{P}(W_1=i, W_2=j) \\
&= P(S=s|W_1=1,W_2=1)\cdot p^2 \\
&= P(X+Y+Z=s|W_1=1,W_2=1)\cdot p^2 \\
&= \binom{6}{s}p^{s+2}(1-p)^{6-s}
\end{aligned}
\qquad (3)
$$

Bar charts in Figure 3 present the calculated peptide compositions under each of the three schemes in Figure 2 when p is equal to 0.75, 0.90, and 0.95. In all the three schemes, the composition of the targeted peptide in the reaction product, hexamer, increases as p increases. To achieve a 50% hexamer, it requires at least a 90% conversion at each step. The slightly higher hexamer composition is expected in the linear single-chain process as additional smaller fragments are introduced late in the synthesis using the convergent two-chain and three-chain processes.

Ratio of Hexamer and Pentamer

It is often chemist's interest in purification to design a synthetic route that maximizes the ratio of hexamer and pentamer, i.e., the two largest peptides. As shown by the equations in Table A, the ratio p/(6(1-p)) is the same for the three schemes. This equation can be extended to a more general formulation to any length of peptides as:

$$\frac{p}{n(1-p)} \text{ for } n \geq 1 \text{ and } 0 < p < 1 \qquad (4)$$

The ratio only depends on the total number of amino acid units in the synthesis and the coupling yield at each step. The total number of amino acid units is the same, i.e., six for the above three described schemes; this produces the same ratio of the two largest peptides (hexamer and pentamer) for any 0 < p < 1.

The above probability and ratio calculations apply to the convergent schemes where the mixture of peptides from the multiple chains react together to produce hexamer without separating the largest peptide from the mixture in any chain. In the two-chain scheme, for example, the chain 2 oligomer mixture (monomer, dimer, and trimer) will react with the chain 1 mixture. When purification is the main concern of the process, adding a purification step to eliminate smaller fragments before the last coupling reaction can improve the ratio of the two largest peptides, as demonstrated for a modified three-chain scheme shown in Figure 4. In this case, the ratio of hexamer and pentamer will be the same as the ratio of trimer and dimer in the first chain $\frac{p}{3(1-p)}$. This is a great improvement, a 50% increase on the ratio, when compared to the original process with n being 6 in Equation (4).

Similarly, separating out dimers from monomer in chain 2 and chain 3 after cleavage in the three-chain scheme provides an improved ratio, $\frac{p}{2(1-p)}$, for hexamer and pentamer. Shown on the left in Figure 5 are

the ratios of hexamer and pentamer under different synthetic schemes and coupling probabilities. The red line represents the ratio for the original three schemes without additional fragment purification, while green and blue lines represent the ratios for the two- and three-chain schemes with purification. The ratios from the latter are 2 times and 3 times higher than any original schemes respectively, providing guidance in selecting synthetic routes when there is a need to balance process efficiency with product purity.

In Equation 2, the ratio of the largest two peptides applies to any target length, i.e., n > 1. The value of n is the total number of amino acid units in any chosen chain where the last coupling reaction has taken place. For example, to synthesize a dodecamer, a peptide with twelve units of amino acid, five schemes can be contemplated with a linear one-chain, and four convergent two-, three-, four- or six-chains. The values for n will be 12, 6, 4, 3, and 2, respectively. Shown on the right in Figure 5 are the calculated ratios of the two largest peptides, dodecamer and undecamer, under different schemes. The six-chain scheme with additional fragment purification has an optimal ratio that is six times higher than any of the schemes without fragment purification.

Figure 3: Peptide composition distribution under the three synthetic schemes in Figure 2 when p = 0.75, 0.9, and 0.95

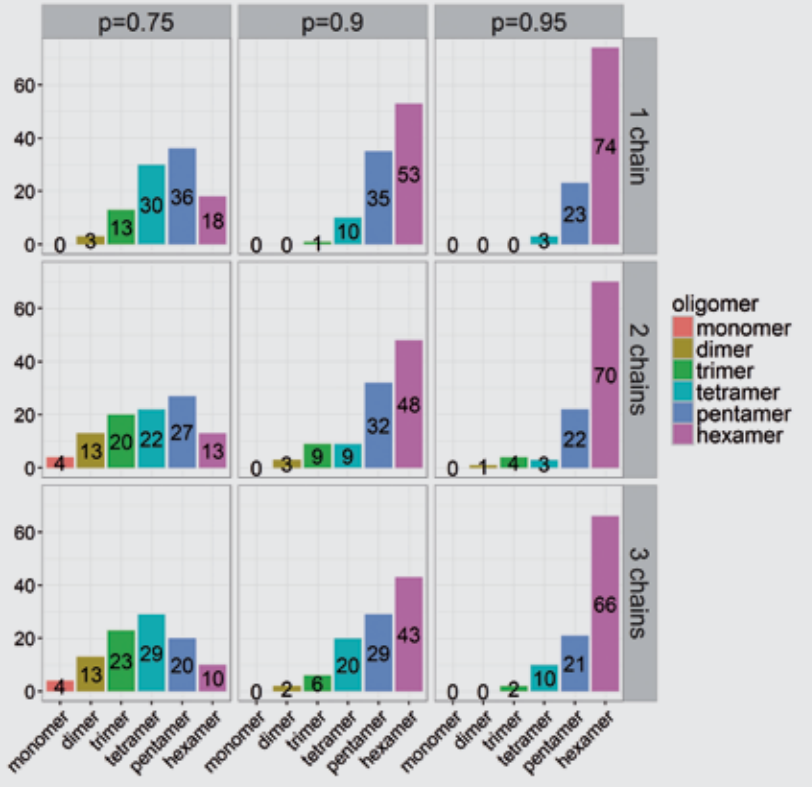
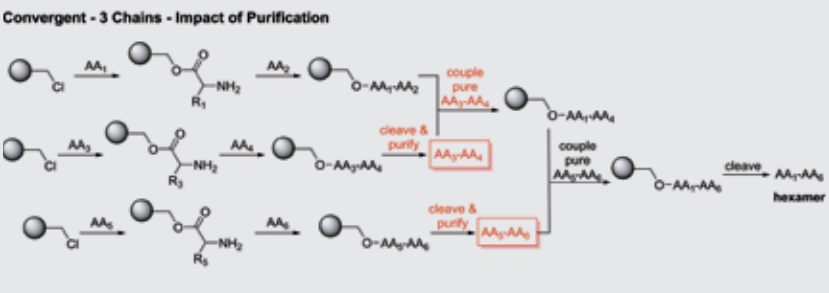


Figure 4: Modified convergent three-chain synthetic scheme with fragment purification



Conclusion

A probabilistic approach was taken to estimate the peptide compositions in the solid phase oligomerization. This paper evaluated the theoretical peptide compositions for both linear and convergent synthesis strategies. A general formulation of the largest two peptide ratios was derived through a synthetic hexamer and dodecamer. While a slightly higher composition of the targeted peptide was present in the linear synthesis, the ratio of two largest peptide compositions is significantly improved in the convergent strategy with fragment purification. This computational exercise in synthetic peptide design is still in the understanding and exploratory mode; when there is a need to balance process efficiency with product purity, however, its potential applicability and flexibility in guiding synthetic strategy and facilitating the purification of the final desired product has been demonstrated. ■

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Figure 5: Ratios of hexamer/pentamer (left) and ratios of dodecamer/undecamer (right) under different schemes for p=0.75, 0.8, 0.85, 0.9, and 0.95

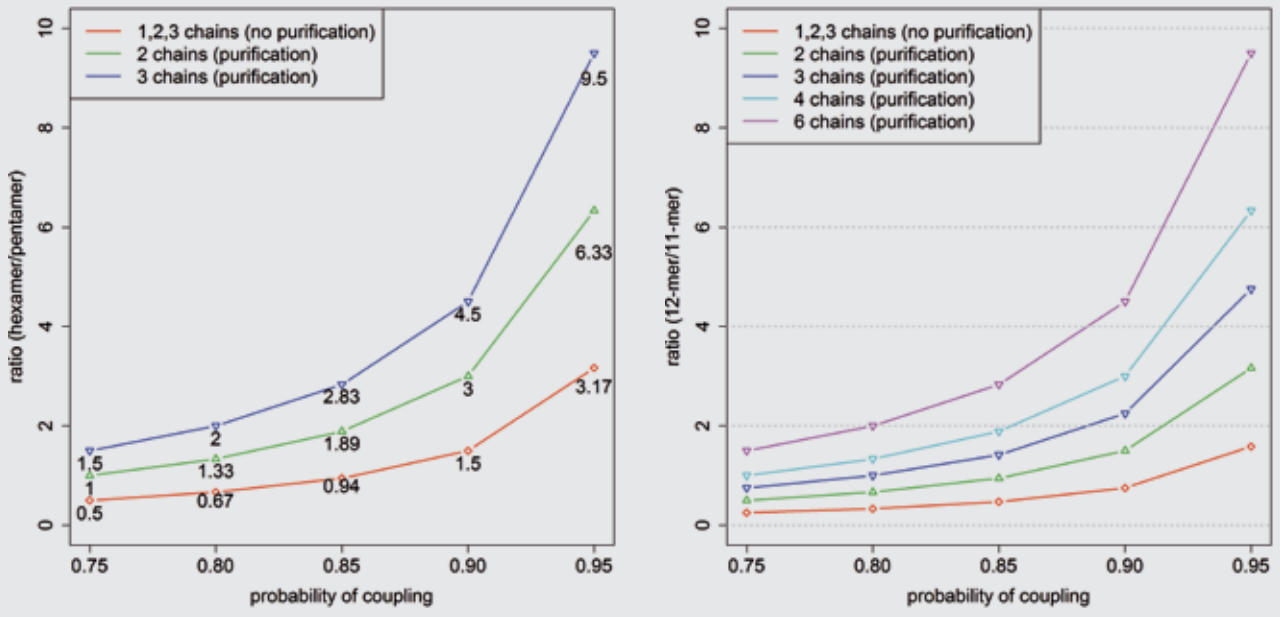


Table A: Mathematical expressions of each oligomer composition for hexamer synthesis under the three postulated schemes in Figure 2, where $0 \le p \le 1$

	1 chain	2 chains	3 chains
monomer	$6p(1-p)^5$	$6p^2(1-p)^5+3p(1-p)^3$	$2p(1-p)^3+8p^2(1-p)^4+6p^3(1-p)^5$
dimer	$15p^2(1-p)^4$	$15p^3(1-p)^4+3p^2(1-p)^2$	$p^2(1-p)^2+12p^3(1-p)^3+15p^4(1-p)^4$
trimer	$20p^3(1-p)^3$	$20p^4(1-p)^3+p^3(1-p)$	$8p^4(1-p)^2+20p^5(1-p)^3$
tetramer	$15p^4(1-p)^2$	$15p^5(1-p)^2$	$2p^5(1-p)+15p^6(1-p)^2$
pentamer	$6p^5(1-p)$	$6p^6(1-p)$	$6p^7(1-p)$
hexamer	p^6	p^7	p^8

About the Authors

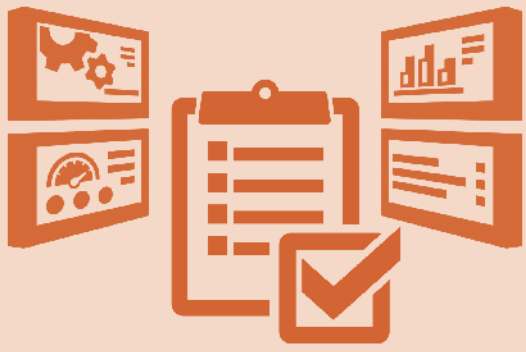
Ke Wang, PhD, received her BS and MS degrees in chemistry from Wuhan University in China, and her PhD in Statistics from Colorado State University. Ke joined Pfizer in Groton, Connecticut, in 2008; she is now an Associate Director in Pharmaceutical Science and Manufacturing Statistics group. Her primary responsibility is to provide statistical support to Pfizer Chemical Research and Development in Groton and Sandwich as well as the Analytical Development of drug substance.

Fangfang Liu, PhD, received her BS degree in statistics from the University of Science and Technology in China in 2010, and her PhD degree in statistics at Iowa State University in 2015. Fangfang joined Pfizer in 2015 and started as a Manager in Pharmaceutical Science and Manufacturing Statistics group to support Pfizer Chemical Research and Development.

Stéphane Caron, PhD, received his BS and MS degrees from Université Laval in Canada under the direction of Robert Burnell, then joined the group of Clayton H. Heathcock at the University of California–Berkeley, where he received his PhD in 1995. He started his industrial career at Pfizer in Groton, Connecticut, where he is now an Executive Director in Chemical R&D.

Kimberly Vukovinsky is Head of the Pfizer Pharmaceutical Sciences and Manufacturing Statistics Group. Kim has coauthored several publications on statistical considerations in QbD, large-sample-size lot release for content uniformity, and general statistical methods. She is currently contributing to the application of statistics within the three-stage process validation framework. She earned a BS in business administration and mathematics from Trinity University, San Antonio, Texas, and an MS in statistics from Iowa State University, Ames, Iowa.

REGULATORY COMPLIANCE



Quality Culture Case Study: The Importance of Understanding the Process

Norman Howe and Nicole Leitz

For the purposes of the change initiative outlined in this article, "quality culture" is defined as the habits and behaviors that result in quality products. This is an adaptation of the definition outlined in "Juran's Quality Handbook," 5th ed.[1]

The US FDA has acknowledged the importance of quality culture in an organization. In its July 2015 "Request for Quality Metrics" draft guidance, the agency outlined its plans for the pharmaceutical industry to report specific quality metrics; it also included optional metrics that reflect the culture of the company. This action reaffirms the principle that traditional specification-based measurements of product quality may not by themselves ensure efficacy and safety for the consumer.[2]

This article tells the story of a journey to improve compliance with FDA regulations within our company. We recount our experiences here to illustrate how objective measures helped improve quality, reducing errors by two orders of magnitude and cutting costs as well.

Status Quo Ante

Like many companies, we spent a great deal of time writing procedures and training our employees. Despite this, many errors still occurred during the execution of these procedures, and we spent too much time and money correcting them. When we dug into the numbers we found that our actual error rate was low—less than 1%. Due to the complexity of our processes, however, the absolute number of errors was outrageous.

When we added up all the steps involved in making our product—from raw materials through manufacturing, testing, and paperwork—we discovered that there were more than 10,000 tasks that had to be done correctly and in chronological order. This meant that achieving even a 99.9% right-the-first-time rate produced ten errors per batch.

We tried all the typical management tools to improve the error rate: retraining, disciplinary actions, "inspirational" speeches by managers, automation, etc. Nothing worked. Everyone's time was constantly being consumed with deviations and nonconformances.

In a typical scenario, an employee who had made an error on a simple task—say recording raw data on a batch record—would become the subject of an investigation. Because there were so many of these errors, the investigator would quickly conclude that the operator had been inattentive. The next step was to march the employee to the training room in front of the whole shift. The employee was then processed through the same training that he or she was given initially.

And we somehow expected different results.

The real root cause, of course, was invariably more nuanced than simple inattentiveness, but our actions ensured that the employees were afraid to speak openly during investigations. Thus, our best source of information for process improvement dried up.

We began by identifying the behaviors we wanted to encourage and determining how to measure them

Changing the Paradigm

Then we tried a more bottom-up strategy. While it was devised and supported by management, the employees steered the project at a tactical level.

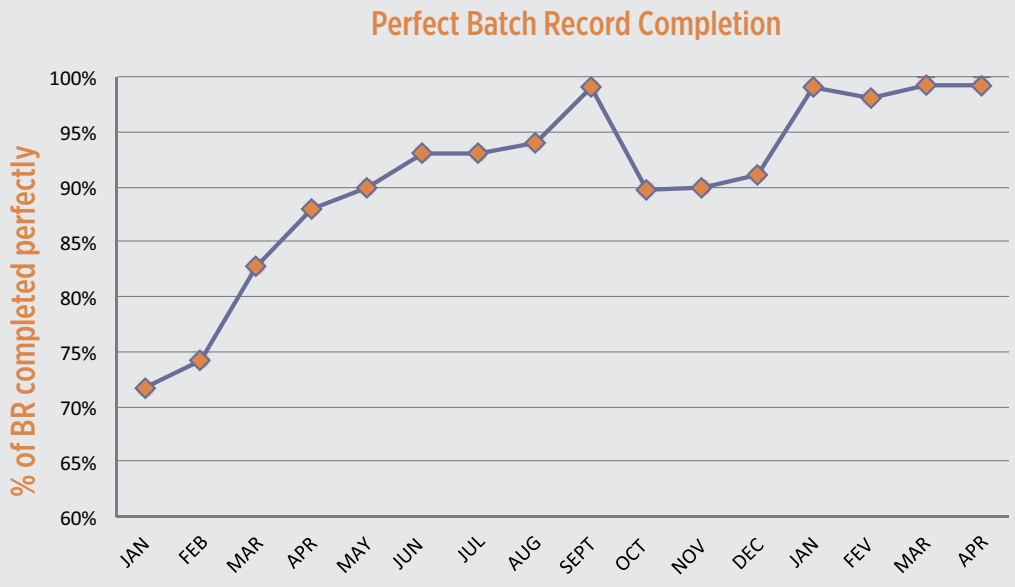
We began by identifying the behaviors we wanted to encourage and determining how to measure them once they were enacted. The types of behaviors on which we focused are not complex activities. Rather, they are the myriad simple tasks that happen every day, like good documentation practices, correct garb, or proper floor cleaning. If not done correctly 100% of the time, these simple tasks can kill your costs.

We then promoted and encouraged those quality behaviors, transforming them into employee habits. Our ability to measure any given behavior allowed us to improve it, because we could directly see the results of any changes we made to the system.

Positive Training

At the start of the program, management met with employees to explain what we were going to do. We prepared carefully for these meetings, producing charts and data to illustrate how much these errors were costing us. We also told the employees that while they would have great latitude in the implementation of the process, their participation was not optional.

Figure 1: Percentage of batch records completed perfectly, by month



Note: The October performance drop shown was judged to be due to the introduction of a new product. This uncovered an opportunity for us to improve our new-product procedures.

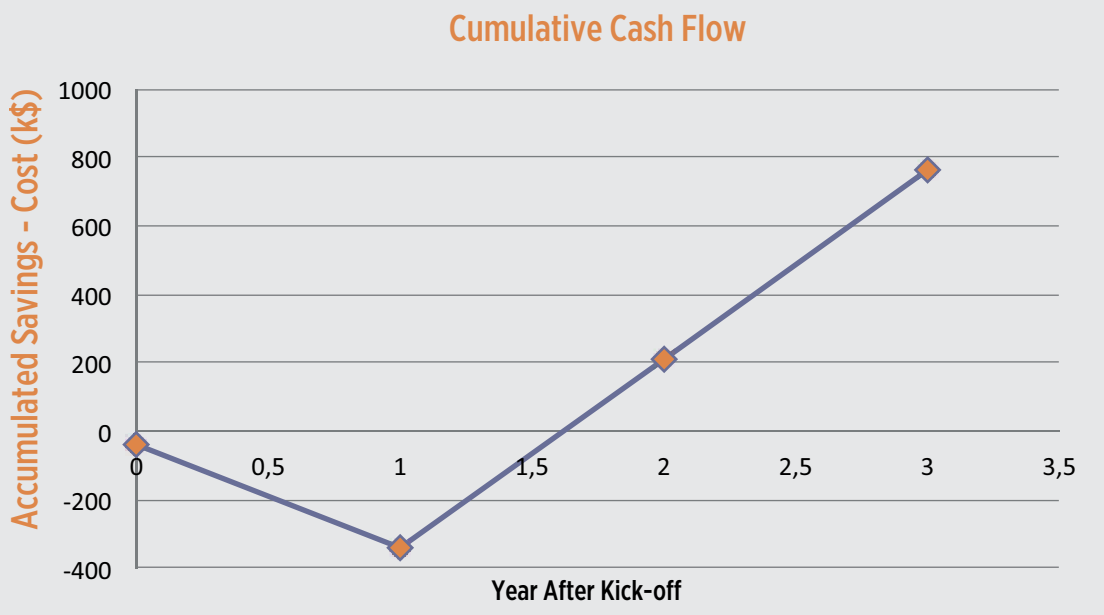
We organized employees into teams that reflected the normal workplace, such as a shift of production operators, shipping/receiving, management, laboratory, and process development. The initial target for the project was accurate batch record completion. Each team was asked to think of something that they did that affected batch record accuracy. They were then asked to develop SMART (specific, measurable, attainable, relevant, time-bound) goals that, if achieved, would improve batch record accuracy.

The key was to train the teams to select goals over which they had control. An operator team could not change the product formulation to make the batch record easier to complete correctly, for instance. So operators were kept within their range of control. When they noticed that there was one space in the batch records that was prone to errors, for example, they decided that their goal would be to have a peer informally check that entry on the spot. Their goal was set at 90% compliance.

This illustrates a central feature of this process: the positive nature of the measurements. Previously we had measured failures and then reacted, usually with negative feedback. Now we held employees accountable and

When a team reached its goal, the achievement was recognized by top management

Figure 2: Savings from cultural transformation



they felt empowered; this allowed them to perform positive actions that affected process input.

Progress and Perspective

The teams made steady progress on the batch record accuracy project, learning the change process as they progressed (Figure 1). Once that was completed, they moved on to other identified improvement goals and repeated the process.

While it would have been nice to be able indicate the baseline for the percentage completed perfectly before the start of the project, we simply didn't have that information. We believe that the variability was about the same as that shown in the figure, except that the trend line was horizontal. It's important to remember that this was not a research project. The patient was (metaphorically) bleeding to death and we had to apply a tourniquet immediately. We didn't have time to measure the blood flow. Perhaps these results could inspire others to conduct more research on this subject.

We then promoted and encouraged those quality behaviors, transforming them into employee habits

This type of improvement process is not a get-rich-quick scheme, but we achieved substantial dollar savings by reducing the time spent correcting batch records. While the outlay to install the system initially created a negative cumulative cash flow, the time consumed by this cultural transformation was minimal: only about an hour per employee per week.

Motivation

How did we induce the employees to do this?

The answer comes from Frederick Herzberg, a professor in the David Eccles School of Business at the University of Utah,[3] whose research has demonstrated that the most effective motivators come from within the employee.

Here are the factors that motivate employees as researched by Herzberg, in order of effectiveness:

- Achievement
- Recognition
- Work itself
- Responsibility
- Advancement
- Growth

Money, you will notice, is not on the list. While important, it's an "outside" influence that requires increasing quantities to maintain its effect. Engaging employees' internal motivation is far cheaper than giving away the company's money, and amazingly, more effective.

In our change initiative, we used Herzberg's two most important factors, achievement and recognition, to motivate employees. Achievement in this

case meant visible progress toward a tangible goal. Each employee team appointed a scribe to record the results on a weekly basis. The record was usually a graph that was posted in a highly visible common area, like a lunch room. This feedback showed the employees that their efforts were making a difference. After the teams achieved their goals we conducted follow-up audits of the behaviors showing that the behaviors had been sustained.

When a team reached its goal, the achievement was recognized by top management in the form of a pizza lunch (served by management) or a banner unfurled across the plant entrance. If you doubt the effectiveness of such nonfinancial recognition, check out the stickers on the helmets of college football offensive linemen and you'll see what they're playing for.

Fundamental to the success of the project was the role of top management. They did not have to spend a large amount of time on the project—about an hour per week was sufficient for them, as well. But their continuing support was critical.

Results

Constructive results began to appear after several weeks. As people began to understand and trust the process, productivity gains began to mount. Within a year and a half, the hemorrhaging had stopped (Figure 2) and the savings continued to roll in. Our exposure to FDA enforcement had fallen substantially, and we had the measurements to prove it!

In addition, we reaped the following benefits:

- Teams learned how to measure simple employee behaviors.
- Everyone learned how to find the performance inputs in their jobs that affected business-critical outcomes.
- Managers learned to be better delegators.
- Managers learned how to turn their analytical mindsets into an asset when interacting with people.
- Managers learned how to better motivate employees.
- Employees became more willing to help one another.

For the organization as a whole, the most satisfying result was seeing employees take responsibility for improving daily operations. ■

Previously we had measured failures and then reacted, usually with negative feedback. Now we held employees accountable and they felt empowered; this allowed them to perform positive actions that affected process input.

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About the Authors

Dr. Norm Howe, Senior Partner, Validation Control Institute, has held many management positions in FDA-regulated industries, most in production at BASF. He has led a number of cross-functional cost-reduction, product-development, and business-optimization teams that have developed more than a dozen new products and installed many capital projects. An ISPE Member since 2003, Norm earned a BS in chemistry at the University of California–Berkeley and a PhD in chemistry at University of California–Los Angeles under Donald J. Cram. He can be contacted at: howen@vcillc.com.

Nicole Leitz, Senior Partner, Validation Control Institute, has focused her consultative efforts in the performance of audits for 21 CFR–regulated industries for food, dietary supplements, pharmaceuticals and medical devices. She has written and provided training sessions on quality system elements and practices, and has also worked as a remediation consultant, writing documentation such as SOP, WI, investigations, CAPAs, and complaints for corporate clients. Nicole earned an MS in organic chemistry from Bucknell University, Lewisburg, Pennsylvania, and a BS in chemistry from Hope College, Holland, Michigan.

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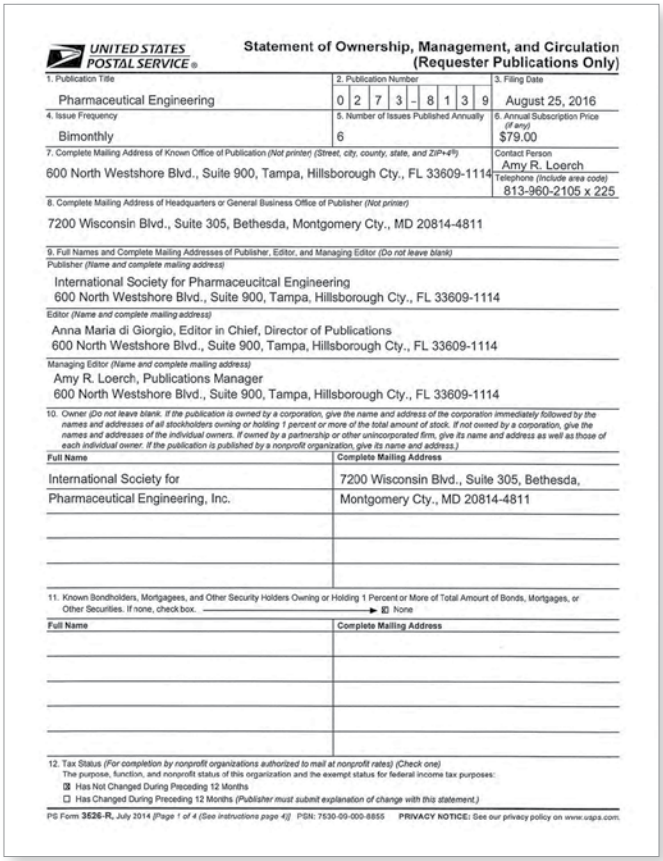

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1. Publication Title	2. Publication Number	3. Filing Date
Pharmaceutical Engineering	0 2 7 3 - 8 1 3 9	August 25, 2016
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price (If any)
Bimonthly	6	$79.00

7. Complete Mailing Address of Known Office of Publication (Not printer) (Street, city, county, state, and ZIP+4®): 600 North Westshore Blvd., Suite 900, Tampa, Hillsborough Cty., FL 33609-1114 — Contact Person: Amy R. Loerch; Telephone (Include area code): 813-960-2105 x 225

8. Complete Mailing Address of Headquarters or General Business Office of Publisher (Not printer): 7200 Wisconsin Blvd., Suite 305, Bethesda, Montgomery Cty., MD 20814-4811

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor (Do not leave blank)

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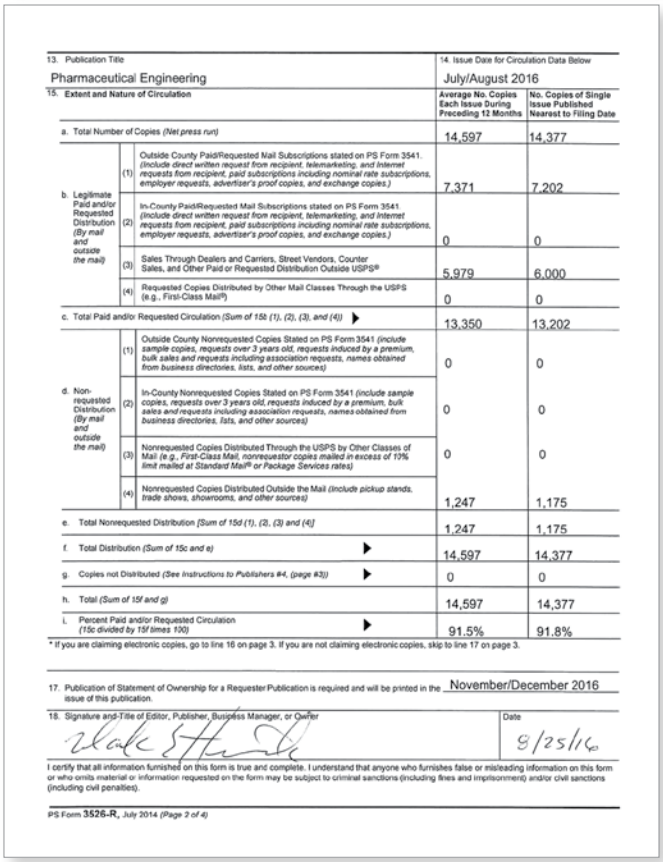

13. Publication Title	14. Issue Date for Circulation Data Below
Pharmaceutical Engineering	July/August 2016

15. Extent and Nature of Circulation			Average No. Copies Each Issue During Preceding 12 Months	No. Copies of Single Issue Published Nearest to Filing Date
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Conditions that might have gone untreated in the past now benefit from the application of human drugs to dogs and cats

Among the human pharmaceutical breakthroughs that have been translated into veterinary care are treatments for anxiety, chronic pain, allergic itching, and cancer. One of the first notable successes was fluoxetine (Prozac), a human drug that was modified to relieve separation anxiety in dogs and to curb inappropriate urination due to stress in cats.

For years vets and pet owners struggled to treat allergic itching in dogs. Kinase inhibitors, such as Apoquel (oclacitinib) made by Zoetis, have changed the landscape in canine dermatology by dealing with pruritis quickly and effectively, while sidestepping the notorious side effects associated with steroids, the traditional treatment of choice.

Cancer therapy for pets is becoming more frequent in clinical practice, and researchers at vet colleges are applying breakthroughs in human oncology to the treatment of animal cancers. Oncept (Merial), the first DNA-based cancer vaccine, is being used by oncologists and internists to treat canine oral melanoma. Among other promising treatments on the horizon are monoclonal antibodies (mAb) that act as checkpoint inhibitors, and oncolytic viruses. Nexvet is developing an anti-PD-1 immunotherapy to treat cancer in dogs, and Aratana markets mAbs that have been licensed by the US Department of Agriculture (USDA) for B-cell and T-cell lymphomas.

In the United States, biologics, including vaccines, are regulated by the Center for Veterinary Biologics at the USDA, while vet drugs are approved by the FDA Center for Veterinary Medicine (CVM). While many drugs, including fluoxetine and oclacitinib, have been approved by the FDA, 54% of the animal drugs currently in use are unapproved for pets.[1]

Beyond cancer, conditions that might have gone untreated in the past now benefit from the application of human drugs to dogs and cats. Pain management is one such exciting area. Older drugs, such as local anesthetics (e.g. lidocaine), are being used in continuous-rate infusions for routine clinical treatments. Ketamine can be applied in low, subanesthetic doses to prevent spinal cord windup in dogs; NSAIDs, many of which are human drugs, often provide pain relief as well. Biologics are also finding their way into the treatment for pain in animals. Nexvet uses mAbs that have been approved in humans to develop biologics to treat pain.[2]

A drug's effectiveness, however, does not always translate directly from humans to animals. Dogs metabolize tramadol, a pain medication, differently than humans. Because they do not produce M-1, the main metabolite that acts as a narcotic in humans, the drug has a shorter half-life in dogs.

Health care costs continue to rise for both humans and their pets. Americans spent almost $16 billion on vet care in 2015 and almost double that when OTC medicines and supplies were included.[3]

One problematic area is the treatment of infections. Vets limit the use of antimicrobials by performing culture sensitivities on microbes to determine the most effective antibiotic. If a pet owner balks at the cost of such tests, vets have to make an educated guess at which antimicrobial will work and in doing so may unwittingly overprescribe. This is a problem because resistance factors can be transferred between animals and humans that share a home.

For novel treatments that can be prohibitively expensive, such as experimental immunotherapies, pet owners can avail themselves of a twist in the use of animals in drug trials The One Health Company pairs sick pets with expensive human treatments that are at the preclinical testing stage.[4–5] The hope is that, in some cases, this will benefit both human drug development and owners wanting to alleviate their pets' suffering. ■

—Scott Fotheringham, PhD

References

Thanks to the following for background information: Dr. Paul Woods DVM, head of oncology at the Mona Campbell Centre for Animal Cancer at the Ontario Veterinary College, University of Guelph, Ontario; Dr. Nigel Gumley, DVM; and Dr. Suzanne Chenard, DVM.

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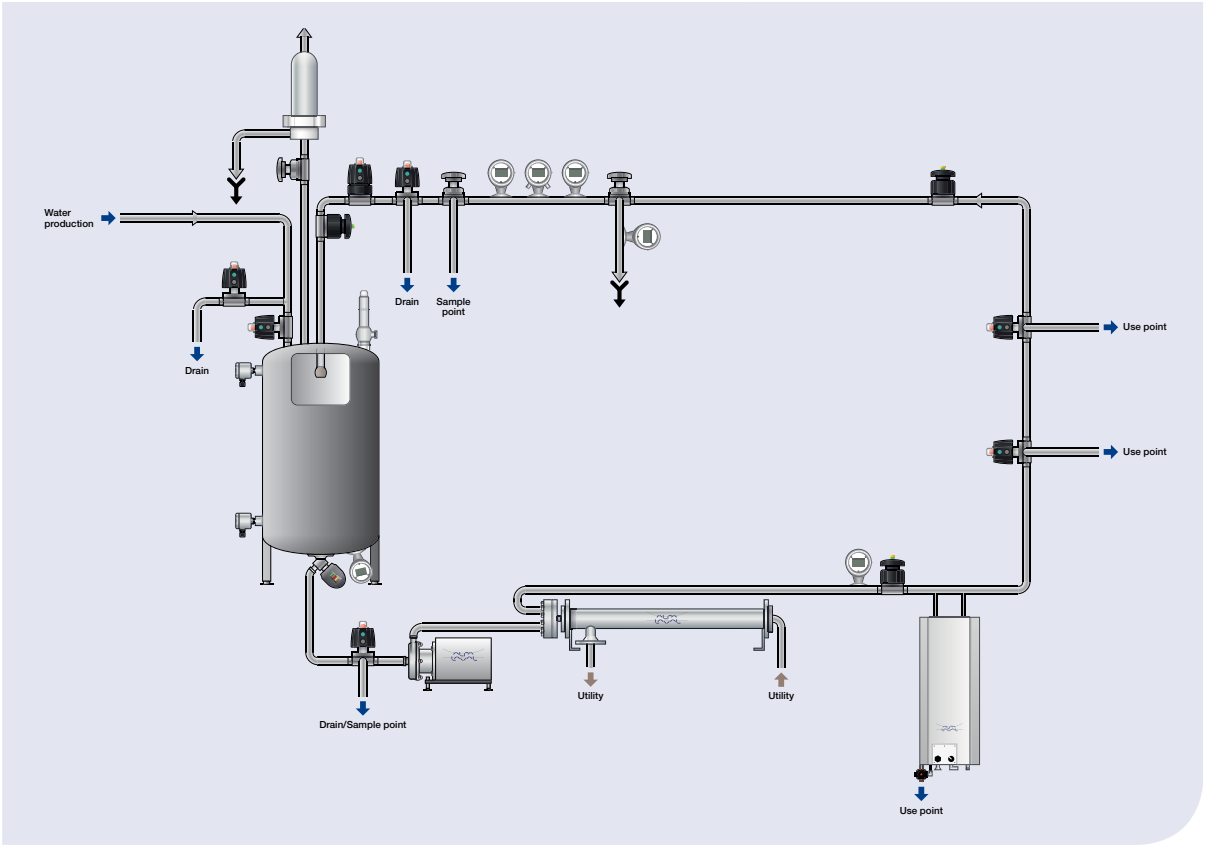

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