PHARMACEUTICAL ENGINEERING®

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The New Face of Leadership

Pew/ISPE Study Results Revealed

The Catastrophe of Drug Shortages in Pediatric Oncology

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THE PROMISE OF HOPE

Anna Maria di Giorgio
Editor in chief

A new year typically begets resolutions and the promise of change from most people. The promise of hope, really. Industry does the same, as well, albeit under different monikers—better drugs, better access for patients, better facilities, and stronger returns. Certainly, there is much pressure on industry to "perform" in the year ahead.

The ISPE conferences of the last quarter of 2016 focused almost exclusively on what industry needs to do to move forward, be it on the manufacturing, regulatory, or human resource levels. The world of robots, 3D bio printing, and breakthrough drugs for millions are all on the horizon, as is the opportunity to improve patients' ability to access and comply with medical protocols. This is exciting, yet it will be happening against a global backdrop that threatens to disrupt world markets and shatter hope. Pundits are quick to remind us that as we mark the centenary of the Bolshevik Revolution, we may see new ones taking place on every continent. Media show-and-tells carry the voice of human suffering as it reverberates across continents. And it is a very dark sound.

Yet what of the suffering wrought by disease without remedy? It should evoke the sound captured captured by Edvard Munch in his 1893 painting "The Scream." And yet the demeanor of those suffering from disease is anything but dark. We've only to remember Gavin Pierson's story to know that hope is more than just a byword.

Last December, I left the ISPE Biopharmaceutical Manufacturing Conference in San Francisco invigorated by much of what I had heard and the conversations I had. Yet a single phrase lingered, a phrase whose aspiration seemed so large it felt impossible: "Delivering the [bio] pipeline is an opportunity to alleviate human suffering on a scope and scale that hasn't been seen before." The speaker was conference Co-Chair Britt Petty, who delivered the statement during his closing remarks. There wasn't a sound in the room after he spoke that sentence. By giving voice to that silence, Britt verbalized the hopes of millions. He was referring to Alzheimer's disease, other types of dementia, and some forms of cancer.

Yes, the industry faces hurdles of reputation, harmonization, manufacturing capacity, shortages, and scarcity of talent. You'll read about them in the pages of this issue. We asked industry leaders to share their perspectives for 2017 (page 36). Dr. Yoram Unguru weighs in with a distressing portrait of drug shortages of pediatric oncology (page 33). Dr. Scott Fotheringham looks at the looming crisis brought on by a lack of effective antibiotics (page 72).

But the industry also faces pathways to hope, designed by science. And surely the desire to alleviate human suffering has greater power than mankind's proclivity for creating it?

Millions are counting on us to carry on with *that* revolution. ‹›

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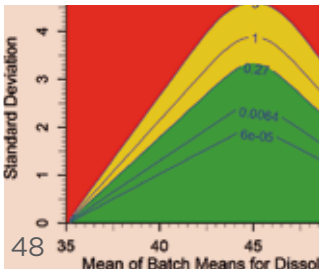

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WE'RE GETTING YOUNGER

Mike Arnold, Senior Director at Pfizer, and Chair of ISPE's 2016-2017 International Board, Member since 1998

Happy 2017 and welcome back from the holiday season! I hope you all enjoyed some quality downtime with family and friends.

2016 went out with a roar around the world: the ISPE Brazil Annual Conference, the Nordic Affiliate Annual Conference, ISPE's first Facilities of the Future conference in Bethesda, Maryland, and first Biotech conferences in Frankfurt, Germany, and San Francisco, California. These events are covered in the People + Events section of the magazine (see page 17), so I won't get into them here. I will say, however, judging from the feedback I received, that our "firsts" were well attended and well received. As chair, this pleases me because it means that first, our team did a great job bringing together the right content and presenters; and second, that our strategic direction is on target.

When we set the 2016–2019 strategy, you'll remember we identified biotechnology and facilities of the future as areas of strategic focus. We have been thinking hard about how to define ISPE's imprint in these two areas of great importance to the industry and, consequently, ISPE members. The Biotechnology Steering Committee, led by Britt Petty, past ISPE Board member and an executive at Biogen, decided to hold both European and North American events as a first step in building ISPE's presence in this exciting space. Feedback from the conferences will be guiding the committee, which is fine-tuning its plans for the coming year (more on that in a future column). The Facilities of the Future conference, with its stellar lineup and international scope, offered a glimpse into what our Facility of the Year awards may well look like in the not-too-distant future. Good thing we introduced a Facilities of the Future category award last year! Manufacturing and innovation are common to both strategic areas, and are in many ways ISPE's strengths. Yet as we look ahead, we know that the roles technology and regulation play in the design, development, delivery, and access to both, will be top of mind among our members.

Certainly, our Young Professionals, in particular, are familiar with the mounting role technology plays in innovative design of quality delivery systems, facilities, and, ultimately, medicines. Both John Bournas and I made the point at the Annual Meeting in Atlanta that we want to better represent our Young Professionals, the association's future, within ISPE. We've established a Young Professionals Task Team to look at opportunities for engaging and collaborating more frequently, to determine how ISPE can be an integral component to YPs' developing careers, and how we might leverage their skills and insights in developing our strategic plan. The team will be led by Brody Stara, International YP Chair; Dr. Michael Ku, Vice President, Global Clinical Supply, Pfizer; and ISPE Board Director Antonio Moreira, Vice Provost, University of Maryland. The Task Team is planning two events: one in Boston, Mass in August 2017 and the other in San Diego, CA at ISPE's 2017 Annual Meeting. Watch this column for more information.

At the 7 December 2016 Board meeting, we approved updates to our governance documents that will allow the International Co-Chair of the Young Professionals to join Board meetings as an invited guest. Throughout 2017, Brody Stara will represent the Young Professionals at each of our Board sessions, and share updates from the Young Professionals community. Welcome Brody!

Additionally, efforts are underway to identify opportunities for enhancing the Annual Meeting poster competition, so that we may increase Young Professional participation and attendance. If you are an interested Young Professional, and want to get involved, please contact Brody Stara (bstara@amgen.com) or Ciara Durkin (cdurkin@ispe.org).

This year will be an exciting one for ISPE and its members as we begin to reap the benefits and rewards of the strategic plan we set in motion two years ago. The steps we took last year especially have helped us develop a strong foundation upon which to grow.

I look forward to sharing more exciting news with you in future issues. ‹›

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JANUARY

10 Delaware Valley Chapter
GSK High Purity Water
King of Prussia, Pennsylvania

12 San Francisco/Bay Area Chapter
Program
San Francisco, California

18–19 Poland Affiliate
GAMP 5 Step by Step
Lodz, Poland

19 ISPE Singapore Affiliate Annual
General Meeting & Dinner
Singapore

Boston Area Chapter
Educational Program
Boston, Massachusetts

23–25 GAMP® 5, Annex/Part 11 Update (T45)
ISPE Training Institute
Tampa, Florida

26 Boston Area Chapter
New Year's Social
Boston, Massachusetts

26–27 DACH Affiliate
Workshop Projekte & Ihre Steering Committees
Frankfurt, Germany

28 Carolina–South Atlantic Chapter
Winter Gala
Raleigh, North Carolina

30–31 Quality Risk Management (T42)
ISPE Training Institute
Tampa, Florida

31 Jan–02 Feb DACH Affiliate
Vortrage und Stand auf den Lounges 2017
Stuttgart, Germany

FEBRUARY

1–3 Process Validation (T46)
ISPE Training Institute
Tampa, Florida

6–7 A GAMP Approach to Data Integrity (T50)
Water Generation (T04)
ISPE Training Institute
Tampa, Florida

8–9 Water Storage, Delivery, and Qualification (T23)
ISPE Training Institute
Tampa, Florida

8–10 HVAC (T14)
ISPE Training Institute
Tampa, Florida

9 San Francisco/Bay Area Chapter
Commuter Conference
San Francisco, California

10 Belgium Affiliate
SIG Operational Excellence
Wavre, Belgium

13–14 Clean in Place (T03)
ISPE Training Institute
Tampa, Florida

15 Belgium Affiliate
Young Professionals Networking Event
Beerse, Belgium

16 Boston Area Chapter
Educational Program
Boston, Massachusetts

Delaware Valley Chapter
27th Annual Vendor Night
Philadelphia, Pennsylvania

23 Rocky Mountain Chapter
22nd Annual Vendor Exhibition
Westminster, Colorado

23–24 Science- and Risk-based C&Q (T40)
ISPE Training Institute
Tampa, Florida

24 Rocky Mountain Chapter
Ski Day
Copper Mountain, Colorado

MARCH

6–7 Pharmaceutical Facilities Management (T26)
ISPE Training Institute
Tampa, Florida

7–8 Aseptic Conference
Reston, Virginia

8 DACH Affiliate
CoP GAMP D/A/Ch Forum Mit Vortragen
Ettlingen, Germany

9–10 GAMP 5 Process Control (T21)
ISPE Training Institute
Tampa, Florida

Managing Cross Contamination (RiskMaPP) (T41)
ISPE Training Institute
Tampa, Florida

14 CaSA Chapter
24th Annual Life Sciences Technology Conference
Raleigh, North Carolina

23 France Affiliate
Atelier Reflexion GMP EU Draft Annexe 1
Paris, France

Nordic Affiliate
Multipurpose Facility Biotech & Containment
Sodertalje, Sweden

27–28 Process Validation in Biotech Manufacturing (T32)
Risk-Based C&Q (T48)
ISPE Training Institute
Tampa, Florida

27–29 Basic GAMP 5, Annex 11/Part 11 (T45)
Manchester, England, UK

28 San Francisco/Bay Area Chapter
26th Annual Vendor Night
San Francisco, California

30–31 Technology Transfer (T19)
ISPE Training Institute
Tampa, Florida

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- Validation
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- **Bio Manufacturing Overview**
  - 3 – 4 April, Tampa, FL
  - 8 – 9 May, Copenhagen, Denmark
- **Bio Manufacturing Process Validation**
  - 27 – 28 March, Tampa, FL
- **Commissioning and Qualification**
  - 16 – 17 May, NIBRT, Dublin, Ireland
- **Commissioning and Qualification Risk Management**
  - 23 – 24 February, Tampa, FL
- **Clean in Place**
  - 13 – 14 February, Tampa, FL
- **Cleaning Validation**
  - 6 – 7 April, Tampa, FL
  - 8 – 9 May, Copenhagen, Denmark
- **Cross Contamination (Risk-MaPP)**
  - 13 – 14 March, Tampa, FL
- **Effective and Efficient Deployment of Operational Excellence**
  - 8 – 9 May, St Gallen, Switzerland
- **Facilities, Systems, and Equipment Verification**
  - 27 – 28 March, Tampa, FL
  - 12 – 13 June, Tampa, FL
- **Facility Project Management***
  - 6 – 7 March, Tampa, FL
  - 10 – 11 May, Copenhagen, Denmark
- **GAMP® 5, Annex II/Part II**
  - 23 – 25 January, Tampa, FL
  - March, Manchester, UK
  - 26 – 28 April, Tampa, FL
  - 12 – 14 June, Lilly MQ Learning Center, Indianapolis, IN
- **GAMP® 5 Data Integrity**
  - 6 – 7 February, Tampa, FL
  - 8 – 9 May, San Diego, CA
  - 8 – 9 May, Copenhagen, Denmark
- **GAMP® 5 Process Control**
  - 9 – 10 March, Tampa, FL
  - 8 – 9 June, Tampa, FL
- **HVAC**
  - 8 – 10 February, Tampa, FL
  - 9 – 11 May, San Diego, CA
  - 8 – 10 May, Copenhagen, Denmark
- **Oral Solid Dosage – *Updated!***
  - 3 – 4 April, Tampa, FL
  - 10 – 11 May, Copenhagen, Denmark
- **Process Validation**
  - 1 – 3 February, Tampa, FL
  - 8 – 10 May, Copenhagen, Denmark
- **Q7A**
  - 5 – 6 April, Tampa, FL
- **Quality by Design**
  - 1 – 2 June, Tampa, FL
- **Quality Risk Management**
  - 30 – 31 January, Tampa, FL
- **Sterile Facilities**
  - 10 – 11 May, San Diego, CA
- **Technology Transfer**
  - 30 – 31 March, Tampa, FL
- **Water Generation**
  - 6 – 7 February, Tampa, FL
  - 8 – 9 May San Diego, CA
- **Water Storage, Delivery, and Qualification**
  - 8 – 9 February, Tampa, FL
  - 10 – 11 May, San Diego, CA

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PLANNING FOR PROGRESS

"The only constant is change."

Brody Stara
International Young Professionals
Committee Chair, Member since 2008

At the beginning of my career, I was like a kid in a candy shop. My eyes were wide with excitement as I looked at all the opportunities! I wasn't sure what career path I really wanted to take; I just knew I was hungry and felt like I needed a strategy.

When I volunteer with students and Young Professionals, I get so many questions about what jobs they should look for and which are the best. My advice, as canned as it sounds, is always the same: You'll never know what you like until you find out what you don't. Take the end-user job that sounds cool; maybe it's perfect for you. Try consulting; maybe that's your thing. Apply for a PhD; maybe research is your calling. You'll never know until you try it. When you find your calling, something that deeply motivates you, look around. If your aim is to be a leader one day, your current leaders should be who you strive to be in 5 to 10 years.

When you start to plan a career road map, it can be very daunting. Your first step could be a simple search on a recruiting website. It can turn up hundreds of jobs, so use keywords to narrow down your scope to find roles that match the leaders you look up to. On a job posting, you'll find basic requirements—the minimal prerequisites you need in order to be considered for the position. What do you need to be able to meet those? Is it simple on-the-job training or a certification? Will you need an advanced degree? Will you need cross-training with different groups or departments? Work with your manager to identify how to get those experiences and find out if your company can provide support. Sometimes, the basic qualifications can be assignments in specific areas, and your manager can advocate to get you a cross-functional project.

YOU'LL NEVER KNOW WHAT YOU LIKE UNTIL YOU FIND OUT WHAT YOU DON'T. TAKE THE END-USER JOB THAT SOUNDS COOL; MAYBE IT'S PERFECT FOR YOU.

For those of us who like to plan really far ahead, the position might be a stretch from what you currently do. Look for intermediate roles that will help you get specific experience. Maybe you need management or operations experience that you can't get as an engineer or scientist.

Once you've identified these future roles and responsibilities, try networking with the people who are already there. Set up an informal one-on-one meeting with that person or the manager. These discussions are a great way to learn about a position without the stress that comes with an interview; you can also find out if the role is everything you thought it would be.

By reaching out to new people and getting to know them and their roles, you start to build your network. This is why it's still important to make a good impression in these one-on-one meetings. Be tactful with your requests, have researched questions that are information seeking, and remember to think about what you're asking from their perspective as well. You're seen as an interested candidate who might apply, so this could be your first chance to impress. Be prepared to talk about what applicable skills you have, as well as ones you may still need for the position. If you aren't qualified for the job, find out what experiences a strong candidate would need.

Lastly, and I cannot recommend this enough, send a thank-you note! This person just took time out of their busy day to take a chance and talk to you, so let them know that you appreciate it. Stay in touch with the people you get along with; you might have just met a mentor.

If this whole thing seems wildly overwhelming, or you've just found out that a certain track/role isn't for you, don't worry. You're just starting out, so you're bound to change your mind multiple times. And, as I said earlier: You'll never know what you like until you find out what you don't.

THE NEW FACE OF LEADERSHIP

Robin Kumoluyi
Vice President, Johnson & Johnson Quality Systems and Services

Three generations ago, a university degree granted admission to a well-paying 40-year career at a single company whose end point, often as not, was an engraved watch. Today, things are different. According to the US Bureau of Labor Statistics, the average worker can expect to hold ten different jobs before age 40. Nor is today's job-hopping—essential to learning, growing, and advancing in a career—much different in other parts of the world.

This new normal is best exemplified by the career trajectory of Robin Kumoluyi. Over the course of a 30-year career, Robin has journeyed through eight pharmaceutical companies plus one intriguing non-pharma sidetrack. But more about that later.

If Robin represents the new normal in trajectories of careers, there is a critical factor that is unusual: Robin is a woman. While more women than ever before are reaching executive positions—at GlaxoSmithKline, Emma Walmsley will succeed Andrew Witty as CEO in 2017, making her the first woman to head a big pharma player—the pace of change is glacial. For the most part, the upper ranks of business in all sectors remain the preserve of men. Only 24 women, or 14.2%, hold CEO positions among the S&P 500. Dipping into the next four executive positions below CEO, the percentage barely ticks up to 16.5%.

LEADER VS. BOSS

Reflective, circumspect, highly rational, and measured in her words, Robin has thought long and hard about the moments in her past when a door opened, and a new opportunity for growth and advancement appeared. The willingness to work hard, take bold chances and grasp timely opportunities also figure into her thoughts. After three decades of increasing responsibility for ever-larger teams, she knows that success lies in being a leader rather than a boss.

"Like many women leaders in pharma, my career has never been about the title," she says. "It's always been about growing, learning, and

meeting challenges. I'm always looking for new ways to do things, new ways to contribute and grow.

"As for my leadership style, I believe in helping those entrusted to my leadership to do their best work. If you want to be a leader, you should take care of people. Rule number one is to respect the people that work on your team.

"So it's not about being a boss. It's about developing people, so they give the best of themselves for their own careers and the company. It's about managing talent and energy. If I'm leading and no one wants to follow, there will be no results. I work for the people on my team, not the other way around. I enable them and support them: That's my job as a leader, and I love doing it."

FIRST DOORS OPEN

Robin's first role in microbiology was working for a contract testing laboratory. She explains that while she has always been committed to and diligent in any job she accepted, this was the first true lesson in how hard work pays off. Robin got her first promotion after the lab director noticed that she was clocking out and staying after to sanitize all the lab benches on her own time. The laboratory was in its early days and could not afford to pay overtime. Robin was staying so that all her paid work time could be devoted to assuring all the samples were tested. The promotion provided more technical skills in microorganism identification, which gave her a solid foundation for microbiological quality control work.

Robin landed her first pharmaceutical job as a microbiologist at Block Drug, now part of GlaxoSmithKline. Over the next several years she worked in and managed microbiology quality control labs, eventually landing at Warner Lambert in microbiology R&D. Her timing turned out to be serendipitous. Warner Lambert's corporate audit group needed help in microbiology quality assurance, and she fit the bill.

"Corporate audit was actually looking for a microbiology subject matter expert to support auditing contract labs," she explains. "This was exactly my background; it was a symbiotic relationship: they were leveraging my microbiology expertise while I was acquiring new skills in the auditing process."

A door had swung open, and Robin had her first glimpse of the world of quality assurance. The prospect was immediately attractive, but she also recognized that to make quality assurance her world she'd need a new set of skills. Characteristically, she set her sights on the end goal and mapped out her most efficient route: "I performed a gap analysis on what I'd have to do, so I decided to return to school for a master's in quality assurance and regulatory affairs." Robin earned her master's degree from Temple University in 1999.

Well on her way at Warner Lambert with support from the corporate audit group, her first big opportunity was in the consumer sector quality group, which needed a standard protocol for microbiology methods transfer to contract labs. Robin volunteered and made it happen. If anything, the experience confirmed that quality assurance and compliance was where she wanted to be. She reflects, "It was a perfect amalgamation of work and my education put to good use, and I sensed this was going to be my trajectory."

Next, Robin made what she now says was a "bold move," and asked to meet with the senior director of Warner Lambert's consumer sector quality assurance group. In retrospect, she admits the move was not just bold, but perhaps a little presumptuous: Once in his office, she announced, "Sir, I want to work for you. Tell me how to get on your team." Two months later, Robin was on the team.

The jump into quality assurance and the senior director's orbit also gave Robin that rare asset—a mentor who would stick with her for the long haul. Today, she calls him "a lifetime mentor. For any subsequent job, in any company, I'd always call and he'd ask, 'Why are you taking this, where will it take you?'" The reality check with a trusted mentor—a kind of career GPS—has proven invaluable to Robin time and again.

Robin eventually became a senior quality manager of quality operations and contract facilities, and worked on developing policies and processes for some 70 partners. She also began to build a reputation for collaboration, working with and supporting sites to craft policies for both site and corporate levels, rather than centralizing decision-making and ruling by decree. For most leaders, collaboration and consensus building is hard work, but it's also the kind of leadership that gets noticed, and Robin was soon tapped for Warner Lambert's CEO mentoring program. She was 34.

SCARED BUT STRONG

The next big door swung open when she was offered the opportunity to join the quality leadership team in Puerto Rico as a senior manager of regulatory compliance. As Robin noted at the Women in Pharma session at the 2016 ISPE conference, she was "scared to death" at the prospect. It was 1999, after all. "There really weren't many women VPs in quality at the time," she says. Women in senior positions were still a rarity—let alone women willing to undertake a significant relocation.

Characteristically, her hesitation and fear were short-lived, and she got on with the job. In Puerto Rico, she managed quality systems with a team of 32 colleagues both at the manager and specialist levels, and was charged with implementing a regulatory compliance program. Warner Lambert had been operating similar programs in Europe for a couple of years, so Robin was invited to Paris to observe and benchmark their systems.

"It was very exciting for me," says Robin, "and my French colleagues offered a lot of support." Grateful for their help, Robin wanted to do something special. During her time in Paris, she got to know the director of regulatory compliance, who had expressed admiration for the impressionist artist Monet. Robin bought a card printed with a Monet reproduction and wrote a heartfelt note of thanks. "I even tried to use a few French words," she laughs. "The director was very touched. They were somewhat of a new group and felt they weren't being recognized for the value they brought to the company."

FIRST DIRECTORSHIP

Sometimes even the simplest gesture can generate unexpected ripples. Based on the European office's recommendation, six months after returning to Puerto Rico, Robin was asked to become director of regulatory compliance for the Americas. Did her simple gesture in France tip the balance?

"I really think that saying thank you and appreciating people makes a difference," she says. "There were others who could have done the job and were equally qualified technically. But at a certain point, it's all about how you work with people, rather than just your technical abilities.

That is a big part of my leadership—really respecting people."

Robin spent the next 10 years at various director-level jobs. This included three as director of global manufacturing compliance–contract operations, during which her responsibilities grew to include manufacturing compliance for 470 external contract manufacturers, which was a $2-billion-plus product portfolio at the time.

The next stop, at Schering-Plough, as director of worldwide quality supplier management, followed on the heels of that company's consent decree. She says she amassed "tons of experience as the process owner for the supplier management system, ensuring deliverables under the consent decree work plan. Companies enter into a consent decree to address FDA's apparent belief that the organization is not capable of complying with good manufacturing practices," says Robin. "The FDA has most likely determined that the company is not sufficiently managing itself at this point because of the number of violations. Supplier management was part of the work plan, and there was a lot of work to do to meet the deliverables under that work plan. Through collaboration at the corporate and site levels, we successfully met our work plan obligations."

"IF YOU'RE READY TO TAKE A CHANCE, POSITIVE THINGS HAPPEN. SO YES, I TEND TO GO FOR IT."

A "CRAZY DECISION"

At this point in her career, Robin says she made "a crazy decision"—heading up quality assurance and regulatory compliance for a Colorado-based biotech company. This meant heading west with her one-and-a-half-year-old son while her husband was still working in Long Island, New York. For the next few months, as Robin juggled baby (with help from her mother-in-law from London) and career, her husband took red-eye flights to join them each weekend.

"That was a tough time," recalls Robin, but the fire that drives her tempered the fatigue and doubts. "It was also an opportunity to run all aspects of the quality (GxP) from R&D quality assurance to commercialization. " she says. "This was a small start-up biotech, so I got to wear many hats and utilize all my previous experience. I developed the overall quality and compliance strategy along with the associated processes and systems."

While she really enjoyed the arduous work of building the quality unit, this was not the best for her young family: "My husband was still taking red-eye flights, and I needed something that was a little more stable," she says. "The regret was that I did not stay long enough to enjoy the fruits of my labor. The company did exceptionally well when it went public."

THE SIDETRACK

Robin has learned and grown at every stop in her career because she looks carefully, performs the necessary benefit/risk analysis … and then leaps in with both feet.

"If you're ready to take a chance, positive things happen," she says. "So yes, I tend to go for it."

Whether her next role supplied the much-needed stability Robin was seeking is debatable. What it did supply was excitement and professional growth. Offered several opportunities in the pharmaceutical industry, she opted instead to go sideways, taking an interview in Atlanta, Georgia, for the head of quality audits with Coca-Cola.

"I went for the interview and was offered the position of director of global quality audits. This was on a Friday," she says. "I was very happy with that. But they called back on Sunday and said they'd been looking for a couple of years for someone to be director of analytical services and my background fit. It's a bigger role, and we'd be happy if you'd consider it. Needless to say, I took it on."

Coca-Cola's global footprint meant managing quality control labs on several continents while building new analytical labs in South Africa, China, and Mexico, an experience that Robin describes as "awesome … I'm so glad I took it because it's sometimes good to get out of your element."

Indeed, adaptability is among the many lessons she picked up. At first, her buttoned-down "pharma ways" didn't quite click at Coca-Cola.

"I remember making a presentation, and they're all looking at me strangely," she recalls, laughing. She admits she had to start at square one when it came to PowerPoint and much else: "Coke sells a lifestyle, they sell happiness, so I had to be more animated, less corporate."

After two-and-a-half years at Coca-Cola, implementing a global lab strategy, understanding the business and what goes into "selling happiness," Robin decided it was time to return to her roots. She was thriving but was starting to miss the pharmaceutical industry. She also recognized that two-and-a-half years is a long time to be away from any industry—especially the pharmaceutical industry—and that it might be a barrier to resuming where she'd left off.

THE OPPORTUNITY TO USE IT ALL

"I was at the opening ceremony of one of the new labs I was overseeing, which we had just built in Pretoria, South Africa, when the call came in from Novartis," she recalls.

The career door was opening again, and Robin was soon global head of quality for Novartis's animal health division. This was a big step up, to vice president, reporting to the division president. "A whole different ball game," she observes.

Robin says her experience at Coca-Cola proved invaluable at Novartis and for her subsequent career: "At Coke, it was all about using quality as a strategic advantage, it was about learning the business, about presenting to senior management—all of which was helpful to me at Novartis. I was also very fortunate to have a woman on the Novartis animal health executive leadership team, someone in marketing, who also helped me."

After three-and-a-half years at the animal health division, Robin joined the Novartis Group Compliance and Audit team as vice president and global head of audit, before ascending to her final role with the company as vice president, global head of group quality, third-party operations.

THE ENABLER

When *Pharmaceutical Engineering* spoke to Robin, she just had been recruited a week earlier for a position at Johnson & Johnson Quality and Compliance. "I'm already very impressed with the team here," she says.

"At J&J, I have seen an impressive number of women in senior level roles. We are committed to Our Credo and practice what many call servant leadership. I was grateful to find that this is authentically the J&J way. This really drew me to the company because it resonates with what I believe as a leader."

As usual for Robin, her job is still about the people around her. "I love managing people," she says. "Which means I like bigger roles where I can work with and support even more people."

Robin is now also a "lifelong enabler," noting that she continues to talk to and mentor friends and individuals she managed at organizations where she worked over a dozen years ago. "I've had the opportunity to be mentored so, definitely, I should give back. Which means I now have people calling me to discuss their next career move."

Her generosity is not just about taking phone calls and dispensing advice. It's about digging deep to understand what makes someone tick and how they can improve.

"I can see how people grow incrementally, and I like to encourage this growth," she says. "I had a young woman on an improvement plan, and we decided to perform a strength-finding exercise with her. After the exercise, we realized that, given her strengths, she wasn't going to succeed in her current role. So we moved her into a more suitable one. The following year, she was an 'A player.' That's what I find most fulfilling—helping people find their flow. I don't believe in fixing weaknesses but rather building on strengths. We still keep in touch."

She also recalls, with some emotion, an encounter at Novartis before she left. "I mentored a fellow from France who was on my animal health team. He said, 'You not only say that you will help colleagues, but you actually do it.' This really touched me."

If leadership's ultimate purpose is to serve others, as Robin's career has demonstrated, it's a purpose shared by the pharmaceutical industry. The industry's fundamental job is also about improving lives. Indeed, as Robin's son recently reminded her, "Medicine is important; it helps people." ‹›

—Spyro Rondos

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- Professional Development/Career Enhancement

www.ISPE.org/2017-Annual-Meeting

Also in this section

A QUALITY STATE OF MIND

ISPE AND PEW CHARITABLE TRUSTS RELEASE REPORT ON DRUG SHORTAGES

Quality issues continue to be a driving force behind sterile injectable drug shortages in the United States. This is one of the key conclusions of a Pew/ISPE joint study that interviewed 50 executives from 10 pharmaceutical companies in the United States. Released on 11 January, the report, *Drug Shortages: An Exploration of the Relationship between U.S. Market Forces and Sterile Injectable Pharmaceutical Products*, indicates that drug shortages revolve around several factors. Consequently, reducing shortages will require a multi-dimensional solution. "By reaching out to industry leaders to understand the factors affecting their relationship with market forces in the US," said ISPE CEO and President John E. Bournas, "we have firsthand insight into possible solutions."

Sterile injectable products are often cited as being the most vulnerable to supply disruption. They are also some of the most technically challenging products to manufacture. Choosing to look at sterile injectable products was a deliberate choice, added Dr. Theodora Kourti, ISPE's Senior Vice President, Regulatory Affairs. "By zooming in on this niche market, we were able to see if the macro theories and hypotheses that we have been addressing since the first ISPE survey of drug shortages in 2013 hold true in more 'micro' environments."

The joint study was announced in October 2015 and conducted over a six-month period with 50 executives from 10 pharmaceutical companies in the United States. To maintain confidentiality, PricewaterhouseCoopers was engaged to conduct the interviews with the participating companies and aggregate the anonymized data for analysis.

Findings support ISPE research

The Pew/ISPE study sought to look at manufacturing, supply chain, and US market forces that have a bearing on drug shortages, explore the relationship between these forces, and how they contribute to the shortage of sterile injectable products. The study further sought to determine whether the decisions companies made to reduce risks of future shortages were influenced by elements other than quality-focused factors.

Among the elements identified by the 10 participating pharmaceutical companies as the reasons for shortages are market withdrawals, ineffective supply chain design, few purchaser-manufacturer incentives, limited market insight into future demand, and regulatory expectations. In addition to improvements in product and manufacturing quality and current Good Manufacturing Practice (cGMP) compliance, the report concludes that drug shortages could be reduced with improvements in internal-demand-forecasting abilities; overall supply chain maturity; and the relationships between a manufacturer, a provider, and regulators.

The Pew/ISPE study's key findings are:

- Product supply chains are increasingly complex and need strengthening. Instead of a uniformly strategic approach to the portfolio, a product-by-product approach is often used, although patient needs are generally prioritized.
- Limited incentives inhibit the ability to mitigate shortages, deterring companies from entering a market to resolve a shortage issue or build the systems needed to prevent shortages.
- Inadequate forecasting mechanisms are inhibiting investments to mitigate or prevent shortages. Companies worry that their inability to reliably predict the economic returns for investments in new capacity may result in financial losses, especially for legacy products with low volumes and low margins.
- Perceived regulatory challenges to expanding or updating capacity are limiting investments.

"These findings are consistent with ISPE's 2013 drug shortages survey," stated Bournas. "However, market forces are also contributing to drug shortages as companies wrestle with investment decisions with uncertain regulatory or economic outcomes." The Pew/ISPE study makes several recommendations for industry in this regard:

- Develop a collaborative approach to improve market forecasts.
- Establish or enhance incentives between purchasers and manufacturers.
- Strive for further collaboration opportunities with regulators, for example,

identifying a simplified process that enables a more effective way to update market authorizations for legacy products.
- Develop systems to proactively identify and resolve quality issues across increasingly complex supply chains.
- Improve understanding of the risks across the supply chain.

ISPE has been conducting research and collecting data on global drug shortages since 2011. Its 2013 survey found that issues within the quality systems of manufacturing were identified as the leading cause of drug shortages. At that time, the number of drug shortages in the United States stood at 204, according to the University of Utah Drug Information Service. By 2015 that number had dropped to 142, and further declined to 49 by the end of first-quarter 2016. Yet few would disagree that hurdles abound before the industry can confidently claim to have eliminated drug shortages altogether.

ISPE published the *ISPE Drug Shortages Prevention Plan* (DSPP) in 2014 and the *ISPE Drug Shortage Assessment and Prevention Tool* in 2015. The DSPP informed ISPE's contribution to a multi-association response to the European Medicines Agency's request for an actionable plan to address drug shortages caused by manufacturing and quality issues. ISPE also offered a Drug Shortages Introductory Webinar in early 2016. Additionally, drug shortages prevention recognition is now included in the association's flagship Facility of the Year Awards program.

"The data collected points towards a need for greater collaboration among all parties, at all levels," stated Bournas. "ISPE is well positioned to enable this collaboration, as it is the cornerstone of ISPE's philosophy and its raison d'etre. We look forward to continuing our relationship with Pew Charitable Trusts."

As both organizations move forward sharing the survey results within industry, Pew/ISPE will assess whether follow-up surveys will be required, or the scope broadened to include other products and geographies.

"We will be presenting the study results and conclusions at the 2017 ISPE Aseptic Conference, this coming March 7-8," stated Dr. Kourti.

FDA ISSUES REVISED DRAFT GUIDANCE ON QUALITY METRICS

On 23 November 2016, the US Food and Drug Administration (FDA) released a much-anticipated revision of its draft guidance on the collection of quality metrics. The revised "Submission of Quality Metrics Data Guidance for Industry" is a response to industry concerns that the original guidance was too demanding.

In a Federal Register notice published two days later, FDA identified the revisions:

The revised draft guidance includes the following changes from the earlier draft guidance: Adoption of a phased-in (voluntary) approach, reduction in the number of data elements requested (i.e., reduction in reporting burden), support for both product reports and site reports, modifications to the quality metrics data definitions, addition of clarifying examples for the definitions, addition of comment fields, and clarification of special considerations for non-application and OTC [over-the-counter] product reporting.

Both the revised "Submission of Quality Metrics Data" Guidance for Industry and an explanatory webinar are available online. Links to both of ISPE's Quality Metrics reports are also available on the FDA website.

ISPE 2017 CONFERENCE ON QUALITY CULTURE

The first ISPE Conference on Quality Culture and Quality Metrics will 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.

Conference attendees 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 help shape and contribute to quality culture
- Which best practices enable a collective mindset to drive toward improving quality
- Gemba's key role in coaching and mentoring desired attitudes and behaviors
- How to use a practical new tool to target and measure behaviors 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.

For more information on the conference, see the Quarterly Report on Quality Culture in the November/December 2016 issue of *Pharmaceutical Engineering*.

QUALITY CULTURE IN ACTION AT ISPE 2016 ANNUAL MEETING

The well-attended Quality Metrics session at the 2016 ISPE Annual Meeting & Expo in Atlanta, Georgia, on 21 September featured excellent thought-provoking and informative presentations followed by a lively Q&A discussion. Session themes were understanding quality metrics applied to assess quality performance and the underpinning importance of a quality culture. Presenters were Marie Mathews, Compliance Officer, CDER/OC/OMQ, FDA, and Dr. Nuala Calnan, Research Fellow, Dublin Institute of Technology, Ireland. In a separate, related session, Mairead Goetz, Global Head Analytical Science and Technology, Novartis, provided a company perspective.

Counting the hard to count

Marie Mathews presented an FDA field perspective on quality metrics and culture. Building upon the maxim "Not everything that can be counted counts, and not everything that counts can be counted," she reflected that a traditional approach to quality metrics may capture out-of-specification results, deviations, trends, rejects, complaints, and recalls, among others, but the values can be rendered useless unless the correct information is used and the appropriate action is taken promptly. "At first glance, some of the more out-of-control companies I've seen look pretty good with these metrics," she said. It may not be until the FDA (or another agency) steps in that gaps are revealed. By then, the company will have already lost control and an extraordinary amount of effort will be required to get it back on track.

Many companies are good at creating mission or value statements but not so good at assessing their culture. Mathews cited an example of a very out-of-control plant that had a laboratory with

100% turnover of staff in two years. The plant had not recognized this huge red flag.

Mathews cited four "misconceptions about quality culture":

1. If an employee sees something objectionable, they will let someone know.
2. We have an internal whistle-blower line, so employees will use it.
3. We would know if one of our employees contacted the FDA.
4. If I find out about a problem, it makes me personally responsible.

What does work, she said, are actions such as conducting a survey of all employees on culture, with guaranteed anonymity, and a review of employee incentives, both monetary and nonmonetary, to encourage wanted behaviors and discourage unwanted behaviors. She closed by discussing the issues of empowerment and transparency as quality culture enablers.

ISPE cultural excellence

Dr. Calnan gave an update on the ISPE Cultural Excellence Program. She explained that the program is aimed at promoting, coaching, and leading specific desired behaviors while identifying and preventing specific undesired behaviors.

Over a period of 2 years, 35 members from 28 companies in six subteams are collaborating to produce a series of deliverables, which will be completed by the end of 2016. Each subteam is working on one of the dimensions in the outer circle of the diagram.

Dr. Calnan described these deliverables as tools that companies, sites, and individuals can use to move toward cultural excellence.

Quality culture and performance: A Novartis perspective

Mairead Goetz described Novartis's challenge following several acquisitions that have combined different business models, cultures, and standards across 67 plants employing more than 6,600 people. The goal is to evolve a strong, consistent, and sustainable quality culture throughout Novartis, with sites having ownership and commitment from the top down.

The company chose 15 basic culture actions to inform specifically tailored site change plans. Even within a large organization committed to quality improvement, each site has its own culture, requiring specific initiatives to improve its individual culture maturity.

Progress is assessed biannually, using a 12-question company-wide survey. Results are summarized using a scorecard matrix of survey findings, key performance indicators (KPIs), and key quality indicators. To approach these goals, Novartis has one quality standard for the whole network, uses KPIs constantly, and has a strong foundation of values and behaviors sponsored by senior management.

Goetz stressed that movement of quality performance requires more than just numbers. Quality culture change is a long journey and requires perseverance. Sites tend to initially overestimate their quality maturity, which is a subjective assessment. Management has the critical responsibility of fostering and enabling the change journey, and the ongoing surveys are an extremely important tool to provide visibility about each site's progress.

HOST OF ISPE 2017 EUROPE ANNUAL CONFERENCE

BARCELONA HAS IT ALL

Park Guell, one of Barcelona's UNESCO World Heritage sites

With deep cultural roots, gorgeous architecture, thriving industry, and inviting climate, Barcelona has it all. From 3–5 April 2017, the city will play host to the ISPE 2017 Europe Annual Conference.

"Barcelona is a hot spot for the pharmaceutical industry and a perfect site for the Europe Conference," said Thomas Zimmer, Vice President of European Operations for ISPE. "Situated on the Mediterranean, it offers attractions far beyond manufacturing."

Spain's second-largest city, Barcelona is the capital of the autonomous community of Catalonia. Known for its ornate buildings dating from the Gothic era to Gaudí's modernism, it's the only city to have won the prestigious Royal Gold Medal for its architecture. It's also home to multiple UNESCO World Heritage Sites, and a forward-thinking city that is experimenting with "superblocks"—closing off areas of the city to traffic—to encourage parks, museums, and gardens that make the city more pedestrian friendly and vibrant. Its reputation as a cultural, tourist, and industry mecca has made it an attractive destination for global conferences.

Life Sciences Industry

"Catalonia has a firm commitment to innovation and creativity," said Núria Betriu, general director of industry and CEO of Catalonia Trade & Investment, the government's public agency for attracting foreign investment. "Combined with a solid industry, diversified economy, and an openness to the world, they position us as one of Europe's most dynamic regions."

Catalonia is the most prosperous region in Spain and an industrial powerhouse within Europe. It has become a key investment destination for biopharmaceutical projects, which employ more than 22,000 people. Both big pharma firms and large local manufacturers have API, dosage forms, and fill and finish plants in and around Barcelona. There are almost 200 biotechnology companies in the region.

"We have become more internationally focused; we have been able to blend talent from abroad with our local talent, and we firmly believe that the future lies in value-added activities," said Betriu. "Catalan companies have made continuous efforts to innovate, develop new products, take risks, and to internationalize. Catalonia has built a world-class life sciences industry on the foundation of its long tradition of research, medicine, and pharmaceuticals."

There are 56 research institutes, 11 universities offering life sciences courses, and 17 university hospitals, providing both a skilled workforce and infrastructure to support R&D at the many companies in the region. Catalonia has more pharmaceutical companies per capita than any other European country except Belgium.

"Education is the pillar supporting this industry and is the motor driving know-how and development in this sector," said Betriu. "It is one of the main reasons behind this concentration of pharmaceutical and life sciences companies in Catalonia. This has generated synergies between industry and research, [as well as] greater intensity in technology transfer. It facilitates talent attraction, and forms a hub with high added value from a production, academic, and research point of view."

Barcelona has been on important trade routes for over 2,000 years, with proximity to critical markets in Europe, the Mediterranean, and North Africa.

"We enjoy a privileged geographical position that makes Catalonia a strategic and logistic bridge for investment into Europe," said Betriu. "This is a highly internationalized industry that connects and opens us up to the world."

Business-Friendly Environment

"Because the regional government in Catalonia sees manufacturing as a boon to the local economy, it has an industry-friendly policy," said ISPE's Zimmer. "Its government representatives get involved in our conferences and will be hosting a reception at our Europe Annual Conference in Barcelona."

Over the last five years, Catalonia has attracted 46 foreign investment projects from life sciences companies that have created 2,300 jobs. These have been mainly companies from Germany, the United States, France, Switzerland, and India.

"Catalonia's corporate tax is lower than in neighboring countries and it has one of the most effective tax-deduction schemes for the development of R&D activities," said Betriu. "We have created programs to encourage job creation through grants and discounts on social security contributions."

Catalonia Trade & Investment has dozens of offices worldwide, out of which it offers comprehensive support to foreign investment projects.

"The Europe Annual Conference is a way to experience not only a region with a flourishing pharmaceutical sector, but a city that is a beautiful destination and one of the most beloved places to visit in all of Europe," concluded Zimmer. "During the conference at the beginning of April it should be warm enough that we will be able to sit outside and have dinner. I look forward to that." ‹›

Europe Annual Conference
3-5 April 2017, Barcelona, Spain
For more information visit www.ispe.org/2017-europe-annual-conference

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ISPE EUROPE CONFERENCE ON BIOTECHNOLOGY

Reinventing Commercial Biomanufacturing

Frankfurt, Germany
24–25 October 2016

One hundred fifty attendees met in Frankfurt at Sanofi's wonderfully restored historic building "Alte Färberei," where the Farbwerke Höchst Corporation manufactured fabric dyes a century ago.

With a strong scientific program, exceptional speakers, important regulatory updates, and stimulating presentations, the scene was set for excellent networking opportunities and friendly debate, as well as solutions for and conclusions on the current issues facing the biotechnology field.

DAY 1

Andrew Hopkins, an MHRA GMP Inspector and Chair of the joint EMA and PIC/S working group on the EU GMP Annex 1 update, opened the Quality and Regulatory Session. He discussed the agency's new Innovation Office, established in 2012 to provide a single point of access to expert regulatory information, advice, and guidance to help organizations of all backgrounds and sizes develop innovative medicines, new medical devices, or novel manufacturing processes. Hopkins encouraged industry members to contact to the office with their questions.

Hopkins noted that processes are often not well defined in biologics, a situation that may lead to difficult inspections. In the future, he explained, inspections might be additionally affected by the new "Good Manufacturing Practice for Advanced Therapy Medicinal Products" guidance produced by the European Commission and EMA, which is currently in the public commenting period.

Kavita Ramalingam Iyer, a regulatory professional from Merck Sharp & Dohme Corp., highlighted the influence of Annexes 1 and 2 on biologicals manufacturing. As a Biophorum benchmark study revealed inconsistent room and area classifications, she encouraged attendees to do "proportionate quality risk management" to better support risk assessments with data. In addition, she continued, clarified guidance in Annex 2 would be helpful.

Jörgen Magnus, Research and Development Manager from Bayer Technology Services, demonstrated a model for batch definition and out-of-specification investigation in a continuous biological process.

Leif Poulsen, Global Technology Partner, Automation and IT, NNE Pharmaplan, opened the Knowledge Management session, explaining how to organize knowledge management in a big corporation. He highlighted communities of interest (COIs), ensuring a common language, standardizing processes, and striving for consistent, high-quality solutions. Management bodies in the model are a COI board, competency board, human resources board, quality manufacturing board, and resource management in the whole network.

Ciaran Kelleher, Senior Process Engineer, Janssen Biologics, Ireland, described a systematic cross-disciplinary approach to tech-transfer projects based on the ISPE *Technology Transfer* Good Practice Guide. He demonstrated a range of smart tools for sharing knowledge and experience throughout a tech-transfer project, part of a wiki-like process from development to chemistry, manufacturing, and controls and commercial manufacturing.

This interesting afternoon ended with a presentation by Elena Galiana Jaime, Senior Knowledge Manager, BASF, which demonstrated knowledge-transfer methods and tools in the global BASF community.

DAY 2

Tuesday began with "Data Science as Enabler for Scale-Up, Technology Transfer, and Root Cause Analysis in Manufacturing," presented by Stefan Krahulec, Senior Manager Technology and Innovation, and Georg Klima, Executive Director Process Science Austria, both of Boehringer Ingelheim, Vienna. Their session focused on three case studies from biopharmaceutical operations: root cause analysis, chromatography, and automation.

Next, Safaraz Niazi, Chair and Chief Science Officer of Therapeutic Proteins International, discussed the company's improvements to the biomanufacturing process: combining the fermentation and recovery steps to reduce the number of tanks and eliminate centrifuges, harnessing the power of gravity to diminish the need for pumps, and placing placed single-use bags horizontally to reduce the fluid level and obviate the stirrer.

Dr Imre Molnar, Molnar Institut, Berlin, presented a way to shorten biologicals' time to market using computer-based data modeling. This new technology leads to much better understanding of the analytical process and variabilities affected by the analytical setup, and

facilitates communication between applicants and regulators in the product dossier reviewing process. Experiments can be done in seconds; design spaces are visualized in three dimensions, and can be combined with additional components in the analytical process.

The technology and innovation session featured new concepts for all areas of biologics manufacturing: upstream and downstream processing, followed by fill and finish.

Digitalization will result in much more automation and biologicals manufacturing, said Christian Woelbeling, Senior Director, Global Accounts, Werum Corporation. He previewed an industry-4.0-based production control strategy as a holistic and overarching concept, explaining how the production control strategy would fit into the existing concepts of quality by design, critical process parameters, critical quality attributes, and more.

"Construction and Qualification of a Large-Scale Microbial Manufacturing Plant" was presented by Jean-Luc Roulin, Head of Bio Drug Substance Operations, UCB. He demonstrated the "Edelweiss Project" case study—fast-track design and construction of a large-scale microbial plant for CIMZIA (certolizumab pegol). At its peak, 600 people worked on this project; implementation was done within 30 months. The project strategy was modularization of engineering and construction. Key elements were utilities and distribution, packaging strategy procurement, parallel execution, and integrated on-site installation. The second step was lean qualification using verification and risk-based approaches designed to foster process understanding and focus on critical points, subject matter expert empowerment, and reduced workload.

Britt Petty, Director of Biologics Manufacturing Operations, Biogen, discussed "Preparing Manufacturing Capabilities for Breakthrough Therapies." He explained the technological goals for upstream and downstream processing in building a large-scale biologics manufacturing plant. Focus on upstream processing will help produce more drug substance more quickly while reducing bottlenecks in N-1 perfusion and higher titers in bioreactors. Focus on downstream processing will purify more drug substance by handling higher titers with high-capacity resin, single-pass tangential flow filtration, and buffer concentrates.

"Single-Use Depth Filter with Hyperion Flow: No Centrifuge Requirement in Mammalian Cell Culture Harvesting Applications up to 2000L" was presented by Silke Bergheim-Pietza, Marketing Manager, Pall Life Sciences Corporation.

"Innovations in Fill and Finish Processes" were shown by Frank Lehle, Site Manager, Vetter Pharma Corporation. The company technology standard V-CRT@, Vetter Clean Room Technology, is focused on a sophisticated combination of isolators and restricted-access barrier system (RABS) technology. Industry trends such as a continuous change of products, smaller products, orphan drugs, and ophthalmic drugs have led to increased flexibility requirements. Other timely topics are quality requirements such as "essentially free from particles" to "practically free from particles" and zero colony forming units in RABS and isolators. A fully automated peroxide decontamination is part of this best practice approach. This very-well-thought-through production concept shows how to "improve quality—keep overall equipment effectiveness and flexibility."

All presentations were followed by interactive panel discussions that allowed the audience engage the speakers in lively question-and-answer sessions. ‹›

—Thomas Zimmer, Vice President, European Operations, ISPE

BRAZIL 2016 ANNUAL CONFERENCE

ISPE was present at the recent Brazil Affiliate Conference, held 24–26 October 2016 in São Paulo.

The conference was attended by ISPE CEO and President John Bournas, who spoke on the worldwide status of the biopharmaceutical market and provided an overview of organizational developments. This visit—the first by an ISPE CEO in over 15 years—reaffirmed ISPE's commitment to sharing knowledge on a global basis with all of our Affiliates. In addition, Dr. Theodora Kourti, ISPE's Senior Vice President of Global Regulatory Affairs, discussed ongoing regulatory initiatives that the organization is developing to benefit its international Members.

Also in attendance were representatives from Anvisa, the Brazilian National Health Surveillance Agency, and Sindusfarma, the industry syndicate of pharmaceutical products in the state of São Paulo.

Meeting highlights included the official passing of the gavel from outgoing President Alfonso Izarra to current President Marcelo Decanio, inauguration of a new Board, and recognition of the Affiliate's companies of the year: Nordika Pharmaceutical Engineering and Libbs Farmacêutica. ‹›

NORDIC AFFILIATE ANNUAL MEETING

Henrik Goldschmidt was elected Chair of the ISPE Nordic Affiliate's Board of Directors at the affiliate's Annual Meeting, which was held in Copenhagen on 17 November 2016. Congratulations to Henrik, and many thanks to outgoing Chair Anders Widov for a job well done.

The meeting was attended by more than 75 participants, who listened to interesting presentations on "Industry Challenges in a Global Market," "Our Future Workforce," "Factory of the Future with Information Technology," and "Fighting a Dragon with Nine Heads." ‹›

ISPE BIOPHARMACEUTICAL MANUFACTURING CONFERENCE

DELIVERING ON OUR PROMISE TO PATIENTS

San Francisco, California
4–8 December 2016

It is fitting that a city known for its disruptive innovation (think 1960s) would be the gathering place for ISPE's first US conference on biopharmaceutical manufacturing. Certainly, biopharmaceuticals have disrupted an industry steeped in tradition. Yet that industry is changing and is using ground-breaking strategies to embrace a market that is expected to explode by the end of this decade. Consensus is that both small- and large-molecule players have room to grow in this space, albeit in different ways. And biopharmaceutical's footprint is such that emerging markets may hold the key for traditional pharma's ambitions. So, much change and newness all around.

It was no surprise then, to learn that 216 people from 14 countries descended upon the InterContinental Mark Hopkins hotel on 5 December 2016 for ISPE's three-day conference on biopharmaceutical manufacturing. The conference welcomed 39 speakers, from 7 countries, to share insights, discoveries and concerns. Two education track sessions, Planning and Managing Capacity Challenges and Technology Solutions to Meet Capacity Challenges, were designed to provide participants with an understanding of the potential implications of accelerated growth in this sector.

The conference theme—Delivering on Our Promise to Patients—is one that ran through the presentations and conversations throughout the first day. Following are some highlights.

DAY 1

John Bournas, ISPE CEO and President, welcomed delegates by reminding them that every day they help implement and put into place operations that put more medicines into the hands of people who need them on an everyday basis. "I feel energized every morning, knowing we at ISPE are contributing in some way to achieving that goal," he said.

He underscored the international flavor of the conference, and remarked that the knowledge sharing of the sessions also would be international in scope.

Bournas went on to present an ISPE "state of the nation." He began by announcing the impending release of a seminal project collaboration with Pew Charitable Trusts on drug shortages as they relate to sterile injectable products in the American market. "The results of ISPE's collaboration with Pew contributes to the ongoing discussion on mitigation of shortages." (See page 17 for more information.) He also highlighted the ISPE Training Institute's first year, stating that "we've had tremendous response from industry, with more than 1,000 people trained during the calendar year."

Bournas then looked to 2017 and reminded the audience of the upcoming Aseptic Conference, as well as the Europe Annual Meeting in Barcelona. He also announced the first ISPE Conference on Quality Culture and Quality Metrics, 25–26 April 2017 in Bethesda, Maryland, citing the FDA's recent revision of its Quality Metrics Guidance. "We need to maintain the momentum gained through the Wave 1 and 2 reports," he said, pointing out that the FDA has put both reports on its website, along with the work The Brookings Institution has submitted on the topic.

He closed with a "rallying cry" for participants to attend the 2017 Biotechnology Conference in Dublin, Ireland, next September, and ISPE's 2017 Annual Meeting in San Diego next November. "This is your biggest opportunity to network and promote your services."

My friend Andy

Bournas then introduced the day's keynote speaker, Andy Skibo, an ISPE member for 24 years. He called Skibo a visionary in the manufacturing space and said "I am pleased to no longer have to introduce you as my boss, but rather, as my friend."

Skibo, former ISPE Board Chair and Chair of the Global Pharmaceutical Manufacturing Leadership Forum (GPMLF), which convenes heads of manufacturing and operations from leading pharmaceutical companies around the world, delivered a presentation on "Significant BioManufacturing Capacity Expansion Drivers, Scale, Consequences." Delegates gained an understanding of the key changes in the pharmaceutical industry that are driving unprecedented change in the manufacturing environment, and

what this means specifically to biologics. They also heard about the risks inherent in planning the USD $20 billion in investments and the capabilities needed to deliver them.

The GPLMF, he said, is made up of leaders in big pharma and big bio, and informs what is happening within supply chains. He began by telling the story of recent meetings where the conversation inevitably led to a "can we do this?" moment. "With close to $20 billion in large-scale biologics development, $13 billion in actual hard development, much of this expansion and development relies upon a narrow group of key suppliers for success."

He added that current supply chains, focused upon mature products, will have to become segmented supply chains. "While some portion will still be managed for mature products, critically, a significant portion of the supply chain must be focused on agile and flexible response to new pipeline launches and uncertain demand."

Running the pharmaceutical supply chains are experts from the automotive and apparel industry, among others. And while their skills are being put to good use within the pharmaceutical industry, it isn't enough to "catch the wave." Organizations, Skibo said, must shift from managing a mature product line to one that is less so, as the industry shifts to specialty care, with all the complexities and investment demands that entails.

While the answer to "Can we do this?" is "Yes," Skibo added that proper planning, with focus on the required workforce and delivery methods is imperative for success to occur. And he closed by reminding the audience that "our patients are our drivers."

From data to academia

The keynote was followed by a general session: "New Paradigms for Manufacturing Capacity," led by Jennifer Lauria Clark.

Mrs. Clark introduced Eric Langer, President and Managing Partner, BioPlan Associates, who presented on "Biomanufacturing Global Capacity Trends: New Technologies, Biosimilars, and Innovation," and then Ruben G. Carbonell, PhD, Director, Biomanufacturing Training and Education Center and the Kenan Institute for Engineering, Frank Hawkins Kenan Distinguished Professor of Chemical Engineering, Technology and Science, North Carolina State University, who delivered "Educating the Workforce for the Future for Biomanufacturing."

Langer presented a high-level overview of the 2014–2016 results of BioPlan Associates' annual survey of 222 organizations. He revealed that while there was no standout in the category of most important biopharmaceutical trend, manufacturing production and efficiency is identified as the single most critical trend in bioprocessing, noted most frequently by bioprocessing decision-makers, over the past 3 years. How and when these technologies will be fully commercialized in terms of hiring and staffing, how to find the right people at the right time for staffing bioprocessing facilities will continue to be a challenge.

Dr. Carbonell presented the results of the BioProcess International/Biomanufacturing Training and Educations Council survey on challenges and barriers in education and training. He began his presentation by addressing the increased pressures and opportunities biopharmaceuticals have created, and how a new paradigm is required for the future of biopharmaceutical manufacturing. He spoke of the new levels of expertise industry has identified as must-haves for new recruits: professional skills, such as management scheduling tools, teamwork, communications, leadership, team organization, financial principles, and big data approaches. These workers of the future are perceived as the most important asset of an organization, and training, an investment.

DAY 2

Conference participants woke up to a bright and sunny day 2. Judging by the enthusiasm and energy that permeated the day's events, the boost of vitamin D worked.

The day began with Phillip McDuff, Vice President, Global Engineering, at Biogen, stepping in for keynote speaker Hitto Kaufmann, PhD, Global Head of Pharmaceuticals, Development and Platform Innovation, Sanofi-Aventis Deutschland GmbH, who was unable to attend. McDuff's talk, "Supplying Exponential Demand," focused on Biogen's next-generation manufacturing strategy and how it has been applied to a new facility going up in Switzerland.

McDuff's overriding message was that pre-

paring for expansion is a delicate process involving strategy, data, and good timing. Biogen's greatest challenge now, explained McDuff, is "dealing with an emerging drug in the pipeline with the potential to significantly increase demand on overall supply chain."

Biogen's commitment to patients makes it imperative the company expand. And considering its current pipeline, it has invested in a new facility, which will be built midway between Basel and Zurich, Switzerland.

The new biopharmaceutical manufacturing cell concept will utilize next-generation operations and integrated execution systems. "It's not your typical six-pack," said McDuff. "We modeled our specific processes to come up with the design." Spanning 55,000 square meters, the new facility's first phase of development will accommodate 10 metric tons, and be expandable to 35. The key to the concept, for Biogen, said McDuff "is the high titer cell line drives production."

With closed systems processing, reduced prep times, and high-performance operations that are highly automated and integrated, this new facility holds many of the features of "the facility of the future," not the least of which is sustainability.

"This facility will use 83% fewer carbon emissions, use 79% less energy and 89% less water," explains McDuff.

The project will take 51 months from start to finish, and is expected to be completed in January 2017.

Can continuous biopharmaceutical manufacturing live up to the hype?

That is the question. And the team presenting during the Continuous Processing session offered a resounding "Yes, but," as an answer. Andre Walker, CPIP, Principal, Andre Walker Consulting, led this session that debated whether continuous processing could transform the economics of the highly regulated pharmaceutical industry as it did industries from steel to petroleum; and, in particular, whether the unique nature of biopharmaceutical products represent an insurmountable challenge.

John Bonham-Carter, Director, Repligen Corporation, and Jørgen Magnus, PhD, Manager R&D, Bayer, offered alternatives to current operating paradigms that will help companies achieve continuous biopharmaceutical processing. Bonham-Carter argued that perfusion cell culture methods have matured and are now a viable, even preferred, alternative to fed batch technology, while Dr. Magnus presented his successes with novel downstream methods that have been incorporated into a working prototype.

Making medicines available to those who need them

During an afternoon session on New Therapies and Their Manufacturing Challenges, three academics presented inspiring talks on the ongoing efforts in their laboratories to develop innovative technologies for bringing needed medicines to the patients who need them.

This was a rock-star session. Remember your university professor who kept you on the edge of your seat for the duration of class, and left you wanting more? That's what this trio delivered: Board Director Antonio Moreira, PhD, Vice Provost, University of Maryland Baltimore County (UMBC); David Wood, PhD, Associate Professor, Chemical and Biomolecular Engineering, Wood Lab for Applied Engineering, The Ohio State University; and Jay Keasling, PhD, Professor of Chemical Engineering and Bioengineering, Synthetic Biology Institute, University of California, Berkeley.

Dr. Moreira talked about a paradigm-shifting technology being developed to make a small number of doses of therapeutic biologics right at the site where the patients will be administered such medicines. The technology will produce these medicines in 6–12 hours from start to finished dose, instead of the weeks- or months-long processes that are currently the norm. Implemented in briefcase-size factories, the technology can potentially be used in battlefield situations, hospitals, or clinics in a distributed manufacturing system. UMBC, The Ohio State University, Thermo Scientific, and Latham Biopharm are collaborating on this project.

Dr. Wood described a potentially universal technology for purification of proteins in a single-step process resulting in purities above 95%. The technology uses molecules known as inteins, which are attached to both the protein of interest and to an affinity tag. During chromatography processing, these intein molecules self-cleave through a simple process step such as a change in temperature or pH. The result is a native protein product that does not contain any of the affinity tag or the intein residues attached to it.

Keasling described his team's work on engineering microorganisms, such as yeast, to produce needed pharmaceutical products. He gave the examples of artemisinin, used for malaria treatment, and taxol, used for cancer applications. These pharmaceuticals, currently sourced from plant materials, can thus be manufactured through technologies that assure a reliable and consistent supply of these compounds to the patients who need them. He highlighted his hope for the establishment of a network of biological foundries where technologies like these can be more efficiently developed to make new therapies for human disease available through a faster path.

DAY 3

The last day of the conference focused on regulatory perspectives on the lifecycle management and manufacturing of biotech drugs, including biosimilars, and was hosted by Joseph Famulare, Vice President, Global Compliance and External Collaboration, Pharma Technical Quality, Genentech, a member of the Roche Group, and Past ISPE Chair.

"Biotech therapies have increasingly comprised a greater portion of pipelines and approvals for both new molecular entities by global health authorities," said Famulare, "with approvals of biosimilars coming along." He highlighted the importance of these programs and their effect on all markets, including those in emerging economies. As the biotech industry matures—at great speed—with new technologies and players regularly entering the space, the need to adapt to new realities and switch gears is incumbent upon all.

To introduce the morning's speakers, Famulare articulated what he qualified as "the most common question"—"How did you handle the regulatory component when you retrofitted that plant?"—and suggested the regulatory and industry speakers would provide answers and insight. The speakers were: David Doleski, Deputy Director (Acting) Office of Process and Facilities, FDA/CDER/OPQ/OPF; Joslyn Brunelle, PhD, Product Quality Team Leader (Lead Biologist), FDA/CDER/OBP/DBRRIV; Jennifer Cheung, Director, Head of GMP Compliance Audit, Americas and Asia Pacific, Global Quality Compliance and External Collaboration (PTQG), Genentech, a member of the Roche Group; Jonathan Harris, Director, Regulatory Medi BioVentures, MedImmune/AstraZeneca, discussed licensing of biosimilars; and Roger Nosal, PhD, Vice President, CGMC, Pfizer Inc. Presentations were followed by a Q&A session.

Conference Co-Chair Britt Petty closed the conference by acknowledging the assistance of his Co-Chair Andy Skibo and the program committee's work over the previous eight months, and thanking all ISPE staff members who participated in the planning and operations of the conference. He recalled a conversation with John Bournas 18 months ago about how to carve out a unique space for biologics manufacturing within ISPE. He said their goal was to create platforms for conversations about learning, trends and challenges in biologics manufacturing. "Thanks to John's strategic leadership and vision, we established an ISPE biologics strategic steering committee and have held two successful conferences, one in Europe and one in the United States."

He concluded with a bold statement that the audience reacted to with much acclaim. Alluding to the products in development for Alzheimer's disease, other forms of dementia, and various types of cancer, he said "Delivering the pipeline is an opportunity to alleviate human suffering on a scope and scale that hasn't been seen before." ‹›

2016 ISPE FACILITIES OF THE FUTURE CONFERENCE

"The future is already here—it's just not very evenly distributed." That quote by sci-fi novelist William Gibson captures an important component of ISPE's successful 2016 Facilities of the Future Conference, which brought together diverse experts sharing their ideas and the latest innovations on "bricks and brains" issues—everything from smart building design and robotics to continuous manufacturing, additive manufacturing, and collaboration to meet specialized workforce needs in biopharma. On the other hand, explained keynote speaker Enno de Boer, Operations Leader and Partner, McKinsey & Company, there are fundamental issues that we are only beginning to grasp, such as the true potential impact of data analytics as a disruptive force across industries.

The conference, held 14–15 November in Bethesda, Maryland, drew 137 attendees and 12 exhibitors. There were 28 speakers from eight countries, with attendees from 13 countries.

Conference Co-Chairs were ISPE Board Member Jim Breen, Lead, Biologics Expansion, Janssen Pharmaceuticals, and Jim McGlade, Science Market Leader, BHDP Architecture. Program committee members who helped shape the conference were Mark Butler, Senior Vice President, Integrated Project Services Ltd.; Tony Crincoli, Executive Director, Bristol-Myers Squibb; Richard Fecteau, Vice President, Business Development, SNC-Lavalin; Gert Moelgaard, President, Moelgaard Consulting; and Bob Chew, President/CEO, Commissioning Agents, Inc.

"'Facilities of the Future' is one of ISPE's six Strategic Priorities," Breen noted. "This conference attracted a global audience from industry, large pharma, CMOs, equipment suppliers, service providers, academia, and government."

McGlade commented that the conference "provided a wide breadth of valuable content to the attendees over two days. I returned to my 'day job' with the following themes resonating in my mind:

- Projected growth of the large-molecule market, necessitating innovation
- Diverse types of collaboration, partnerships, and joint ventures that can increase the probability for success and reduce risk
- Growing investment across the industry in modular, flexible manufacturing
- Innovative approaches often result from combining existing technologies
- Today and tomorrow's workers must be more agile to sustain the industry's evolution."

ISPE's inaugural Facilities of the Future Conference combined practical solutions that are making a difference today with inspiring visions of where things may be headed. In addition to representation from leading pharmaceutical industry companies and suppliers, the conference featured presentations by BioBots, a company pioneering new frontiers in additive manufacturing; Honeywell, an engineering firm; and the National Institute for Bioprocessing Research and Training in Dublin, Ireland. Led by keynote speaker Rick Friedman, Deputy Director, Science and Regulatory Policy, OMQ/CDR/FDA, the conference also featured speakers from the White House, BARDA, and DARPA, addressing topics that ranged from leveraging current technologies to the potential impact of emerging technologies like pharmacy on demand, enabled by miniaturized, mobile drug manufacturing.

"Based on the great success of this event," Breen said, "ISPE will plan future Facility of the Future events, which will be open to all to attend." ‹›

Q1 2017

ISPE TRAINING INSTITUTE COURSES

9–10 March 2017

Are your process control systems fit for use?

Using a lifecycle approach for the development and management of process control systems, ***A Risk-Based Approach to GxP Process Control Systems: Applying the GAMP® Good Practice Guide: A Risk-Based Approach to GxP Process Control Systems (2nd Edition) (T21)*** course demonstrates how the principles and concepts of GAMP® 5 may be practically applied.

The course covers both regulated company and supplier quality management systems and the full system lifecycle from concept to retirement. You will learn how appropriate QRM and specification and verification activities should be an integral part of the normal system lifecycle and how to leverage supplier documentation and activities to avoid unnecessary duplication, cost and waste.

27–28 March 2017

Can you successfully develop and validate your bioprocess?

The inherent complexity and uncertainty of biotechnology makes developing and validating bioprocesses for manufacturing proteins and biopharmaceuticals very difficult. The ***Process Validation in Biotechnology Manufacturing (T32)*** course is designed to provide a clear understanding of the regulatory (USFDA's Process Validation Guideline), scientific, and engineering tools required to successfully develop and validate bioprocesses.

Course topics includes a long list of activities required to validate biopharmaceutical processes, comprehensive strategy development, review of important biotechnology manufacturing processes, and the regulatory requirements for their validation.

30–31 March 2017

Does your technology transfer reflect an enhanced approach to current best practices?

Technology transfer includes knowledge transfer, science and risk-based principles including ICH Q8, Q9, Q10, Q11 and efficient processes to meet evolving business needs. As the industry continues to experience changes, technology transfer for APIs, finished dosage forms and analytical methods between development and manufacturing sites and contract manufacturing organizations (CMOs) have become increasingly important.

This ***Practical Application of Technology Transfer (T19)*** course uses current industry challenges and real-world examples as tools for industry and regulators to use when conducting and evaluating technology transfer activities. Through the identification of successful technology transfer, we have developed "how-to" examples that can be individually tailored, depending on the type and scope of transfer. ‹›

ISPE GUIDANCE DOCUMENTS

COMING SOON

ISPE SAMPLING FOR PHARMACEUTICAL WATER, STEAM, AND PROCESS GASES GOOD PRACTICE GUIDE

The intent of sampling is to take a small but representative portion of a much larger stream where the sample collected accurately represents the content of the larger stream. The sample collected should not be altered or changed in any way because of the sampling process, but this is an almost impossible proposition as all sampled utilities come into contact with air, containers, etc., during the sampling process.

Effective sampling is of paramount importance to the success of any pharmaceutical critical utility system. Extracting a representative sample from a utility system can be an involved and complicated process and either an error or errors may be introduced. Improper sampling may have a negative impact on company image, cost, productivity, ethics, and regulatory liability.

This *ISPE Good Practice Guide on Sampling for Pharmaceutical Water, Steam, and Process Gases* affects users of water, steam, compressed air, or process gases and impacts facilities, production, and quality control personnel within a facility. This Good Practice Guide applies to manufacturers of pharmaceuticals, medical devices, biologics, cosmetics, and related products as well as equipment manufacturers, vendors, and other industries outside of the pharmaceutical arena. ‹›

MEET YOUNG PROFESSIONAL JAMIE SIGMON

Jamie Sigmon

Jamie Sigmon readily acknowledges that she has done a lot in her young, yet varied career. "I have really been fortunate," she says. "I have worked as an intern in manufacturing sciences for a regenerative medicine company, I worked in technical development in the vaccines division of another company, I worked in biologics manufacturing, and now I'm in a different area of technical development at Biogen."

A PASSION FOR PHARMA

Following the completion of her bachelor of science degree (major in biochemistry) at North Carolina State University (NCSU) in 2011, Sigmon was not sure what she wanted to do next. "I didn't really feel prepared for the working world, but I knew that I wanted to use that degree," she says.

She took a position as a QC chemical technician at the Novozymes North Carolina facility. "Working in quality control meant that I was testing samples from the production floor. This piqued my interest in biotech manufacturing and I knew that's where I aspired to be. So with that, I made the decision to go back to grad school," says Sigmon.

In January 2012 Sigmon began her master's degree at NCSU with the benefit of a fellowship from the National Science Foundation, which allowed her to concentrate on her studies without having to work full time. Her degree, which concentrated on upstream and downstream biomanufacturing, was completed in December 2013. "My graduate degree was very specific toward biopharmaceutical manufacturing," she says. "That's how I focused my passion on the biopharmaceutical industry, and it just thrived from there."

AN INTRODUCTION TO ISPE

During the first semester of her graduate degree, Sigmon was first introduced to ISPE. "I contacted the NC State student chapter, and have been involved with ISPE ever since."

Sigmon transitioned from the public relations director role in the NCSU student chapter to the CaSA professional chapter upon completing her studies. "I immediately became Co-Chair of the Young Professionals Committee for CaSA, stayed active, and then became the Chair of the Committee. I just completed my two-year term as Chair," she says.

"There aren't enough great things that I can say about ISPE," she says. "It has everything that a pharmaceutical engineer would want. It's not just a professional organization. It's also a network of amazing people. The people at ISPE are truly some of my closest friends and also some of my best contacts for process-related or facility-related questions."

CAREER DIVERSITY

While pursuing her graduate studies during the summer of 2013, Sigmon was an engineering intern in the Manufacturing Technical Sciences department at Shire's former regenerative medicine facility in La Jolla, California. In that position, she was responsible for executing a gap analysis on regulatory submissions and gathering key parameters for process-transfer to a new GMP facility.

Her first job following the completion of her graduate degree was as a technical development engineer at Novartis Vaccines in Holly Springs, North Carolina, starting in early 2014. There she worked in both cell culture and purification areas of the cGMP vaccine drug substance pilot plant. She additionally had the opportunity to author clinical drug substance batch summary reports and develop technical data review presentations.

Sigmon transitioned to Biogen in 2015 and is now an associate scientist in fill/finish process development. Her team is involved in the building of a pilot-scale process development lab.

"We'll be doing facility startup activities for the rest of the year. Once the equipment is fabricated, we are traveling to the manufacturing sites to conduct factory acceptance testing. The next major step is the site acceptance testing of the equipment once installed in our facility. When the lab is up and running, we will be able to do characterization for end-to-end fill/finish processing. Our capabilities include vials, syringes, and cartridges. Additionally, our analytical lab will enable us to characterize and further develop our product," she says, noting that it will be the first of its kind at Biogen.

LOOKING AHEAD

As she looks ahead to the next steps in her young career, Sigmon sees herself continuing to pursue her passions and developing new skills. "I love to be challenged and I love to learn," she says. "I really like the technical development realm because it allows me to experiment and stay up-to-date with the latest trends, what new technologies might be coming, and how the industry is transforming."

Regarding her involvement with ISPE, Sigmon says, "Typically, someone on the local committee will also be involved at the international level to be the liaison between the international and the local committees. I look forward to becoming more involved in the international committee while working with the local YP committee as a member and letting some other folks get their turn at leadership." ‹›

—Mike McGrath

IN OTHER WORDS: i.e., e.g., et al., etc.

Four Latin abbreviations are staples of scientific writing: i.e., e.g., etc., et al. Despite their ubiquity, however, their meanings and usage are often confused or misunderstood. How can this be—especially when the terms are used so frequently?

Although Latin is no longer the West's academic language, many of its abbreviations have remained part of the scholarly lexicon. With the passage of time, however, the original phrases and meanings have been forgotten and fallen into misuse.

Let's start with the two most frequently confused terms:

i.e. and e.g.

i.e. stands for *id est* ("that is"). It provides a precise definition or explanation of a preceding statement or term. Here are some examples:

- Canada's Therapeutic Products Directorate regulates prescription and nonprescription pharmaceutical (i.e., chemically synthesized) products and medical devices.
- "Drug design" means the design of a small molecule that will bind tightly to the required target, i.e., ligand.

i.e. is specific and describes an exclusive set.

e.g. stands for *exempli gratia* ("for example"). It denotes nonexclusive examples or illustrations of a term or category, as shown below:

- Microorganisms typically used within the pharmaceutical industry include prokaryotes such as bacteria, e.g., *Escherichia coli, Staphylococcus aureus*.
- Patient advocates (e.g., AIDS and cancer activists) have generated the strongest and most public political pressure to shorten the FDA regulatory process.

e.g. is nonexclusive and indicates one or more elements of a set.

Usage

You can distinguish i.e. from e.g. by remembering that the "i" in i.e. means "it" (a specific thing) and the "e" in e.g. means "example" (a nonspecific thing). You can also double-check your sentence by substituting the abbreviation with its meaning. If it sounds right, then you've chosen correctly.

etc. and et al.

Etc. and et al. both indicate an abbreviated list, but each has a specific function.

etc. (*et cetera*), which means "and others of the same kind," indicates a list of things too extensive to include in its entirety. It should never be used in reference to people. For instance:

- An effective barrier to light, moisture, oxygen, bacteria, volatiles, etc., packaging protects the physical and chemical stability of pharmaceuticals.
- Medical devices (stents, prostheses, catheters, etc.) are regulated by the FDA.

et al. (*et alii*), which means "and others," indicates a list of people (usually authors). The abbreviation may be part of an in-text citation, a reference list, or shorthand for a previously mentioned (or well-known) publication. Here are some examples:

- Website usability for blind and low-vision users (Miller et al., 2009) is critical to a fully open society.
- Paul, S. M., et al. "How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge." *Nature Reviews Drug Discovery* 9 (2010): 203–214.
- In the EU alone there are more than 3,000 APIs; several authors, including Hammond et al., indicate that these are emerging pollutants.

Usage

Both etc. and et al. end with a period, even if they fall in the middle of a sentence. A comma may precede or follow both terms if necessary. Never use "and etc.," because the "et" in "et cetera" means "and." Don't use etc. to end a list that begins with e.g., since it is by definition a list of examples. Finally, there's no need to follow etc. with an ellipsis (…). Trust your readers to know that "etc." means "and so forth." ‹›

—Amy R. Loerch

Do you have a writing or grammar question? Send it to aloerch@ispe.org.

Term	Latin	English
i.e.	*id est*	that is
e.g.	*exampli gratia*	for example
etc.	*et cetera*	and other things
et al.	*et alii*	and other people

MAKE THE MOST OF YOUR DAY AT A JOB FAIR

Hi Dave: I plan to attend a job fair soon, and would like to know if you have any tips on how to navigate it successfully.

A job fair can offer a unique opportunity to speak directly with hiring managers and recruiters, and provide information that that may not be easy to find online. Success, however, is determined greatly by your preparedness.

These events tend to be very busy, and job seekers typically have a very limited time to make meaningful connections and obtain important information. During the time you spend with company representatives, it is critical to be as efficient as possible with your questions while making the best impression you can. Here are some other tips to maximize your opportunity.

BEFORE

- Most job fairs offer a directory of the companies that will attend. Evaluate and prioritize the list. Review company websites, social media feeds, and other online sources to determine which are good matches for you.
- Review each company's career section for open positions and information on how to apply for them.
- Rank your targeted companies, find their locations on the job fair map, and plan to visit them in order of priority.
- Create a folder for each company you plan to target. Write questions based on your research, then rank them in order of importance. This will help answer your most pressing questions during the limited time you may have.
- Review registration requirements, or register online in advance, if possible. Forgetting your ticket or ID could cost a great deal of time or even force you to miss the event, so make sure you are prepared.
- Map your commute to the event location or make a test drive so you know how long it will take to get there.
- Bring a portfolio, pen, and notepad; breath mints; business cards; copies of your resume; event map with target companies highlighted; and a handkerchief to dry your hands.

Don't bring your research folders—use your notepad to list questions and information for each company. This will put everything you need in one place and keep you on task. Leave some blank pages between companies so you have plenty of room for notes.

Next, be ready to answer questions about yourself. You should be able to provide a brief account of your background, why you're interested in each organization, and the type of opportunity you are pursuing. A concise and focused "elevator pitch" should take about 30 seconds. If you don't want to target just one type of job, be ready to describe the function or kind of role that you are most interested in.

DURING

Make sure that you create a great first impression: Conservative suits in black, navy, or gray are best. Avoid flashy, colorful items, and strong perfumes or colognes. Wear a watch, but keep other accessories to a minimum. Remember—you want the attention on you, not what you are wearing. Make sure you get a good night's sleep before the event. Coffee or an energy drink may make you more awake, but they can also drive anxiousness and jitters.

Once through registration, stop for a moment to take in the room. Assess the crowd and match your map to what you see. Job fairs are networking opportunities, so try to make connections throughout the day. While waiting in line or walking to the next company, pay attention to the conversation around you. You may overhear valuable information about the companies you want to contact. Be aware that allies in your search could just as easily be a fellow job seekers or career fair workers. Bring energy and enthusiasm to your conversations. Show your interest with a firm handshake, good eye contact, and a smile.

Collect as many business cards as you can, and write critical information directly on each. When it's time to apply for a position, you can stand out by referencing that connection in your cover letter or in future communications.

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

AFTER

Assess the day: Evaluate how effectively you achieved your objectives and note any obstacles you encountered.

Once you get home, organize your notes, cards, and company material in your folders to prepare your list of follow-up action items. Even though you may have given a company your resume, you may still need to apply online for positions you spoke about at the job fair. When you do, incorporate any information you gained from speaking with the company representative, and reference the connection in your cover letter.

Follow up with every contact that you made, remind them of your conversation, and any next steps you discussed. Act quickly to keep the momentum going.

CONCLUSION

Job fairs are a great way to discover new companies, obtain hard-to-find information, get career advice, and develop important connections. When approached with an open mind and a professional attitude, they can help take you to the next step in your career. ‹›

ISPE will hold several events across the globe this coming year. I hope to see you at one of them, and I look forward to hearing your success stories. In the meantime, let me know if you have additional questions about your career. I may be able to answer them in a future article.

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.

THE CATASTROPHE OF DRUG SHORTAGES IN PEDIATRIC ONCOLOGY

In the 1960s, almost all children diagnosed with the most common pediatric cancer, acute lymphoblastic leukemia (ALL), were dead within 5 years. The steady and dramatic rise in survival rates since then means that today these kids have a near-90% chance of surviving.[1] Similar statistics exist for all pediatric cancers.[9]

It would be easy to attribute this to advances in drug technology or the discovery of new medicines, but the drugs used to treat leukemia—prednisone, methotrexate, and vincristine among them—were developed in the 1950s, '60s, and '70s.

These impressive cure rates rely on a stable supply of these older generic drugs. Yet 80% of the most common drugs used to treat ALL have been in short supply over the past decade, a situation that exasperates pediatric hematologist/oncologists like Yoram Unguru, MD, MS, MA at the Herman & Walter Samuelson Children's Hospital at Sinai in Baltimore, Maryland and Johns Hopkins Berman Institute of Bioethics. He sees firsthand how drug shortages can increase medication errors, delay lifesaving treatments, and lead to patient deaths. "Children with cancer are particularly vulnerable to drug shortages," says Unguru. "Shortages prevent my colleagues and me from providing a reasonable standard of care and represent a national disgrace."

In the first three quarters of 2016, the American Society of Health-System Pharmacists, which gathers data on national drug shortages, recorded 120 new occurrences and 174 active drugs in short supply, including a significant number of chemotherapeutics.[2] The bulk of shortages are caused by economic factors, manufacturing and quality problems, and, to a lesser degree, regulatory concerns.

"We see the most shortages with generics, specifically generic injectable products, because they have low profit margins and are difficult to make," says Erin Fox, Director of the Drug Information Service at University of Utah Health Care in Salt Lake City, Utah. This affects chemo treatments, which are mostly delivered by injection. "Capacity is also an issue. Most manufacturers are running 24/7 so there isn't additional capacity for a supplier to make up the difference if a problem on a manufacturing line occurs."


Yoram Unguru

Shortages of sterile injectables are strongly associated with the consolidated marketplace, which has resulted in fewer suppliers, as well as with the issuance of FDA warning letters indicating manufacturing problems at facilities.[3] "When only one or two companies produce a generic injectable and a company opts to stop making the drug or has a problem with manufacturing, we all feel the pinch," says Unguru. "To have another company pick up the slack is time-consuming, labor-intensive, expensive, and far from guaranteed."

Unguru would like to see the federal government step in to help. "The FDA Safety and Innovation Act in 2012 resulted in fewer new shortages, but the fact that we continue to have 170 to 200 ongoing shortages suggests that something remains broken," he says. "One reason for this predicament is that unlike many other countries that directly negotiate drug prices with companies, the US government is not allowed to negotiate drug prices. The government stepped in to bail out the auto industry and insurance companies. Why can't they step in to do something about drug shortages?"

"People are paying $100,000 and more per patient per year for innovative therapies to treat hepatitis C, melanoma, or cystic fibrosis, and there's no shortage of these impressive new drugs. The shortages primarily affect old drugs, drugs that we rely on in pediatric oncology for curative and life-saving regimens. And it's not just chemo; it's essential supportive care drugs like anti-nausea medications, it's critical care drugs, it's antibiotics, it's essential electrolytes and minerals. We recently had a shortage of saline in Maryland. It's absurd."

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WHO SHALL LIVE?

This ongoing emergency in pediatric oncology forces physicians to make difficult ethical decisions at the bedside about the allocation of scarce resources. "If we have drug shortages, then the need to prioritize drugs is unavoidable," says Unguru. "Bedside rationing is inefficient, uncomfortable, and probably unethical."

Oncologists respond to drug shortages by switching chemotherapy regimens, substituting for a different drug during treatment, delaying treatment, excluding some patients, or skipping doses. Yet 70% of medical oncologists do not have guidance from their cancer centers on how to allocate limited drugs.[4] Such guidance would allow prioritization decisions to be made before treatment, liberating physicians from making difficult ethical choices under challenging circumstances.

Unguru is part of a transnational working group (WG) on chemotherapy drug shortages in pediatric oncology that initially developed a consensus statement focused on the core ethical values and practical actions needed for a coordinated response to the problem of drug shortages.[5] The statement focused on novel ways to prevent and mitigate chemotherapy shortages. More recently, and largely as a result of ongoing shortages, Unguru led a subcommittee of the larger WG, an allocation task force (TF) that has recommended a two-step process to deal with drug shortages.[6] The first step is to mitigate the effects by maximizing efficient use and minimizing waste. This is followed by prioritization that maximizes benefit depending on the number of total lives and life-years saved. The TF has many recommendations, including that drug shortages be viewed as a national emergency, which allows for policy changes or remediation.

Because more than 80% of raw ingredients come from outside the United States, the FDA has on occasion made exemptions for the importation of chemotherapeutics from other countries in response to domestic shortages. "This points to how problematic shortages are in this country," says Unguru. "It's not that shortages don't exist outside the United States, but they don't occur to the same degree, depth, and enduring nature as they do here; unfortunately, we own this problem."

Such exemptions have created a dilemma for the FDA, as the quality of imported medication has sometimes been a concern. A shortage of the cancer drug doxorubicin in 2015 led the FDA to allow the importation of the drug from a Chinese plant that had previously received a warning letter for data manipulation.[7]

DRUGMAKERS' ROLE IN SHORTAGES

Prevention and mitigation of drug shortages are the steps in which drugmakers can have an impact. "ISPE, through its drug shortages initiative, has been actively involved in trying to help manufacturers improve quality and therefore ease shortages," says Fox.[8]

Unguru suggests that pharmaceutical companies can act as gatekeepers to prevent hoarding. "Eighty-five percent of hospitals purchase excess inventory to offset shortages," he says. "This doesn't help anybody." He cites a theoretical example of a hospital that normally orders 1,000 milligrams of a drug and then starts ordering 10,000 milligrams. "Such a scenario is an opportunity for the company to question the order."

Unguru would like to see companies address the convoluted way that drugs are currently distributed, in which he says manufacturers often lose control of product once it's passed to a distributor. "Drug companies need to be part of the solution to drug shortages," he says. "Without their input, the problems that relate to scarce drugs and the shortages themselves are not going to be solved." ‹›

—Scott Fotheringham, PhD

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DRUG SHORTAGES

THEORY INTO PRACTICE

John Berridge
ISPE Advisor, Regulatory Affairs, United Kingdom

After much focus at recent conferences and in publications on understanding the manufacturing- and quality-related causes of drug shortages, delegates at the 2016 ISPE Annual Meeting & Expo in Atlanta, Georgia, had the opportunity to hear from a panel of speakers how the current range of tools can be used practically to prevent and mitigate those shortages.

Peter Bigelow from xCell Strategic Consulting opened the session by inviting Rafael Lander and Carl Finamore from PriceWaterhouseCoopers (PWC) and Wes Schmidt from AbbVie to explore supply chain resilience, looking at how the risks to the product supply have increased in concert with complexities, especially as more players become involved in the pharmaceutical supply chain. One surprise was hearing that 80% of companies across industries cannot check whether their suppliers have business continuity plans, according to the results of a PWC/Massachusetts Institute of Technology (MIT) survey conducted in 2014. Homing in on pharmaceutical supply chains, we saw that there are unique operational and regulatory risks, including regulatory approval delays, changing regulations, and quality or compliance failures in addition to the more widespread risks such as natural disasters and political risks. Of course, should one of these risks occur, both the business and the patient will suffer.

Again, referencing the PWC/MIT survey, we heard that biopharmaceutical companies are struggling to master the increasing complexity while simultaneously responding to progressively more diverse customer and country requirements. And, it was asserted, avoiding this complexity is not an option for growing companies. Other challenges were seen to be the expansion of novel product types and delivery systems, cost pressures, and the demands of payers.

Looking at real-life examples of major drug shortages, we heard of uncorrelated causes such as product sabotage, cross-contamination, natural disasters, and shortages resulting from quality problems arising at a CMO. While some of the problems can be resolved quickly, sometimes recovery time is measured in years.

The solution is to invest in understanding the end-to-end supply chain risks and proactively develop resilience (business continuity) plans. The resource needed to develop such plans is not to be underestimated. Fortunately, help is at hand and we heard how not-for-profit consortia can help. Identified in the *ISPE Drug Shortages Prevention Plan* was the key enabler of "Robust Quality System" and organizations such as Rx360 can undertake supplier audits that test the robustness of the quality system(s) from raw materials to the pharmacy.

Other tools for shortage prevention include risk maturity and resiliency models, web data analytics, and ISPE's *Drug Shortage Assessment and Prevention* tool.

ISPE's tool has within it a self-assessment maturity model. PWC showed that maturity models can also help companies evaluate themselves against their peers: Companies with more mature resiliency practice outperform their counterparts. We were introduced to a resiliency model that is based on third-party data and uses simulation techniques to drive a probabilistic view of how supply chain risks impact key metrics. These can then inform resource and investment decisions. For example, the model might show that an industrial dispute in a port could have a major disruptive effect on product distribution and an alternative shipping mechanism might be appropriate. In a similar way, web analytics can provide near-real-time monitoring of risks such as a natural disaster.

The *ISPE Drug Shortages Prevention Plan* and the *ISPE Drug Shortage Assessment and Prevention Tool* together provide a holistic six-dimensional approach to the prevention and mitigation of shortages. The tool is an easy-to-use self-assessment approach that translates theory into practice and is globally applicable.

In the subsequent panel discussion, which included Larry Kranking (Commissioning Agents), Lance Minor (Medimmune), and Peter-Jost Spies (Janssen), we were treated to candid feedback from early adopters of the ISPE prevention tool who had practical experience with its use. While implementing it across all six dimensions demands significant resource investment, this is not always necessary as one can "pick and choose" the areas of most importance to the user. The holistic approach was seen to be very powerful, although it was recognized that other, perhaps more limited product-specific tools are available. Members of the ISPE Drug Shortages Task Force welcomed the feedback and heard that the use of the tool could be facilitated by its conversion to an electronic spreadsheet format. Readers, what are your views? Have you used the prevention tool? Would making it electronic improve its utility?

Attendees were also alerted to recent regulatory developments, including the new law enacted in France that requires that essentially all products have shortage-prevention plans available. While at the time of the conference the full requirements had still to be published, the ISPE shortages prevention tool was proposed as a cost-effective way of assessing a site or an organization's product portfolio and demonstrating that plans to prevent or mitigate a shortage are available.

Finally, we were given a taste of ISPE's latest contribution to the understanding and prevention of shortages—a collaboration with Pew Trusts (see page 17). The joint ISPE/Pew research study, due for publication in early 2017, will examine the drivers that inform and influence companies' decisions about whether to invest in areas such as new facilities, contingency production capability, or backup stock to mitigate a potential shortage, with focus on sterile injectable products. ‹›

LOOKING AHEAD

What does 2017 hold in store? What will be the most important industry drivers, its innovations, if any? What indeed!

During the ISPE 2016 Annual Meeting *Pharmaceutical Engineering* caught up with a few industry leaders and asked for their perspectives. Here's what they had to say.

Peter Bigelow

President
XCell Strategic Consulting, LLC

1. What do you believe the global industry needs to move forward in 2017?
We need to continue to provide new and innovative products at prices that are fair and reasonable. It's important for the pharmaceutical industry to provide drugs at pricing that fits our health care models. We also need to continue to invest in the research and development of important drugs, as well as continue to innovate in all areas of the business.

2. What will be the most important industry development or innovation in 2017?
There is a need to cultivate practices and tools that allow us to develop products more efficiently and manufacture them with greater levels of consistency. There is interesting work underway to improve processes; if we can continue to innovate in that area and drive best practices throughout global manufacturing, that will be a big enabler for improvement. I'm thinking specifically of things like continuous manufacturing, lean manufacturing, Six Sigma methodology, better planning tools, and using IT solutions so we understand our processes better, making them more efficient so they require less intervention. These solutions are out there, but there's a lot of work to be done to put them into practice.

3. What will be 2017's greatest hurdle and how do you believe industry might overcome it?
Our biggest hurdle is with the reliability of supply and assurance that patients get the medicine they need to support the best medical outcome. This is hugely important for the industry, and we'll continue to struggle with making our supply chains reliable. I see the solution coming from a focus on improving supply chain reliability so that we consistently deliver necessary medicines, driving for consistent and predictable delivery across the industry.

Chaz Calitri

VP, Global Engineering
Pfizer

1. What do you believe the global industry needs to move forward in 2017?
From the regulatory perspective, we need more harmonization. As the global supply chain has become so complex and interdependent on a global scale, there are inefficiencies that are plaguing us.

2. What will be the most important industry development or innovation in 2017?
Right now there is a race to develop biosimilars that is happening globally. There will be a few winners and a lot of losers. A lot of companies, like ours, are investing heavily biosimilars—in many cases the same products—and there's going to be a big shakeout that will start to happen in 2017.

3. What will be 2017's greatest hurdle and how do you believe industry might overcome it?
My response is based on the state in the US. Our greatest hurdle is reputation and society's unwillingness to invest in the future, namely innovative products that require significant investment. This gets to the pricing issue and the availability of generics. I think that innovative, research-based pharma companies will continue to be challenged, particularly in the markets that don't have a favorable system, like the US. The public is naïve about what it takes to bring new medicines to market and seems unwilling to invest in innovation. It is only through innovation that we can continue to advance medicine and greatly improve people's lives.

Steve Leonard
Sr VP, Global Operations
Catalent Pharma Solutions

1. What do you believe the global industry needs to move forward in 2017?

Serialization for product security: More than 70% of global volume is now covered by current or pending legislative requirements for serialization. In 2017, the US requirements begin to come into effect, and in 2018 European ones are scheduled to be implemented. In both cases, implications for manufacturing sites—both in-house and external—are substantial, requiring capital investment, validation, systems, and business process changes. This does not just affect the sites, however; in many countries integration into a complex, interoperative system of data exchange up and down the pharmaceutical supply chain is needed. Catalent has been active in these areas, and has invested to ensure it is sufficiently prepared to serve customers' needs

Ongoing manufacturing network realignments: Larger and mid-size manufacturers continue to face network realignment needs, driven by several key factors: First, a large number of existing (mostly small-molecule) products are approaching patent expiration; products worth about half of current branded market worldwide sales are expected to go off-patent over the next five years (per EvaluatePharma). Second, a focus shift by several large companies to biologics, plus the quantity growth of biologics in development, and increasing penetration of biosimilars—including finally in the US—is moving toward more need for both in-house and outsourced biomanufacturing. Third, the increasing prevalence of smaller demand volume products—whether orphan products for rare diseases or specialty-care products, which comprise a majority of new launches—require more flexible smaller-batch-size capacity, which is easier to change over, versus the large, long-duration capacity in place in much of today's large company network. All of these factors are reasons for organizations to increasingly consider outsourcing as part of their network reconfiguration strategy, as a way to improve return on invested capital.

2. What will be the most important industry development or innovation in 2017?

Complex molecules that dominate the current pipelines will drive an evolution of new manufacturing techniques: There has been a great deal of momentum in the development and scale-up of new manufacturing process technologies to meet functional product needs, and to reduce the potential of deviation. In recent years substantial growth in secondary API processing has improved the bioavailability of the drug product—amorphous dispersions of API molecules, for example, using either hot-melt extrusion or spray dry dispersion—joining more established particle-size-reduction techniques and lipid-based formulation approaches. If innovators have access to multiple technologies at the early stage of development, the potential for drugs not being restricted by issues such as bioavailability is much higher.

Other manufacturing process innovations will continue to evolve: Continuous manufacturing, pushed by regulators to reduce in-process deviations, will have certain applications that make sense. As batch sizes/product volumes decrease, however, economic benefits outside of deviation reduction may be less clear. Also, additive manufacturing techniques such as 3D printing are still in their infancy within the pharmaceutical industry, with the first drug product approved just this year.

3. What will be 2017's greatest hurdle and how do you believe industry might overcome it?

First, there are the serialization challenges already discussed, which will take a coordinated effort across the whole supply chain to progress. Second—and this is not just a problem for 2017—molecules in development are becoming increasingly challenging to deliver, and somewhere between 60% to 90% of those in active development will require some type of advanced technology—synthesis/expression, molecular engineering, formulation, dose form, and/or device—to achieve maximum clinical potential. Many companies do not have all of these capabilities in-house at both development and commercial scale, and often rely on one or two preferred approaches.

It will become more important, however, that early in development companies identify partners that can bring a broad range of advanced capabilities and potential solutions, and so that they can not only develop molecules, but scale-up and deliver full commercial supply. This approach will also help avoid incremental capital investment in new commercial-scale equipment, allowing for reinvestment elsewhere. At Catalent, we believe the investments we have made position us to serve developers and manufacturers of drugs with the broadest range of dose forms and capacity available to the industry.

Manfred Maeder
Head Device Development & Commercialization BTDM
Novartis Pharma AG

Biologics and biosimilars offer a major opportunity for future growth across the industry. We are investing substantially to support our growth in this area to ensure we can keep pace, if not outpace the patient need. Within the shifting in the health care landscape, with a growing and aging patient population, we recognize how significant the advances in this field will need to be and we are taking steps to ensure we are prepared.

There was a huge increase in biologics approvals this year and this will continue in coming years. Companies like Novartis are continuing to invest heavily in biologics, building plants as well as developing and manufacturing new products to meet unmet needs. With that increase, one of the upcoming challenges I see will be finding enough skilled people able to fill the growing demand.

Finding enough qualified engineers to do the work of planning and building the new biologic facilities is one part of the story. I've

heard from engineering companies that are constructing plants now that this is and will continue to be an issue. In the next 5 years, pharmaceutical companies will spend more than $20 billion to build plants capable of manufacturing and producing biologics. This increase is so huge, it's expected that there won't be enough engineers to build these plants across the industry. Second, once these plants are built, we may face another concern when it comes to finding qualified people to run these new sites. So with the number of sites increasing, there is also the potential to face shortages of knowledgeable and/or experienced biotech engineers able to manage the all complexities of biologics from building plants to manufacturing products.

Is it a global problem?

In my opinion, it is becoming a global problem but not one that is unsolvable. Across the industry, biotech needs are growing, which is a good sign, even though having skilled people remains an imminent concern. However, the concern is not just limited to finding the right people. As we develop new therapies, we also develop new technologies and combination products. More than 95% of the biologics in our portfolio are applied in combination with devices. This means we also need more devices; it's very difficult to find and appropriate enough skill first to develop and then commercialize both.

The solution?

Well, we have a couple of options. First, we can try to find people from the medical device industry, but they are facing similar shortages and difficulties finding the right talent. Compounding the issue, of course, are the industry-wide tightening of regulations and increasing expectations and documentation requirements. This means that overcoming the competition for similar types of skillset is part of the solution, as is tapping into other resources like those beyond the industry, which leads me to option two.

Option two revolves around training and building upon the talent available both internally and externally. We can achieve this by investing in and training people who have basic or similar knowledge. The time investment, of course, is higher but the outcome may be worth it Say, for example, we are looking for someone able to perform risk management through human factor studies. While this requires an incredible depth of knowledge—almost a specialized skillset—perhaps with training and a time investment we may develop the right candidates rather than find them.

Opportunities for migration?

Yes, for sure. Short-term solutions can be based in migration. For example, one can be found when we look at shop floor knowledge. This is an area where a significant number of people can be cross-trained to perform successfully within the biotech space.

Guy A. S. Wingate, PhD
VP & Compliance Officer, Global Manufacturing & Supply
GlaxoSmithKline

Looking ahead the main challenges I see facing the pharmaceutical industry are (in no particular order):

- Data integrity issues—technical challenges as well as operational issues driven by behaviors
- Implementing end-to-end integrated supply chain business process solutions to achieve more efficient operations
- Accelerated R&D development with increased outsourcing
- Removing waste and defects to reduce cost of goods in manufacturing facilities
- GMP standards at third-party contract manufacturers and suppliers

ISPE has a key role to play in bringing together regulators, suppliers, and pharmaceutical companies to develop practical standards and working practices that help firms improve performance while ensuring compliance. As professional engineers, we should apply good judgement and risk-based approaches to assure we put in place efficient and effective facilities, systems, and processes. Our organizations need to be brilliant at the basics as well as leverage technology and innovation. From my perspective, we need to spend more time understanding the impact of culture, values, and human factors on sustainable performance. I know ISPE guidance will tackle these challenges (e.g., new ISPE guidance on records and data integrity scheduled for publication early in 2017). We must always remember there are people at the end of the supply chain, and it is important they receive a reliable supply of products that are safe, effective, and meet regulatory requirements.

Fran Zipp
President and CEO
Lachman Consultant Services, Inc.

As 2017 dawns, the pharmaceutical industry will continue to face pressures from all areas. Companies will face external pricing pressures and competition from lower-cost producers, in lower-cost areas. Companies will need to be able to cut costs while maintaining product and process quality and meeting all compliance requirements. This is a continuum and a story we see every year. It's not a onetime-only effort to reduce costs. We need to innovate to survive. I think continuous manufacturing is a way to achieve that, and the industry needs to figure out a way to make it happen in a big way. New products need to be developed with the goal of making them in a continuous process, and older products need to be reimagined. The benefits are worth the effort.

Implementation across the industry requires a commitment not only from the R&D departments of firms, but also from manufacturing, quality operations, regulatory affairs and supply chain. Companies can apply continuous manufacturing across the spectrum, from high-volume to low-volume products, from high profit margin to low profit margin. Continuous manufacturing will not only save costs, it can transform product and process quality as well, while focusing on predictive compliance. Implementation of continuous manufacturing results in elimination of down time, reduced operator error, and avails enhanced controls; these can be transformational to quality and demonstrate industry's commitment to sustainable compliance. ‹›

PHARMACEUTICAL ENGINEERING®

YP VOICES

January-February 2017

SPECIAL REPORT

ISPE®

WHERE ARE THEY NOW?

ISPE knows that the future of the pharmaceutical industry lies with its youth—and to prove it, we've contacted five former contestants to see how the competition affected their careers.

Since 2000 ISPE has hosted annual student poster competitions at the Chapter/Affiliate level and at its Annual Meeting. The competition was established to provide a platform on which an outstanding group of young people could showcase their work and highlight their ideas. The event also allows the organization to acknowledge the scientists and engineers entering the field.

2009: Peter G Millili, PhD

Manager, Biologics Drug Product Manufacturing Science & Technology
Bristol-Myers Squibb

Winner of the Delaware Valley Chapter poster competition in 2005 (undergraduate division) and in 2009 (graduate division), Peter G. Millili did not win the international competition at either year's Annual Meeting; he credits the experience with shaping his career path, however.

"Involvement in the student poster competitions gave me a strong foundation to start my career, providing countless opportunities to broaden my understanding of our industry and how one can serve patients," said Peter.

By exposing him to new ideas and giving him the opportunity to talk with industry leaders, the competition opened a realm of possibilities.

"I received great feedback about the direction of the work, not only on the scientific merits and content, but also on how best to convey technical subjects to a broad audience. The judges at both the local and international levels cared greatly about each participant taking something away from the competition," he added.

INTERNATIONAL STUDENT POSTER WINNERS: 2000–2016

North and South America

- Argentina Affiliate
- Brazil Affiliate
- Canada Affiliate
- US Affiliate

United States

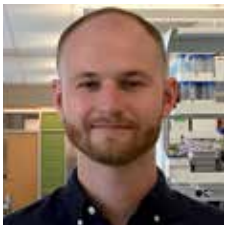
- Boston Area Chapter (*Massachusetts, Connecticut, Rhode Island, Maine, Vermont, New Hampshire, and Upstate New York*)
- Carolina–South Atlantic Chapter (*Alabama, Florida, Georgia, North and South Carolina, and Tennessee*)
- Chesapeake Bay Area Chapter (*Area in and around Baltimore, MD, Washington, DC, and Northern Virginia*)
- Delaware Valley Chapter (*Eastern Pennsylvania, Southern New Jersey, Delaware, and part of Maryland*)
- Great Lakes Chapter (*Ohio, Indiana, Illinois, Michigan, Wisconsin, and Kentucky*)
- Greater Los Angeles Area Chapter (*Los Angeles, Orange, Ventura and Riverside Counties*)
- Midwest Chapter (*Missouri, Kansas, Iowa, Nebraska, and Minnesota*)
- New Jersey Chapter (*New Jersey, New York, and Northeastern Pennsylvania*)
- Pacific Northwest Chapter (*Washington and Oregon*)
- Rocky Mountain Chapter (*Colorado and Utah*)
- San Diego Chapter (*Southern California, north to Orange County*)
- San Francisco/Bay Area Chapter (*Northern California*)
- South Central Chapter (*Texas, Oklahoma, and Louisiana*)

Europe

- Belgium Affiliate
- Czech Republic / Slovakia Affiliate
- France Affiliate
- Germany/Austria/Switzerland Affiliate
- Ireland Affiliate
- Italy Affiliate
- The Netherlands Affiliate
- Nordic Affiliate
- Poland Affiliate
- Spain Affiliate
- Turkey Affiliate
- United Kingdom Affiliate

Asia–Pacific

- Australasia Affiliate
- ISPE China
- India Affiliate
- Indonesia Affiliate
- Japan Affiliate
- Korea Affiliate
- Malaysia Affiliate
- Philippines Affiliate
- Singapore Affiliate
- Thailand Affiliate



2010: Nicholas Pashos

PhD Candidate in Bioinnovation
Tulane University

Nicholas Pashos has had a lifelong passion for innovation and learning. This drive led him to join ISPE and enter the Delaware Valley Chapter poster competition in 2010, and it pushes him toward completion of his PhD in bioinnovation today.

Despite his drive to succeed Nicholas wasn't always sure of his career path; winning the poster competition made a big difference, however. "The entire conference experience was very exciting, especially as an undergraduate," he said. "It was the first large conference that I had attended. Winning helped me to become more comfortable presenting my work to an audience outside my lab."

Even though his poster didn't win, Nicholas used the experience to launch a successful career focused on helping patients. His current research, which he developed into a start-up company called BioAesthetics, is developing a tissue engineering approach to nipple-areolar complex reconstruction for mastectomy patients.

2010: LeAnna Pearson Marcum

Validation Project Manager
Barry Wehmiller Design Group

LeAnna Pearson presented her research thesis at the Carolina–South Atlantic Chapter poster competition and won the chance to present at the 2010 Annual Meeting in San Diego. While she did not win the international competition, LeAnna, like Peter Millili, was greatly affected by the experience.

"That Annual Meeting changed my career path," she said. "I wanted to go into research and development, and that meeting opened the door to how much there was in pharma. I also decided that I wanted to be more involved in my local Chapter once I graduated. Because of this I have been able to develop amazing relationships with strong women in the industry, whom I now count as friends and mentors."

LeAnna continued her involvement with ISPE after the 2010 Annual Meeting; this has helped guide her into her current position as Validation Project Manager with the Barry Wehmiller Design Group, a company that provides engineering and technology services to the world's leading companies.

"I had never heard of ISPE until the poster competition, but once I did I became very intrigued. Looking back, I only wish that I had known about it earlier in my career," she said.

2013: Kassi Taylor Stein Undergraduate Winner

PhD Candidate in Chemical Engineering, MIT

Kassi Taylor Stein became an ISPE member in 2011; just two years later she presented her winning undergraduate poster entry on behalf of the Boston Area Chapter at the 2013 Annual Meeting. Kassi is now concentrating on her chemical engineering studies at MIT, focusing her research on quantitative redox biology in cancer. She knows that the experiences she's had and people she's met through ISPE will add value to her future career.

"I was quite proud of my work in lab and really excited to have had the opportunity to be recognized for it," said Kassi. "Certainly a lot of networking opportunities, as well as an interesting interview talking point have come out of this poster competition win."

2014: Francesca Lynn Undergraduate Winner

Process Engineer, CRB Consulting Engineers

Representing the Carolina–South Atlantic Chapter and winning the undergraduate poster competition at the 2014 Annual Meeting gave Francesca Lynn, above all else, confidence. Confidence that her ideas had merit and confidence that she could stand before a roomful of people and deliver a winning presentation.

"Like most college seniors, I was completely focused on finding a job. Giving some of that attention to networking through ISPE and the poster competition proved to be the best thing I could have done to reach my goal," said Francesca.

The chance to show off her skills before a group of her peers not only helped increase her confidence in her scientific ideas, but it also gave her the opportunity to network with people in all parts of the scientific community.

"In addition to collecting a stack of business cards from my newly formed network, I ended up interviewing with multiple companies at the Annual Meeting," Francesca said. One of those interviews resulted in a job offer, she added.

—J. Alexander Poulton

The ISPE Student Poster Competition is an annual competition held by local ISPE Affiliates and Chapters each year. The poster presentation consists of a visual display of research findings combined with an interactive question and answer period with a panel of judges. Local winners advance to the International Student Poster Competition at the ISPE Annual Meeting.

For more information visit http://www.ispe.org/students/poster-competition.

MY FIRST ISPE ANNUAL MEETING

Chris Slevin, EIT, process engineer with CRB

As I walked up to the Atlanta Marriott Marquis, the magnitude and grandeur of the building set the stage for how much bigger this ISPE event was than any business event I'd previously attended. The atrium was packed to the brim. There were polished professionals, contemporary booths, and fancy hors d'oeuvres. As an engineer with two years of experience in the industry, I wondered how I would mesh with the seasoned experts from all over the globe. Unfortunately, for newcomers to pharma, there can be a steep learning curve. When we find ourselves face-to-face with the subject matter experts and head honchos of the industry, we're prone to drop in a conversation killer or two: "I've got a GMP OSD facility with USP WFI and RO. Which one am I drinking from the water fountain?" or "Why does everyone squirm over the number 483?" In reality, the anxiety as a young professional at the ISPE Annual Meeting quickly subsided as I conversed with fellow members, students, panelists, volunteers, and ISPE leadership. Regardless of background or experience level, I found there is a genuine interest and respect among all professionals, and it fosters great new relationships, educational opportunities, and a renewed pride in the work we do.

NETWORKING

Everyone's heard the saying before, "It's all about who you know." In my short time as an engineer, I've realized this applies in our industry. The vast scope of work involved in running a pharmaceutical facility (operations, compliance, validation, quality, engineering, etc.) makes it virtually impossible to be an expert in all areas. Creating new relationships (and maintaining old ones) lends access to an extensive pool of industry knowledge spanning all focus areas. While the internet can be a valuable resource for information, it's the trusted personal connections established throughout a career that can be counted on when faced with a difficult issue or situation.

At the ISPE Annual Meeting, you are surrounded by individuals with specialized expertise within various sectors of the industry. It's an excellent opportunity to discuss ideas and build relationships. After having spent several hours at the event, I noticed that I had made connections just about everywhere. I had conversations over lunch, on the expo floor, through mutual friends, social events, education sessions, and even in the elevator. Making new connections is one of the greatest benefits of attending the ISPE Annual Meeting, so my advice to other young professionals is to not be afraid to put yourself out there. Introduce yourself often. I am confident the contacts I made may be valuable resources at some point in the future. In fact, I am already partnering with an expert I met on the expo floor for assistance with a project issue.

Chris Slevin

EDUCATION

As professionals, we owe it to ourselves to continually focus on self-improvement and learn about industry excellence. While the networking aspect of the ISPE Annual Meeting is important, the educational sessions provide an opportunity to strengthen the technical skill set. The seminars cover a broad range of topics, but I'll just touch on a few that I found particularly valuable.

I spent several months of my career at a facility that had issues with rouging. The persistence of this elusive problem surprised me—this couldn't be the only facility that dealt with rouging, right? Luckily there was a two-part seminar on "Rouging in Pharmaceutical Production" at the ISPE Annual Meeting. For me, this session alone made the conference worthwhile. I had no idea that this was such a common and complex topic. What causes rouging? How should it be monitored? Do I need to de-rouge? Like many problems, it is complex and there is no clear-cut solution or fix-all. I commend the presenters (Marc Vernier, Thomas Wellauer, Robert Haas, and Andreas Marjoram) for performing and collecting test data on causes, risks, and de-rouging effectiveness, all of which fostered great conversation. It was truly the most collaborative, discussion-based seminar that I attended.

I also thoroughly enjoyed the educational session on Next Generation Biomanufacturing. This gave a detailed look into up-and-coming technologies like inline dilution and inline conditioning as well as the pros and cons of these technologies as evaluated and applied by end-users. Within the same seminar, Dr. Kevin Love gave insight to the groundbreaking research that he is leading at Massachusetts Institute of Technology. His work centers on the push for personalized medicine and the potential for point-of-use manufacture of medications catered to an individual's genome.

As a young professional, some of the education sessions introduced new topics or concepts that could be overwhelming at times. Nonetheless, it was an experience that has driven me to continue seeking experience and knowledge in our complex yet rewarding industry.

KEYNOTE

I would be remiss not to mention the keynote address by Nicole Pierson at the ISPE Annual Meeting. Nicole told the story of her now-10-year-old son Gavin and his battle with a fast-growing brain tumor (a mature teratoma). Over several years, countless hospital visits, craniotomies, and chemotherapies—all attempts proved to be ineffective in stunting the growth of Gavin's teratoma. Seeking other options, the Pierson family applied for a drug made by Pfizer (palbociclib) via the company's compassionate use program. The investigational drug had never before been given to a child, but palbociclib miraculously stopped the growth of Gavin's tumor which then enabled the removal of the mass via a series of laser ablation surgeries. He is now in remission. For more information on Gavin and Nicole Pierson, see "ISPE Hosts 2016 Annual Meeting & Expo in Atlanta," *Pharmaceutical Engineering* 36, no. 6 (November/December 2016): 17–25.

This keynote address was a powerful story of survival, but it also served

as reminder of the underlying reason, the real reason that we do the work that we do. We do this to improve the lives of patients. For many of us, this means our family, friends, neighbors, and pets. We all have a responsibility at work and thus have a hand in ensuring the clean, safe, and successful manufacture of life-changing medications. Following this keynote, the attendees were commended by the Pierson family, who urged us to take pride in our line of work. Ultimately, my hope is that the torch is passed on to the next generation of industry leaders and that we don't lose sight of the importance and impact our work has on the well-being of others.

From my perspective, the ISPE Annual Meeting is worth the investment of time and energy. It's an experience that is as good as you decide to make it. To my fellow newcomers—introduce yourself, ask questions, study the educational topics, take notes, and listen. Be a sponge. You'd be surprised how much you can learn about the industry and others' roles in just a few days. ‹›

STANDING IN THE GRAY

Tiffany Coleman, Business Development Regional Manager—Midwest Region, Sequence Inc., and Secretary of the Midwest Chapter Executive Board of Directors

For eight years I've attended ISPE educational sessions across the country, from Kansas City and Saint Louis to Chicago, from Atlanta and Baltimore to San Diego and San Francisco. I've learned many things. I've been a student volunteer, a committee member, an engaged Young Professional and a Chapter board member. I've gone from working in research and development to quality assurance management, and now I consult on current good manufacturing practice and risk management around the United States. And I ask myself how is it that with all the information, technology, and experience available, the US Food and Drug Administration continues to find the same top 10 issues with compliance around the nation and the globe?

When I was a student, I took it with a grain of salt that every person teaching a class or leading an educational session was an expert—and that every person who said he or she was an expert was, in fact, an expert. I did not know it when I started, but even the experts do not agree on all the issues, and in today's global economy sometimes the experts still treat compliance as a black-and-white issue with minimum standards, even while the regulators elaborate on the importance of holistic quality and compliance rooted in culture.

I have learned that quality systems are not one size fits all. And because of that, the many different perspectives and methods provided by these experts are important tools for solving the myriad of problems that approach our industry every day.

While I revel in the thought-provoking discussion, I am always left wondering which parts to carry forward in my career. I have worked for facilities where I watched the compliance pendulum drift from both

ends of what appeared to be a very wide compliance continuum over the past eight years. I am sure others have, too.

When I look back at the regulations, I do not see significant changes at that same pace. And when I watch the regulatory enforcement trends that are presented to us, I do not see significant changes there, either. This implies that what is being asked of us and its enforcement has stayed the same. As a maturing young professional, I find myself no longer comfortable standing in the gray and looking in both directions.

I now believe that there was never any gray to begin with—that compliance was always a rainbow of colors and not black and white. Since attempting to change my own perspective, I have found that it has become easier to understand my limitations and the limitations of processes around me. It has helped me to see risk differently and broadened my root-cause analyses. I imagine that others in the industry have felt this same thing; perhaps by sharing, they will notice that compliance is not a pendulum or a continuum at all, because compliance in each moment is different and all factors must be taken into consideration. That is the essence of a risk-based quality system focused on continuous and incremental improvements. ❮❯

MAKING A LIVING, MAKING A LIFE

Wendy Haines, PhD, Project Manager for Mangan Biopharm and Vice President of the ISPE Carolina–South Atlantic Chapter

I'm a pharmaceutical professional, toxicologist, project manager, validation specialist, wife, mother, and daughter. I did not get where I am in my career without the support, wisdom, and mentoring of others. My mother, who majored in math and minored in physics in the 1960s, and my pharmacist father encouraged me and let me believe that there was no limit to what I could do or accomplish. I have had an interesting and fulfilling career, with some bumps along the way. But the bumps were where I learned and grew the most. I no longer view challenges and failures as negatives, but as opportunities for improvement and better solutions.

A pearl of wisdom from my PhD advisor Stephanie Padilla was that I would not always be the best employee, the best wife, the best mother, or the best friend. There would be cycles throughout my career and life in which one area would have to "take the back burner" while another needed my time and dedication. Another important lesson I learned is to say "No." I don't have to commit to everything I am asked to do to succeed. I strive not to make commitments unless I know I have the appropriate amount of time and dedication to devote to them.

One of my favorite inspirational sayings is this: "We make a living by what we get, but we make a life by what we give." No one advances in his or her career in isolation; one advances with guidance from peers, mentors, bosses, family, and friends. If you are passionate about mentoring youth, take time to judge a science fair competition, tutor, or volunteer alongside kids in your community. Be a professional who takes time to recognize and invest in young professionals—both men and women. In this world where faults and weaknesses are clearly noted, be an encourager and praise people for their strengths. When you have to discuss a person's need to improve in an area, be supportive and offer solutions; don't just point out faults and failures. Most people know what their weaknesses are—they just don't know how to improve.

> "NOTHING IN LIFE IS TO BE FEARED, JUST UNDERSTOOD."
>
> *—Marie Curie*

I've found that people who are excellent communicators, both in the written and spoken word, are highly successful in their career endeavors. If you are not comfortable speaking in public, join a Toast Masters group. There are also a lot of online writing courses that you can take to improve all types of written communications (emails, reports, executive summaries, etc.). If you need additional skills, seek appropriate training and/or certification. Remember to always be proactive about your career; you have a vested interest in your own success.

I'd like to end with a quote from Marie Curie: "Nothing in life is to be feared, just understood." I hope we never take for granted how important it is to be involved in getting lifesaving medication to patients and that we continue to find new and improved ways to manufacture medicines and discover cures for diseases and ailments. ❮❯

ADVICE FROM A THRIVING ENTREPRENEUR

Tiffany Coleman, Business Development Regional Manager—Midwest Region, Sequence Inc., and Secretary of the Midwest Chapter Executive Board of Directors

In 2007, Karthik Ramachandran graduated from the University of Colorado in Boulder. His graduate studies brought him to the University of Kansas, where he found himself engaged with the school's Institute for Advancing Medical Innovation. Since then Ramachandran has been added to business publication Ingram's "20 in Their Twenties" list and named a Top Young Entrepreneur to Watch by Under30CEO. Ramachandran is cofounder of Likarda, a Kansas City company revolutionizing diabetes treatment in canine and feline patients.

Ramachandran gets his passion from his dad. "You have to love what you do—and mentor," he says. "You have to love what you do, or otherwise you shouldn't do it." And so his company sponsors its employees to engage high school students and create a bridge of community involvement. He has been speaking to high school and college students for years and encourages other to do the same. He believes this might help remedy the perception that companies only need experienced older professionals to innovate; in the real world, it takes both younger and older professionals to find the passion that leads to inspiration for innovation.

WHEN RAMACHANDRAN SPEAKS TO STUDENTS, HE TRIES TO DEFINE THE PATHWAY TO EMPLOYMENT. IT STARTS BY NETWORKING LONG BEFORE YOU NEED A JOB AND CONTINUES AFTER YOU ALREADY HAVE YOUR FOOT IN THE DOOR.

When Ramachandran speaks to students, he tries to define the pathway to employment. It starts by networking long before you need a job and continues after you already have your foot in the door. Most high school students are skeptical—that day is so far away!—but occasionally one or two pick up what he's trying to convey: He's trying to give them tools they can use to engage their passion.

Talking to young professionals a little different. Once they arrive at a conference, it can be overwhelming. Ramachandran tries to encourage to them to think beyond the conference, beyond the sales people in the exhibition hall, and think instead about the executives who are meeting just around the corner. It is the connections you can make behind the scenes, he tells them, that lead to the partnerships that foster innovation. Young people can start making those connections now, and plan meetings with those executives months in advance. That is where the real magic happens.

Ramachandran did not start out thinking that he would be an entrepreneur. When he was in high school, he wanted to become a medical doctor; never did he think that today he would be a biotech engineer. Circumstance that led him to become an engineer, even as his educational work continued to focus on becoming a medical doctor. Numerous attempts at the Medical College Admission Test and pursuing research with Likarda cofounder Lisa Stehno-Bittel changed his path.

He had always been an analytical and mathematical person, and he built on those strengths while doing research in graduate school. And then there was the transition from graduate student to entrepreneur. One of the things he tells high school and graduate students preparing for the path they choose: "Learn to speak different languages: Talk business and science and engineering." Entrepreneurs should be able to talk to a variety of customers, he explains. As a young professional or entrepreneur or engineer, you need to be able to find the value and explain that value in the each "language." ‹›

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ISPE/FDA/PQRI Quality Manufacturing Conference
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ISPE Process Validation/Process Validation Statistics Conferences
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THE HISTORY OF QUALITY AND THE EVOLUTION OF THE MODERN LEADER

Mary Foss and Andrew Deceuster

The Food and Drug Administration (FDA) report "Pharmaceutical Quality for the 21st Century: A Risk-Based Approach"[14] was an introduction to quality by design (QbD), the concept that quality should be built into a product. According to the FDA report "Pharmaceutical cGMPs for the 21st Century—A Risk-Based Approach," QbD involves a thorough understanding of the product and the process by which it is developed and manufactured, as well as a knowledge of the risks involved in its manufacture and how best to mitigate them.[1]

Three other agency Guidance for Industry titles:

- "PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance"
- "Q10 Pharmaceutical Quality System"
- "Process Validation: General Principles and Practices"

further describe this new thinking and introduce a regulatory framework intended to encourage development and innovation within the pharmaceutical industry.[2–4]

While intended for the twenty-first century, each of these documents reflect basic principles first proposed after World War II by Dr. Joseph Juran and Dr. W. Edwards Deming. As agency guidance is increasingly aligned with the principles of these founding fathers of modern-day quality, it is worth exploring Juran's and Deming's views on leadership and learning how they evolved from engineers to philosophers in management.

After World War II, Juran and Deming both traveled to Japan to help rebuild the country's economy. Their efforts helped revolutionize the quality system of Japan and started a quality revolution that the rest of the world could not help but notice. Evidence of Juran and Deming's work is present today in FDA guidance documents and regulations, as well as in other industries that have quality system regulations.

Leaders in the pharmaceutical industry must recognize that as quality systems have evolved, so too have the expectations and responsibilities they must fulfill. Quality cannot be an afterthought with any product, nor can it be the responsibility of any one department. Quality must be instilled within an organization and designed into processes and systems. Most importantly, perhaps, the culture of quality must begin with the leaders in the organization. These concepts are also detailed within the "Q10 Pharmaceutical Quality System" Guidance for Industry.[3]

JURAN

In 1925 Juran joined the Inspection Statistical Department at Western Electric, where he was in charge of integrating statistical sampling and control charting techniques into the system. At this time, quality management systems were focused solely on the end product. But Juran saw things differently. He recognized that this approach was missing something—the human element. Some of the biggest hurdles organizations faced, he realized, were human relations problems and employee resistance to change.[5] Rather than confining quality to a specific department, he said, "It is most important that top management be quality-minded. In the absence of sincere manifestation of interest at the top, little will happen below."[6]

Juran later moved on to management consulting, and by 1951 had written the first edition of his landmark Quality Control Handbook.[7] This publication attracted the attention of the Japanese and earned him an invitation to work with 10 manufacturing companies, including Takeda Pharmaceutical Company, the largest pharmaceutical company in Japan and Asia and one of the top 15 in the world.[8–9]

DEMING

Dr. W. Edwards Deming, who had a very similar philosophy to Juran's, also traveled to postwar Japan. He saw that the root cause of many quality issues came from top management. At that time quality issues were frequently attributed to the worker—and often are today, as well. Deming saw through this and identified organizational culture as a root cause.[10] Quality was not something that could be attained without first designing an entire organization and related processes around it; these concepts are reflected today within the FDA documents mentioned above.[2–4]

Deming began his career working for the US Department of the Census and the Bureau of Labor Statistics. Here he applied the principles of Walter Shewhart by integrating statistical process control to an operation. Shewhart identified problems in manufacturing as the result of either common or special variation. Common variation, which is inherently present in a process, represents the "noise" in a system. Special variation is assignable variation that results in a significant process change.[10]

Deming took this one step further and developed a philosophy of management based largely on Shewart's principles. Management, he said, can lead by understanding what he called his "System of Profound Knowledge":[11]

Appreciation for a system: *Understand the overall processes involving suppliers, producers, and customers (or recipients) of goods and services.*

In the pharmaceutical industry, this would translate to: What are the mechanisms of degradation, drug release, and absorption? How do product components affect quality? What are the critical material and process attributes relating to product quality?[2] Product and process

knowledge should be managed from development through the commercial life of the product up to and including product discontinuation.[3]

Knowledge of variation: *Know the range and causes of variation in quality, and use of statistical sampling in measurements.*

What sources of variability within the process are critical? How does the process manage variability?[2] What is the effect of variation on the process and ultimately on product attributes?[4]

Theory of knowledge: *These concepts explain knowledge and the limits of what can be known.*

In FDA guidance, this is a challenge to back up opinions with data to truly understand what is going on, learn, and thereby continually improve: This is reflected in the FDA PAT guidance, which explains that "Continuous learning over the life cycle of a product is important,"[2] and the Q10 guidance, which outlines a systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes, and components.[3]

Knowledge of psychology: *These are the concepts of human nature.*

In every industry, understanding psychology can allow a leader to create a culture of trust, relationship, interdependence, and pride in workmanship. The FDA Q10 guidance notes that "Leadership is essential to establish and maintain a company-wide commitment to quality and for the performance of the pharmaceutical quality system."[3]

> "IT IS MOST IMPORTANT THAT TOP MANAGEMENT BE QUALITY-MINDED. IN THE ABSENCE OF SINCERE MANIFESTATION OF INTEREST AT THE TOP, LITTLE WILL HAPPEN BELOW."
>
> —Joseph Juran

In addition to his System of Profound Knowledge, Deming developed 14 points for the transformation of management.[12] These points are equally useful for developing an organizational culture of quality and compliance with regulatory expectations:

1. Create constancy of purpose toward improvement of product and service, with the aim to become competitive, to stay in business and to provide jobs.
2. Adopt the new philosophy. We are in a new economic age. Western management must awaken to the challenge, must learn their responsibilities, and take on leadership for change.
3. Cease dependence on inspection to achieve quality. Eliminate the need for massive inspection by building quality into the product in the first place. ›

4. End the practice of awarding business on the basis of a price tag. Instead, minimize total cost. Move toward a single supplier for any one item, on a long-term relationship of loyalty and trust.
5. Improve constantly and forever the system of production and service, to improve quality and productivity, and thus constantly decrease costs.
6. Institute training on the job.
7. Institute leadership. The aim of supervision should be to help people and machines and gadgets do a better job. Supervision of management is in need of overhaul, as well as supervision of production workers.
8. Drive out fear, so that everyone may work effectively for the company.
9. Break down barriers between departments. People in research, design, sales, and production must work as a team, in order to foresee problems of production and usage that may be encountered with the product or service.
10. Eliminate slogans, exhortations, and targets for the work force asking for zero defects and new levels of productivity. Such exhortations only create adversarial relationships, as the bulk of the causes of low quality and low productivity belong to the system and thus lie beyond the power of the work force.
    a. Eliminate work standards (quotas) on the factory floor. Substitute with leadership.
    b. Eliminate management by objective. Eliminate management by numbers and numerical goals. Instead substitute with leadership.
11. Remove barriers that rob the hourly worker of his right to pride of workmanship. The responsibility of supervisors must be changed from sheer numbers to quality.
12. Remove barriers that rob people in management and in engineering of their right to pride of workmanship. This means abolishment of the annual or merit rating and of management by objectives.
13. Institute a vigorous program of education and self-improvement.
14. Put everybody in the company to work to accomplish the transformation. The transformation is everybody's job.

QUALITY

As Deming stated, "There is no substitute for knowledge."[13] Without knowledge we are powerless and are at the mercy of variation within our processes. With knowledge we can achieve a predictable process that produces a product that meets all quality requirements. This is a large step away from quality control (or quality by inspection) and is consistent with current thinking that "Quality cannot be tested into products: It should be built-in or should be by design."[2]

While QbD provides better design predictions, there is also recognition that industrial scale-up and commercial manufacturing experience provides knowledge about the process and the raw materials used. FDA process validation guidance notes the need for companies to continue benefiting from knowledge gained, and continually improve throughout the process life cycle by making adaptations to correct root causes of manufacturing problems;4 these are also core principles of Deming's philosophy.

Deming said, "To manage one must lead. To lead, one must understand the work that he and his people are responsible for."[12] In its time this statement was not only radical but also largely ignored. What does a statistician really know about the management of people, anyway? Deming would go on to explain that 94% of troubles and possibilities for improvement belong to the system or are the responsibility of management while the remaining 6% are attributed to special causes.[12] In other words, today's leader must begin by taking responsibility for nearly all the problems facing his or her organization.

FOUNDATIONS

To truly understand Deming and Juran, one must first appreciate that their ideas for a quality system begin with a basic philosophy about why people go to work and what motivates them. Deming's 14 points reflect his idea that while workers want to do a good job and take pride in their work, leadership often robs them of this.

To take responsibility for problems in an organization a leader must begin by including every worker in the task as a shareholder. This requires effective communication and the belief that each worker brings enormous potential and the ability to improve the quality of not only the product but the organization. According to this philosophy, workers are not the source of quality problems or success. They are merely part of an imperfect system responding to variation.

Deming understood that to achieve remarkable results, an attitude of continuous improvement had to be present in every single worker. He believed that instead of holding workers responsible for production and quality problems that are actually the result of a poorly understood process or one that is subject to too much variation, workers should be trained and given opportunities to develop professionally.

Deming understood what many did not: Work is more than just collecting a paycheck. Leaders must resist the urge to find a scapegoat for problems that exist within their organization. Workers may often be the easiest assignable cause, but the real root of any quality problem is with the system in which it is produced.

Deming's 14 points were first published in the 1980s, but adopting and truly understanding them in relation to pharmaceutical manufacturing has always been a little opaque. For many leaders, taking responsibility for an organization's problems can be overwhelming. This responsibility can be shared, however, by creating a culture in which pride and ownership are present in every worker, and each individual is accountable.

The following is a modern-day take on Deming's philosophy and the leader's critical role in perpetuating it:

Know your employees. There is no shortcut for this step. To truly understand what motivates your employees to come to work every day, you must invest the time to learn what makes them tick and what brings them satisfaction in the workplace. By aligning employees with the tasks that give them the most satisfaction and helping them find ways to increase their satisfaction in other areas leaders can increase the happiness of both individual employees and the entire workforce. Today's leader must want to be a positive force within the organization as well contribute to the end product.

Be trustworthy. Say what you mean and mean what you say. Be clear and specific in your expectations and allow for open communication across your organization. A true leader must be an excellent listener.

Create a culture that fosters individual growth. If an organization is to improve continuously, so must its workforce. Investing in an employee shows that the organization values what the employee can contribute.

Allow employees to rise to challenges without fear and competition. Much of Deming's philosophy involves eliminating fear. At the time of his first publications this was a major stumbling block for leaders. By recognizing that each employee is human and that it is human nature to fail, we can appreciate that valuable lessons can be achieved through failure.

CONCLUSION

By creating a culture that fosters the philosophies of Juran and Deming, today's leader can create an organization that is more capable and driven than any seen before. Production capabilities and quality improvements will be the inevitable side effects and likely, Deming and Juran will look down from above and grin with approval. ‹›

KNOW YOUR EMPLOYEES. BE TRUSTWORTHY.

CREATE A CULTURE THAT FOSTERS INDIVIDUAL GROWTH.

ALLOW EMPLOYEES TO RISE TO CHALLENGES WITHOUT FEAR AND COMPETITION.

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PROCESS AND PRODUCT CONTACT SURFACES IN BIOPROCESSING

Albert Dyrness and Carl Johnson

As part of their quality risk management (QRM) programs, many biopharmaceutical manufacturers have made deliberate efforts to classify systems, equipment, and components by their potential to affect product quality. In assessing these risks, it is intuitive to focus on component surfaces that come into direct contact with process fluid streams and that are integral to the biopharmaceutical manufacturing process. A great deal of effort goes into the specification and verification of these surfaces, particularly those that come into direct contact with active pharmaceutical ingredients (API) or API intermediates. For example:

- Construction materials are specified and documented for traceability to be nonleachable, nonadsorptive, and nonadditive.
- Surface finish and treatment are specified to facilitate cleaning (e.g., alloys are electropolished to a mirror finish and/or chemically passivated to limit rouge).
- Surfaces are cleaned and rinsed to a point at which rinse-water quality attributes meet those established for water for injection (WFI).
- Surfaces are often sterilized to achieve a sterility assurance level (SAL) of 10^{-6} (six-log reduction).

The resources required to design, fabricate, install, verify, and maintain these surfaces are substantial, but the commitment has a commensurate benefit to product quality. It is therefore imperative to have standard definitions by which these select surfaces can be classified in a QRM program.

This article presents definitions for process contact surfaces, product contact surfaces, nonprocess contact surfaces, and product containing surfaces. The American Society of Mechanical Engineers (ASME) Bioprocess Equipment (BPE) standard, beginning with the 2014 edition, provides the most comprehensive and useful definitions for process contact surfaces and product contact surfaces and the implications of distinguishing between them.

There are a number of ways to determine appropriate definitions, but many fall short. This article presents three approaches to demonstrate the clarity and usefulness of the ASME BPE's approach in comparison to other approaches. Additional definitions for nonprocess contact surfaces and product-containing surfaces are proposed for completeness, as well. This article also discusses the importance and implications of formulating such distinct definitions.

DEFINITION PARADIGMS

There are several approaches to defining process and product contact surfaces. Three methods are examined critically here.

Approach 1: Literal definitions

One way to define the difference between process contact surfaces and product contact surfaces is by a literal definition.

Process contact surfaces: *Surfaces of components that may be exposed to process fluids/solids and have the potential to transfer material into the product or onto product contact surfaces.*

Product contact surfaces: *As a subset of process contact surfaces that may be exposed to product or product constituents under design operating conditions, and from which material may drain, drop, drip, or be drawn into the product.*

The phrase "may be exposed" is intended to include surfaces that are not normally in direct contact with the process fluid/solid, but are exposed to the process. For example, portions of a clean-in-place (CIP) rinse tank headspace may not come in direct contact with process fluids, but they are exposed to them. If a contamination were to develop on these surfaces, there is nothing to prevent that contamination from being transferred to product contact surfaces as part of the cleaning process.

The phrase "under design operating conditions" is intended to exclude the failure of components or the use of components for conditions outside of their design basis. The term "product constituents" is intended to extend the definition to API intermediates. The terms "drain, drop, drip, or be drawn" are intended to extend the definition to surfaces that may inadvertently come into direct contact with the product. They are inspired by the definitions in 3-A Sanitary Standards, Inc., (3A)[1] and European Hygienic Engineering & Design Group*—(EHEDG).[2]

3A definition of product contact surfaces: *"All surfaces which are exposed to the product and surfaces from which splashed product, liquids, or material may drain, drop, diffuse {where applicable}, or be drawn into the product or onto product contact surfaces."*

** Both EHEDG and 3A deal with the same or similar equipment and processes as that used in biopharmaceutical manufacturing and are credible sources for seeking a definition for product/process contact relating to hygienic design.*

EHEDG definition of product contact surfaces: *"All surfaces of the machine that intentionally or unintentionally come in contact with the product, or from which product or condensate may drain, drop, or be drawn into the product or container, including surfaces (e.g., unsterilized packs) that may indirectly cross-contaminate product contact surfaces or containers."*

The literal definition approach falls short because an example can always be found that eludes the intent. Drain systems, for example, are exposed to product, but they are generally not considered critical to product quality. In addition, each biopharmaceutical manufacturer is able to define "product" differently, adding further complications.

Approach 2: Surface exposure and conditions

A second approach is to define process and product contact surfaces both by exposure and by specified treatment. A fundamental reason for trying to make the distinction between product and process contact surfaces is to establish rationales for how they should be treated (i.e., cleaned, sanitized, sterilized, and/or isolated). Definitions on the basis of treatment would lead to the analyses and associated definitions shown in Table A.

Table A

Conditions	Process Contact Surface	Product Contact Surface
Exposed to product	No	Yes
Exposed to process fluids/solids	Yes	Yes
Cleaning required for bioburden reduction	No	Yes
Cleaning required to reduce the potential for cross-contamination	No	Yes
Sanitization or sterilization required	Yes, if required by the process	Yes, if required by the process

Process contact surfaces: *Surfaces of components that by design are not directly exposed to product and do not require cleaning of product residue (e.g., clean steam, compendial water, once-through CIP), but may require sanitization or sterilization for bioburden control.*

Product contact surfaces: *Surfaces that are exposed to final product or product intermediates, and require cleaning to reduce bioburden and the potential for cross-contamination (e.g., bioreactor vessels and nondedicated transfer lines), and may require sanitization or sterilization for bioburden control.*

These definitions also fall short in that some bioprocessing components are excluded. Single-use components, for example, could have product contact surfaces, may be required to be sterile, and yet may not be required to be cleaned or sterilized after product exposure.

Approach 3: Establishing requirements

A more comprehensive approach would be to establish up front all the requirements with which the definitions would be required to comply. This would ensure that the resulting definitions apply to the surfaces of the intended components/systems.

Process contact surface requirements must:

1. Be applicable to overall use for hygienic service
2. Be applicable to single-use technology
3. Include solids handling surfaces
4. Include the potential for contact with process materials (indirect contact or exposure)
5. Include contact with raw materials, in-process materials, APIs, clean utilities, and CIP supply
6. Exclude drain systems
7. Exclude abnormal upset events outside the scope of the design

Product contact surface requirements must:

1. Be a subset of process contact
2. Be applicable to single-use technology
3. Allow the affected organization to define "product"
4. Include the potential for contact with "product" (indirect contact or exposure)
5. Include process surfaces that contact "product" and/or have the potential for crossover contamination
6. Exclude drain systems
7. Exclude abnormal, upset events outside the scope of the design

The resulting definitions, as first adopted by the ASME BPE Standard in 2014:[3]

Process contact surface: *Surfaces that, under design operating conditions, are in contact with or have the potential to contact raw materials, in-process materials, APIs, clean utilities (e.g., WFI, CIP, pure steam, process gases), or components (e.g., stoppers), and where there is a potential for the surface to affect product safety, quality, identity, strength, or purity.*

Product contact surface: *Process contact surfaces that are in contact with or have the potential to contact product, where product is defined by the owner/user. Examples of product contact surfaces may include the interior surfaces of bioreactors, transfer tubing, chromatography columns, vessels, and recirculating segments of CIP systems.*

The ASME BPE standard is widely accepted for best practices in hygienic design in the biopharmaceutical industry. Both definitions above can be found in Part GR: "General Requirements" of the standard, and are used throughout to set design requirements for components used in bioprocessing.

As product contact surfaces are a subset of process contact surfaces, requirements for process contact surfaces are applicable to product contact surfaces. Requirements for product contact surfaces, however, are not necessarily applicable to process contact surfaces. The applicability of these definitions with respect to systems that are common to biopharmaceutical processing is examined in Table B.

The ASME BPE Standard does not define nonprocess contact surfaces, but does imply that if the surfaces do not comply with the definition of process contact surface, it is a nonprocess contact surface. For completeness the following definition is proposed:

Nonprocess contact surface: *Surfaces that, under design operating conditions, do not have the potential to affect product safety, quality, identity, strength, or purity.*

Table B

Component Surface	Process Contact	Product Contact
Bioreactor	Yes	Yes
Product transfer lines	Yes	Yes
Media vessel	Yes	No, unless media is defined as product
Chromatography skid	Yes	Yes, but only those portions, which have potential exposure to product as, defined by the organization.
Buffer prep vessel	Yes	No, unless buffer is defined as a product by the organization
Compendial water generation and distribution	Yes	No, unless compendia water is defined as a product by the organization
Process gases pre-final filter	Yes	No
Process gasses post-final filter	Yes	Yes, if serving product containing system
Once-through CIP	Yes	No
Recirculating segments of CIP*	Yes	Yes
Stopper processor	Yes	No
Clean steam generation and distribution	Yes	No
Drain system	No	No
Hydronic fluid system	No	No
Clean steam condensate system	No	No
Plant steam system	No	No

* There remains some debate on whether recirculating segments of a CIP system should be classified as product contact as no "product" contacts the recirculating segments. However, the potential for cross contamination of product fall under the phrase "... the potential to contact product ..." in the product contact definition, and therefore appears in the 2014 ASME-BPE definition.

While nonprocess contact surfaces do not by definition have the potential to affect product quality, there are circumstances in which design requirements for product or process contact surfaces would apply. When there is a concern for worker safety due to exposure to APIs or potent compounds, for example, hygienic design elements may be required to render containment systems clean and free of chemical and biological hazards. For this reason, a specific definition is useful for product containment surfaces.

Product containment surface: *Nonprocess contact surfaces that are in contact with, or have the potential to contact potentially harmful materials (e.g., APIs, potent compounds), where there is a potential for human contact with the surface (e.g., operators, maintenance workers, or the public).*

The Venn diagram presented in Figure 1 shows examples of systems with process contact surfaces, product contact surfaces, nonprocess contact surfaces, and product containment surfaces.

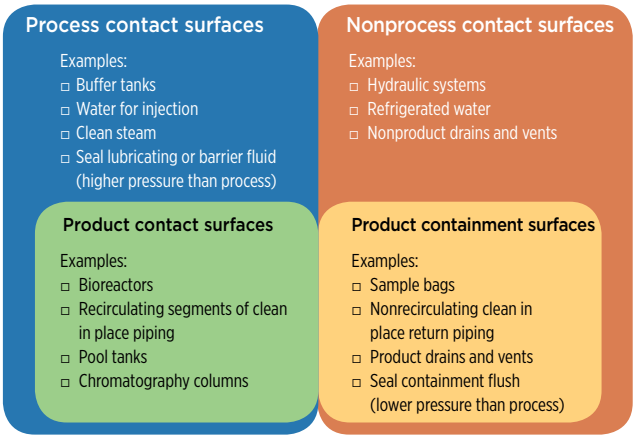
DEFINITION IMPLICATIONS

The benefits of distinguishing among components with process, product, nonprocess, and product containment contact surfaces can be realized in a number of applications within a QRM program or other biopharmaceutical manufacturing business processes.

Design specifications

An important implication is the design and design verification of components used in hygienic service. Construction materials, surface finish, and surface treatment of components with process contact surfaces may be specified to a grade commensurate with the intended service, process requirements, and risk to product quality. WFI distribution piping, for example, which has process contact surfaces, may be specified to be mechanically polished and passivated. In comparison, the surface finish of a bioreactor, which has product contact surfaces, may be specified to have an electropolished surface finish.

Figure 1



Risk-based commissioning and qualification

Distinguishing among product, process, and nonprocess contact components does not simply save the cost of over-specification. It can also reduce the cost of installation and operational verification substantially. In a risk-based qualification program, the components can be categorized as product contacting, process contacting, and nonprocess contacting.

The level of verification documentation can vary as commensurate with the level of risk to product quality. For nonprocess contacting components, the verification might be limited to catalog information such as manufacturer and model number, while process contacting components would require verification of materials of construction, material joining, surface finish, etc. On the basis of a risk assessment, operational verification testing might also be justified in treating process contacting components as those that require commission testing with engineering oversight, and limit testing with quality oversight to systems with product contact surfaces.

Cleaning requirements and cleaning validation

Cleaning requirement specifications could be based on component exposure to product, or only to process fluids. If an organization does not consider chromatography buffers to be "product," for example, then buffer preparation components may be designated as process contacting components. Such a designation would justify the use of compendial water for cleaning and avoid the use of chemicals required for cleaning product contact surfaces, where the focus is on product carry over. For equipment that contains both product and process contact surfaces, maximum allowable carry over limits may be based only on the product contact surfaces, effectively increasing the acceptable bioburden in the cleaning acceptance criteria for that unit operation.

The product contact and process contact definitions are focused on product quality risks, identified as safety, quality, identity, strength, or purity. Waste or vent systems, according to the ASME BPE definitions, would be

classified as nonprocess, as they would not present a risk to product quality. When dealing with potent compounds or any materials at or above Biosafety Level 2, however, the concern for safety of operators and maintenance staff could result in applying cleaning requirements commensurate with those associated with product contact surfaces, replacing "product safety, quality, identity, strength, or purity" with "worker safety."

Steam sanitization vs. steam sterilization

The distinction between process and product contact can used as a basis to determine which system surfaces should be steam sanitized and which should be steam sterilized. Steam sanitization of process contact surfaces might be specified for the reduction of bioburden for hygienic service, even though the component surfaces are not exposed directly to product. Steam sanitization verification or validation could be limited to monitoring of system temperature elements. Steaming of product contact surfaces, however, might require validating that steam sterilization achieves a specified SAL based on the risk to product quality.

Validating steam sterilization of product contact surfaces requires a significant amount of test data to demonstrate sterility. Multiple test runs would be required, as would in situ temperature mapping, biological indicator testing, and steam saturation verification. It might also be necessary to perform significant cycle development work before testing for sterility, as well as post-sterilization testing, such as sterile hold testing.

Supplier auditing and discrepancy evaluation

As part of a risk-based vendor audit program, making a distinction between components with product contact surfaces and components with only process contact surfaces could help limit the number of suppliers considered "critical" for auditing. Further, if a qualified supplier discovers and reports that a component provided to a customer has a quality attribute outside the reported specification, the risk to product quality can be assessed more readily if the component is known to be a part of a system with product contact surfaces, process contact surfaces, or nonprocess contact surfaces.

Technology transfer

When product manufacturing is outsourced to a contract manufacturer or expanded to another site, a risk-based methodology may be employed to limit physical differences in manufacturing equipment, based on the potential to affect product quality. System components with product contact surfaces are more critical than those with only process contact surfaces. Components with product contact surfaces might be required to be identical to the original site to limit the risk of noncomparability. For components with only process contact surfaces, the degree of similitude could be limited to demonstrating an equivalent function. Nonprocess components could have complete design latitude.

CONCLUSION

All of these business processes benefit from distinguishing process contacting, product contacting, nonprocess contacting, or product containing components. Depending how an organization defines "product," the fidelity could be refined even further. Product contact could be divided into API product contacting and non-API product contacting. Under this scenario, a bioreactor could be API product contacting, but a media vessel could be non-API product contacting.

Whatever the breakdown, there are clear benefits to crafting definitions for process contact surfaces and product contact surfaces to distinguish between critical and noncritical components. Further, embracing this distinction within an organization's QRM program demonstrates to regulatory authorities that the manufacturing processes are well understood relative to their impact to product quality.

Using these definitions to understand the risk to product quality will help organizations decide which components should be fabricated under the most stringent design requirements, which equipment should be qualified, which surfaces require cleaning validation, which surfaces require sterilization (and not just sanitization), which spare parts from a supplier are critical, and which design aspects are critical to technology transfer. ‹›

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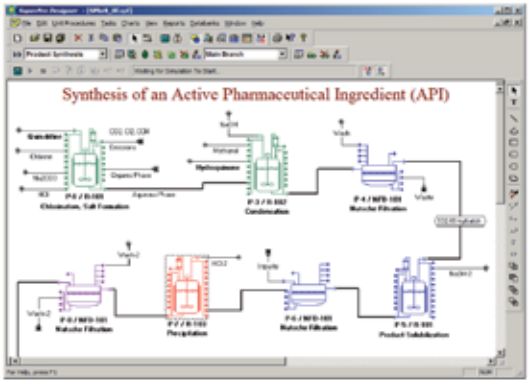

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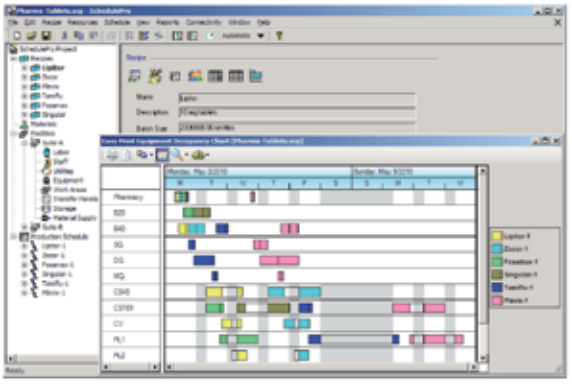

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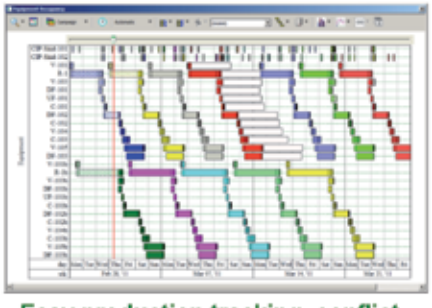

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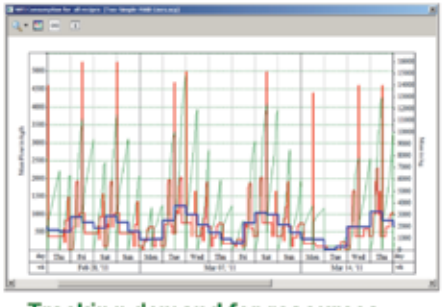

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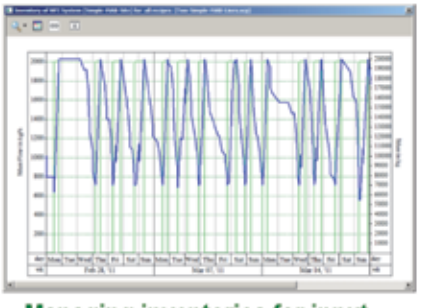

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CPV SIGNAL RESPONSES IN THE BIOPHARMACEUTICAL INDUSTRY

Mark DiMartino, Abdelqader Zamamiri, Kevin Pipkins, Jim Heimbach, Eric Hamann, Syama Adhibhatta, Richard Falcon, Kevin Legg, and Robin Payne

This paper was written by members of the BioPhorum Operations Group CPV and Informatics team and widely reviewed across the BPOG collaboration. As such, it represents the current consensus view of process verification subject matter experts in the biopharmaceutical industry, but does not represent the procedural details of any individual company. It is designed to be informative for industry members, regulators, and other stakeholders. It does not define statistical methods in detail, as these definitions are readily available elsewhere.

This paper describes how signals can be developed and evaluated in support of CPV in the biopharmaceutical industry. Implementation of CPV, in addition to meeting regulatory expectations, can also provide a basis for continuous improvement of production processes and hence greater consistency of product quality and assurance of supply.

CPV involves gathering data related to CQAs and CPPs, as well as analyses that reveal any statistical signals that become evident over time. It is designed to detect variation within specifications. Thus, CPV is about maintaining control within specification and so does not normally lead to a formal investigation. This paper provides several examples of signal response and escalation within the quality system where necessary as a model of a risk-based approach to CPV.

In 2011, the FDA introduced guidance on the process validation life cycle, including continued process verification (CPV).[1] While implementation is becoming a regulatory expectation, CPV can provide benefits beyond compliance by identifying opportunities to improve production processes and ultimately, the reliability of drug quality and supply.

CPV is the third stage of the process validation life cycle. It is a continued assessment of the parameters and attributes within the control strategy identified in Stage 1 (process design) and refined at the end of Stage 2 (process qualification). Its principle objective is to detect variability in the process and associated quality attributes that may not have been evident when the process was characterized and introduced. CPV provides continued verification that the control strategy remains effective in maintaining product quality.

Additional parameters and/or attributes not considered critical to quality or otherwise not specified in the control strategy may also be included in the CPV program (or an associated process monitoring program) to enhance process learning and support investigations to identify the root cause and source of unexpected variability.

CPV can also identify opportunities to improve process performance and/or optimize process control. Using statistical methods, data from historical manufacturing or characterization studies are evaluated during CPV implementation to define signal criteria, set limits, and implement appropriate response procedures for ongoing operations. Signals are thus selected to identify process behaviors of interest and indicate when statistically meaningful variation may be affecting the process.

A critical aspect of CPV is establishing a procedure that provides a consistent response to these signals as they become evident. Ideally, perhaps, signals would be detected as soon as they occur, but this is not practical in most cases. Practically, the signal should be detected and a response mounted before the indicated trend leads to a true process deviation or out-of-specification (OOS) event. Good practice is to respond as soon as possible based on risk assessment.

The purpose of this document is to provide best practice guidance for responses to CPV signals that occur within the process's acceptable control space.

There are five main steps in establishing CPV signals and associated response procedures.

1. Define parameters and signal criteria
2. Establish monitoring and evaluation frequency
3. Establish signal evaluation criteria and actions
4. Escalate actions if necessary
5. Document signals and response

Although this paper is focused primarily on responses, some discussion of signal selection is required since the magnitude of the response should be commensurate with the severity of the signal.

SIGNAL SELECTION

Define parameters and criteria

In general, CPV signals assess predicted performance based on previous process experience. The development and effectiveness of these signals depend on statistical techniques sensitive to the size and inherent variability of the existing data set. While not ideal, some signals will be due to existing and acceptable variation that was not fully captured and characterized in the initial data set. This is a common occurrence in biopharma, given the complexity of manufacturing processes and raw materials. Although these are sometimes referred to as "nuisance signals" or "false positives," such signals may prove to be useful learning opportunities over time and used to augment the data set.

Definitions

Capability indicator	The ability of a process to deliver a product within specification limits. The concept of process capability can also be defined in statistical terms via the process performance index, Ppk, or the process capability index, Cpk
Continued process verification (CPV)	A formal process that enables the detection of variation in the manufacturing press that might have an impact on the product. It provides opportunities to proactively control variation and assure that during routine production the process remains in a state of control.[1]
Control strategy	A planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control
CPV limit	Limit derived statistically, or justified scientifically, for use in process trending. Limit is meant to predict future process performance based on past performance experience and is not necessarily linked to process or patient requirements. In a capable process, CPV trend limits will be tighter than other limits, ranges, or specifications that are required by the molecule's control strategy.
Critical process parameter (CPP)	A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.[5]
Critical quality attribute (CQA)	A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.
Escalation	To respond to a signal by following the deviation/ nonconformance system to investigate for potential product or process impact.
Evaluation	An analysis of data and related circumstances around a statistical signal, with the intent of identifying the cause of the signal.
Noncritical parameter (NCP)	A noncritical parameter has no impact on quality at the process step in question. *Note: It may have an impact on the performance of the next process step and so may be monitored for process control purposes.*
Quality management system	The business processes and procedures used by a company to implement quality management. This includes, but is not limited to, investigations from process and laboratory deviations, commitments, and change control.
Signal	An indication of unexpected process variation, triggered by a violation of a predetermined statistical rule that is used to identify special cause variability within a process. Process behaviors with assigned signals include (but are not limited to): 1. Outlier (such as Nelson rule 1) 2. Shift (such as Nelson rule 2) 3. Drift (Such as Nelson rule 3)
Triage	An initial read on the signal by SMEs to determine if the signal should fall in the default category, and be either escalated or de-escalated.

Identify variation

The focus of CPV signals should always be to identify variation within specified limits defined in the control strategy. This applies when critical quality attributes (CQAs) are maintained within specifications and critical process parameters (CPPs) are maintained within proven acceptable ranges. Signals that are outside the control strategy (i.e., OOS) are investigated primarily within the quality management system (QMS).

This paper is concerned primarily with evaluation of responses to CPV signals within the design space. There would be benefit, however, in capturing and integrating lessons learned from both formal investigations and CPV-related evaluations for improved long-term process control.

Establish monitoring and evaluation frequency

As stated previously, the ideal scenario for CPV monitoring is to identify signals in real time during manufacturing and react accordingly. This scenario is not always practical, however, since that many signals require multiple data points (i.e., signals for drift or shift) and specific data-capture and analysis technologies are required to perform the calculation. Given that these signals are by definition within the specified limits defined in the control strategy, the risk inherent in disassociating the identification and reaction to signals from batch release is low, allowing for a more periodic review.

The review frequency should be established with the monitoring plan and should consider:

- Relative risk of a parameter or attribute deviating from its acceptable range
- Manufacturing frequency
- Level of historical process knowledge
- Manufacturing plant's technological capability to collect and analyze the data

Establish evaluation criteria and response

A CPV signal is designed to identify potential new variation or unexpected patterns in the data. Because these conditions are within the control strategy, signals should not automatically be considered formal good manufacturing practice (GMP) deviations. There may be cases, however, in which a signal is significant enough to indicate a product quality or validation effect that requires tracking and resolving within the QMS. When this happens, a cross-functional data review and escalation procedure should be in place to ensure the signal is addressed appropriately.

This paper provides an example of a procedure that can be used or adapted for responses to CPV signals using risk-based decision-making to determine when a signal should be escalated. The procedure has four key elements that should ideally be in place as prerequisites (Table A).

Table A: Prerequisites for an effective response to signals procedure

Element	Description
CPV plan with signal criteria identified	Plan outlines the parameters analyzed for CPV and rules for identifying signals. This provides guidance on what process behaviors merit further analysis.
Default responses to signals and parameters	Default responses are predetermined actions for each parameter/signal combination. These are based on the criticality of the parameter and the nature of the signal to ensure the response is commensurate with the level of risk being signaled.
Data signal review and escalation process	Signals and their default responses should be reviewed periodically by a cross-functional team of SMEs to evaluate the appropriateness of the default response and determine if alteration (escalation or de-escalation) is needed.
Documentation system	Signal response and rationale must be documented and approved.

Table B: Signal-response action terms

Action	Description
No action	No response required. This response is associated with signals that are not considered significant enough to warrant further root cause analysis and require no corrective or preventive action (CAPA). Document the decision and rationale per approved procedures.
Evaluation	This response is associated with signals of unexpected variation from historical processing experience that are considered significant enough to warrant a technical evaluation to understand the cause of variance; it is not significant enough, however, to warrant a product quality impact assessment. A subsequent CAPA may be required. Evaluations can span a wide spectrum of complexity, from a simple review of a batch record or starting raw materials to a complex, collaborative, cross-functional evaluation. The size of the evaluation is based on the technical input of process SMEs.
Escalation to QMS	This response is associated with signals of unexpected variation from historical processing experience that are considered significant enough to warrant a technical evaluation to assess potential product/validation impact and establish a root cause. A subsequent CAPA may be required. The signal response is tracked within the QMS and requires a product/validation impact analysis, root cause identification, and any associated CAPAs within the timelines mandated by the relevant quality procedures.

CPV PLAN

At the completion of Stage 2—process performance qualification (PPQ) [2]—a CPV plan shall be established with the following components, including a rationale for each:

- □ Parameters and attributes to be monitored
- □ CPV limits for each parameter and attribute combination
- □ Frequency of trend evaluations
- □ Statistical signals to be evaluated
- □ Default responses for each parameter-signal combination

The rationale can be risk based and should include an explanation of which process behaviors may merit further analysis. Ideally, each default response should be determined from a risk-based strategy that considers the criticality of the parameters, the nature of the signals, and the performance/capability of the process parameters.

The CPV plan should reference company-specific procedures that specify reporting formats, designate escalation procedures, identify roles and responsibilities for CPV trending, and define terms.[3] For illustration, this paper uses the signal-response action terms shown in Table B.

Default responses to signals

Table C provides an example of a risk-based strategy that could be used to determine minimum default responses for each parameter and signal in the CPV plan. The example uses classic signals, which indicate departures from established behavior for normally distributed, independent data. Actual strategies may vary by CPV plan. The default response assigned for an individual parameter-signal combination may vary from the proposed default if a proper justification is provided in the plan.

Table D illustrates how default responses and modifications can be presented in a CPV plan.

Escalation process

During CPV plan execution, data is collected and analyzed at a predefined frequency. Once a signal is identified, a cross-functional team (CFT) of subject matter experts (SMEs) with knowledge of the process, manufacturing operations, quality control, and/or quality assurance reviews the signal to determine the appropriate response. Others, such as quality control laboratories, regulatory sciences, or continuous improvement and process development may also participate.

The CFT reviews the signal against the default response, and determines if escalation to a higher level or de-escalation to a lower level of response is appropriate. Factors that may be considered when altering the default response include (but are not limited to) the CFT possible review outcomes shown in Table E.

When product is manufactured at more than one site it is advisable to have a system to share CPV data and or observations. In all cases alteration of any default response to signals requires justification and proper documentation.

Document signals and responses

Once the CFT triage is complete and outcome aligned, the team will perform the recommended actions or ensure they are done. If the action is to escalate, the appropriate quality system document will be initiated and procedures that govern it will be followed. If the action is evaluation, additional analysis or experimentation will be required to determine the cause of the signal.

Results of any evaluations should be documented following GMP principles. If no action is taken, that decision and rationale must also be documented, but no further action is required.

Signal and response documentation typically falls within one of the types described in Table F.

Any changes to control limits, signals, or processes that result from evaluation should be managed by the system most appropriate for the change (i.e., change control or CAPA). Quality approval is required to close out a response to signal for all three categories (escalation, evaluation, no action).

Table C: Classic signals

Signal	Signal Type	CQA*	CPP	NCP
Outlier	**Nelson Rule 1:** 1 point outside of a control limit	If process capability is acceptable,† evaluation	Evaluation	No action
	Western Electric Rule 1: 1 point outside of a control limit	If process capability is marginal, escalation		
Shift	**Nelson Rule 2:** 9 consecutive points on same side of center line	If process capability is acceptable, evaluation	Evaluation if process capability is marginal	No action
	Western Electric Rule 4: 8 consecutive points on same side of center line	If process capability is marginal, escalation		
Drift	**Nelson Rule 3:** 6 consecutive points, all increasing or all decreasing	If process capability is acceptable, evaluation	Evaluation if process capability is marginal	No action
	Western Electric Rule 5: 6 consecutive points, all increasing or all decreasing	If process capability is marginal, escalation		

* Where existing procedures require formal quality investigations, those procedures supersede this strategy (e.g., OOT/OOS). Where possible, CPV plans should be aligned with OOT procedures.

† Acceptable and marginal process capability can be defined in a procedure, in statistical terms.[3,4]

Table D: Default response examples

Parameter	CPV plan response			Comment
	Outlier	Mean shift	Drift	
NCP1	No action	No action	No action	N/A
NCP2	No action	Evaluation	Evaluation	No impact to quality. Evaluate shifts and drifts to limit business impact.
CPP1	No action	Evaluation	Evaluation	No action for outliers due to high process capability.
CPP2	Evaluation	Evaluation	Evaluation	Marginal process capability.
CQA1	Escalation	Escalation	Escalation	Escalate all signals due to marginal process capability.
CQA2	Evaluation	Evaluation	No action	No action for drift signals due to inherent drift in the process. Escalation not required for outliers or mean shifts due to acceptable process capability.

Table E: CFT review potential outcomes

Factor	Potential outcome
Compare signal to historical performance	Escalate if the data is significantly different from historical data or is unusual based on SME knowledge of process performance
Proximity of the data point to specifications	Escalate if the CFT concludes there is a risk of OOS
Recurrence of similar signals	Escalate to determine the cause
Signals for multiple parameters and/or attributes in the same lot	Escalate to determine the cause and any potential process impact not highlighted by CPV trending
Related events within the quality system	De-escalate if an attributable cause has been identified and investigated in the quality system
Related planned deviation, technical study, or validation protocol	De-escalate if the signal is attributed to the related study. Exceeding an existing time limit, for example, as part of validating an extension of a unit operation's hold time.

Table F: Documentation used to record signals and responses

Document Type	Description
Form	Can be used on a lot-to-lot basis to explain special causes and document their effects on the product and/or process. Form comments can also be summarized in CPV reports. Information may also be captured in a database, typically outside the QMS.
Meeting minutes	Used to document periodic reviews of CPV trends, signals, and discussions of the CFT responsible for the reviews. If part of the established periodic CPV review, meeting minutes should be approved by QA and stored in a formal document control system.
Technical report	May be used to document an evaluation, as directed by the CFT. A report is typically used to document additional data gathering and/or analysis outside the scope of a periodic CPV report.
CPV report	Used to summarize all signals and attributable causes. May include brief discussions for readily explained signals that do not require evaluation in a technical report or a quality record.
Quality system record	When the CFT decides to escalate to QMS, a record within the quality system is initiated to track the root cause investigation and product quality impact assessment. This record may involve differing levels as a result of the root cause investigation and the outcome of the product impact assessment. This record should be referenced in the CPV report.

SAMPLE RESPONSES

The following scenarios, frequently encountered while performing CPV activities, offer guidance on assessing and responding to observed signals under similar circumstances. They are classified into three categories:

- Default response vs. modulated response
- Addressing long-term special cause variations during control chart setup
- Signals indicating improper control chart setup

Default response vs. modulated response

In these three examples the CFT, after routine review, must decide whether to proceed in accordance with the prescribed default response or modulate the response.

Example 1: Default response

The CFT is monitoring a noncritical process parameter (NCP) using a control chart. By definition, NCPs have no effect on any critical quality attribute over a wide range of operation. They may be step yields, in-process hold durations for stable intermediates, or final cell density in seed steps. Typically, NCPs are monitored as performance or process consistency indicators that could have practical or financial implications. While trend signals of such parameters have no effect on quality, monitoring them offers an opportunity to learn and collate process knowledge. Observed signals for NCPs may indicate suboptimal operation or undesirable process changes.

In this scenario, the control chart shown in Figure 1 indicates that the monitored NCP is typically within the control limits, with a few exceptions where outliers are observed. The CFT believes that this NCP is well understood and all previous excursions were explained. According to the CPV plan, the default response for the observed outlier signals is no action.

The CFT wants to decide whether to escalate the response for the most recent outlier signal. Examining the figure, and considering SME's input, a member of the CFT argued that neither the magnitude of the excursion is exceedingly alarming nor does the frequency of the outlier signals seem to have increased. Given this conclusion, a reasonable course of action in this

case was to follow the default response of "no further action is required." An additional consideration is that the noted excursion may be considered part of common cause variation, therefore a reassessment of control limits may be warranted.

Example 2: Escalated response

In this scenario (Figure 2), a well-behaved NCP is monitored for outliers, shifts, and drifts. An outlier signal was observed for the latest batch manufactured. Upon review, the CFT concluded that the magnitude of this excursion was of significance, compared to recent manufacturing experience. The CFT was also concerned because outliers were not frequently encountered for this parameter, so there was little process knowledge with respect to the impact of this one, especially considering its magnitude. While the default response for outliers of this particular NCP is no action, the CFT determined that such a significant outlier signal should be escalated to evaluation to determine its cause. Escalation to QMS was not deemed necessary since the associated critical parameters were well within the control strategy.

Example 3: Reduced response

In this example, a CPP is being monitored for outliers, shifts, and drifts. The control chart in Figure 3 shows that the CPP experienced an outlier signal for the third-most-recent batch produced. However, the dominant observation from the chart is that this CPP is very well behaved from a statistical perspective.

Figure 4 shows that the process capability for this parameter is marginal (1.00–1.33). Because the direction of the excursion is away from the closest specification limit (the lower specification limit or LSL), however, it does not signify a risk to process capability.

According to the CPV plan, the default response for outliers of this CPP is evaluation. To determine if the default response is appropriate, the CFT considered several factors: the magnitude and frequency of outliers, the direction of the excursion in relation to process capability, and the lack of similar outlier in the next two batches. The CFT determined that this single outlier with relatively small magnitude is well within the specification limits and poses low risk to product quality. Therefore, the team decided that further evaluation is not necessary, reducing the response in this case to no action.

Addressing long-term special cause variations

Many parameters and attributes experience long-term variation due to special causes; these include changes in raw materials over time, aging equipment, campaign-to-campaign variation, and cumulative process, equipment, material, and test method changes. Addressing such long-term variations depends on the nature of the variation, its frequency, and the ability to identify or predict it.

Treatments generally fall into one of two categories: If the special cause can be identified and doesn't change too frequently, the control chart can be stratified at the different levels of this special cause, otherwise, a relatively large data set should be used when setting control chart limits. It should be large enough to fully express the voice of the process, including the effect of special causes on long-term variation.

Control chart stratification is desirable when the special causes for the long-term variation are easily identified and have low frequency. This allows for a statistically meaningful number of data points within each stratum. Examples of special causes that can be treated through stratification include (but are not limited to): variations due to campaign manufacturing; variations caused by the introduction of significant changes to the manufacturing process, equipment, or test methods; and variations due to changes in materials (such as chromatography resins) that affect a number of subsequent batches.

If, on the other hand, the materials changes are too frequent or the long-term variation is gradual due to small cumulative changes, stratifying the

Figure 1: NCP experiencing infrequent outlier signals

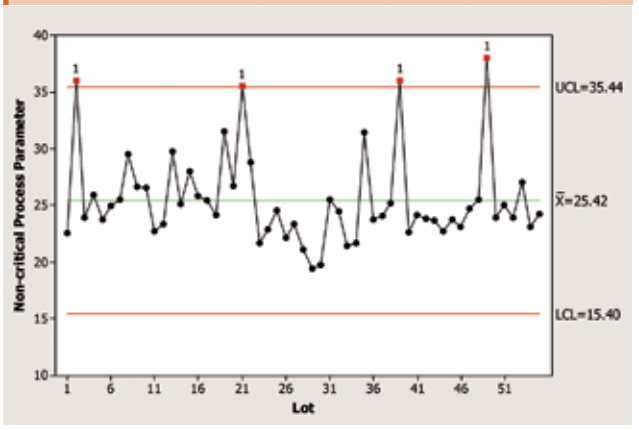


Figure 2: NCP experiencing a large outlier signal

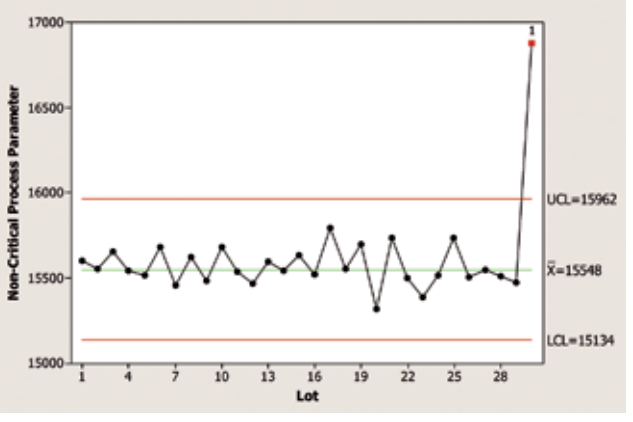
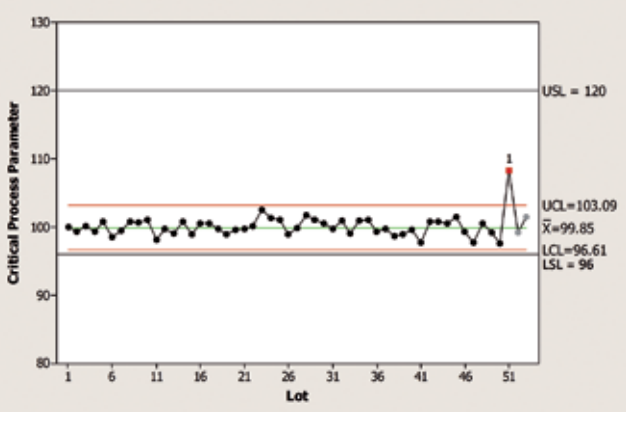


Figure 3: CPP with marginal capability and a single outlier



control chart becomes impractical and challenging. The best approach in the case of too-frequent changes is to build a robust control chart with relatively large data set that demonstrates these variations. Temporary control limits are initially established and then recalculated at some frequency by introducing additional data until the SMEs feel that the data set expresses the true voice of the process, including long-term variation. The CFT may also consider "no action" for shift signals since these are expected for parameters that are sensitive to long term variation.

Example 4: Control chart stratification

In this example, a CPP for a product that is manufactured in campaigns is monitored for mean shifts, drifts, and outliers. Figure 5 shows a control chart of the CPP over three 10-run campaigns (A, B, and C in the top axis). In this case, it is typical that several months may elapse between successive campaigns. Different products/processes are often run in the interims.

Signals for multiple mean shifts and outliers became evident with continued production. Because the parameter was a CQA, the signal was triaged against a default response of "evaluation."

The important consideration is the existence of subtle shifts from one campaign to the next. These can be the result of different raw material batches, new column packs, etc. All are considered normal process variables, but when viewed on a campaign basis they can display marked shifts in the process. To account for the campaign effect on the CPP and avoid false signals, the most appropriate treatment for the control chart was to stratify it per campaign, as shown in Figure 6.

Important considerations:

- All data are within specifications (0.84–1.60). This can be qualified via capability analyses or simply checked relative to specifications.
- Data within each campaign are considered "in-control" or stable. There are no violations to the run rules as described in previous sections.
- Variation within each campaign is similar. Homogeneity of variance can be checked across all campaigns using various statistical tests. The most important consideration is that the process variation is not getting worse (i.e., wider control limits) with each successive campaign.
- Any shifts between campaigns should be acknowledged and documented in CPV plans and/or more formally in a QMS.

Example 5: Accounting for long-term variation in setting control chart limits

In this scenario, a CPP was found to be sensitive to a number of known and unknown long-term special-cause variations. The top half of Figure 7 shows a scatter plot of the CPP with a line representing a moving average. The figure is also segmented into three parts representing three different column packs. The moving average for this CPP shows slow and somewhat alternating variation within and across the three segments. In addition, the variation within each segment appears to be of the same magnitude, if not larger than the variation between segments. In this case, control chart stratification may help avoid some false positive signals, but will not eliminate them.

Given the long-term dynamics of this CPP, setting control chart limits with a limited data set would create excessive false positives. In cases like this, therefore, it's a good idea to use the largest practical data set when calculating limits that take into account the natural long-term variation of this CPP. The long-term standard deviation should also be used when calculating limits. The lower part of Figure 7 shows a control chart with limits calculated using the entire data set and without stratification.

Figure 4: Process capability analysis for a CPP with marginal capability

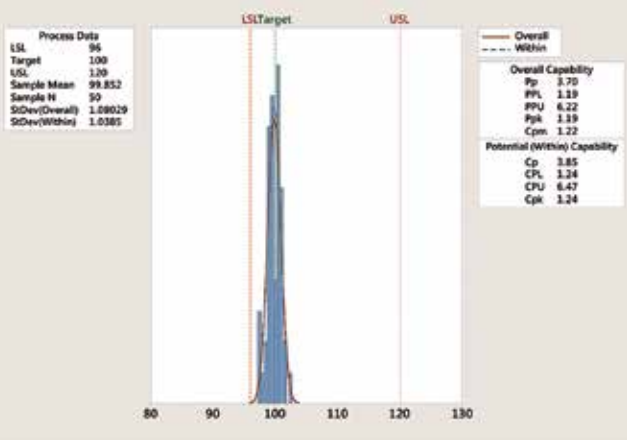


Figure 5: CPP over three 10-run campaigns

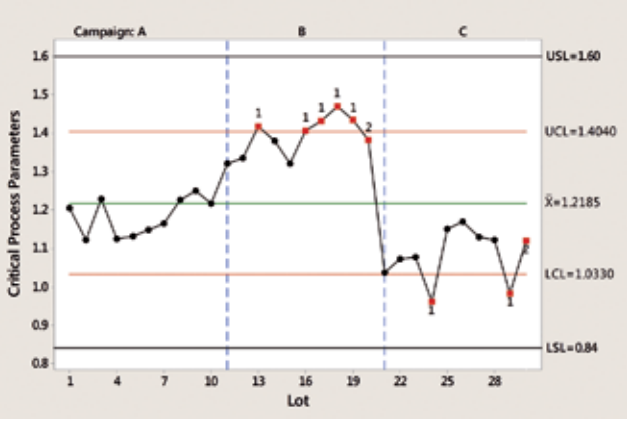


Figure 6: CPP stratified by campaign

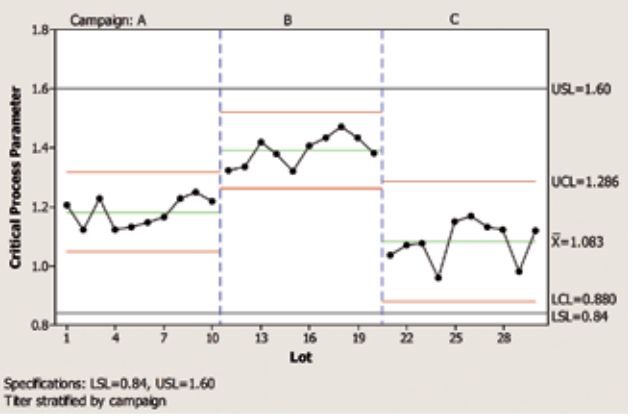


Figure 7 indicates that despite the long-term variation observed for this CPP, it is actually a well-behaved parameter. There are few trend signals and the process capability is markedly high, considering the width and location of the control chart with respect to the specifications.

Signals that indicate improper control chart setup

When calculating control chart limits for trending, the idea is to collate a statistically significant data set that captures the common cause variation expected to persist in the future. In practice, though, most CPV plans for new products are created with limited number of batches. Control limits, therefore, may need to be updated once a sufficiently large data set is available.

Even for legacy products, there are cases where the historical data set is not representative of current manufacturing due to cumulative process, equipment, materials, or test-method changes. While it is not advisable to continually and arbitrarily modify the data set baseline and recalculate control limits, applying control limits that do not represent the current manufacturing process is not any better. A balanced approach is preferred, where control limits are assessed periodically and updated when necessary.

Both the mean and variance of monitored parameters and attributes are subject to change; they can also be purposefully introduced as the result of process optimization or continuous improvement. Ideally, the mean should move in the direction of a predetermined target and the variance should diminish over time, in accordance with process knowledge gained and the addition of controls fed back through active monitoring.

One of the advantages of control charts is that signals within them can alert practitioners to changes in mean or variance. One valuable control chart run rule not frequently exploited in the industry is 15 data points in a row, all within ±1 standard deviation of the mean, which indicates that the variance has decreased over time. This behavior is often observed as a wide space between control limits and the mean.

Persistent outlier signals in one direction and/or persistent shift signals can also indicate long-term shifts in the mean. In this case, the parameter in question should be examined to determine if the change is acceptable and new control limits are needed, or if the change is not acceptable and further action is needed to bring the mean back to target. The following two examples illustrate these types of situations.

Example 6: Variance reduction over time

In this example, while monitoring a CPP, the CFT observed a wide space between the control limits and the data, which was clustered around the mean as shown in Figure 8. The signals highlighted on the chart indicate that 15 or more data points are within ±1 standard deviation of the mean.

Figure 7: Long-term variation in setting control chart limits

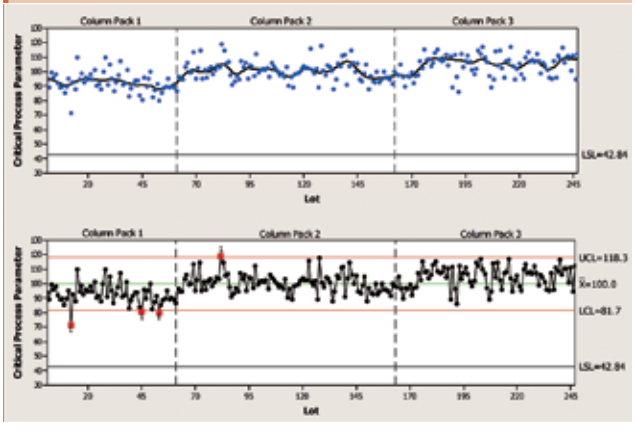


Figure 8: Wide space between control limits and data

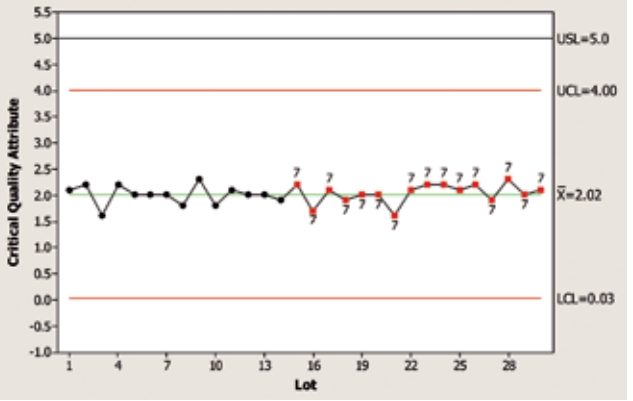


Figure 9: Updated limits due to variance reduction

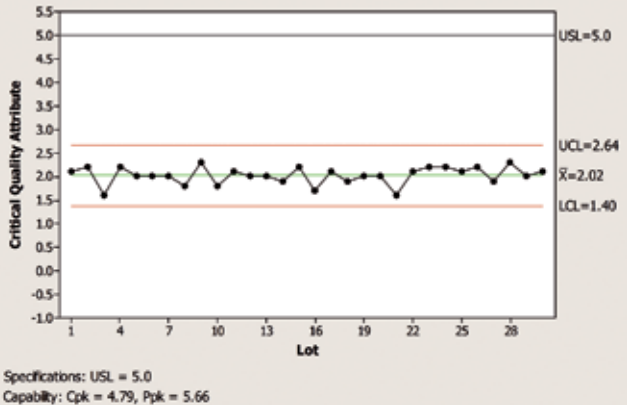
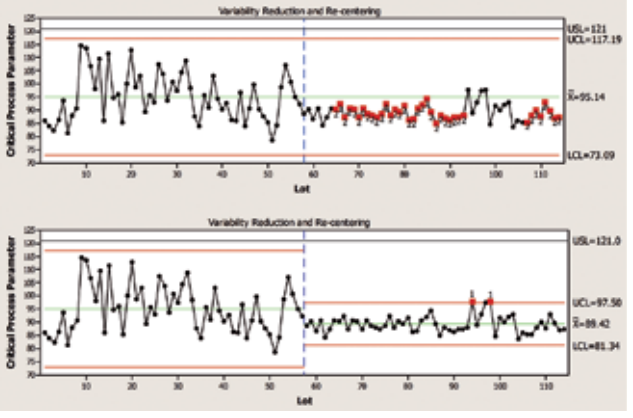


Figure 10: Correcting control limits due to process improvement, before (top) and after (bottom)



Such a scenario can result from one of two things: 1) A phenomenon called "stratification," wherein the samples are systematically pulled from multiple distributions, or 2) the process variation has narrowed, indicating a significant process shift. Both require that control limits be re-evaluated.

Upon further assessment, the CFT ruled out stratification. Reviewing the history of this chart indicated that the control limits were established using a limited data set when the process was first transferred to the site.

Documented evidence showed that a number of process improvements and tighter controls were implemented over time. The CFT concluded, therefore, that the current limits were inappropriate and new limits were needed.

Figure 9 displays the same data set, using control limits that reflect the true nature of the data. In this case, control limits were recalculated to reflect the process improvement that led to the improved (narrowed) control limits.

Example 7: Mean recentering and variance reduction over time

In this example a process had undergone an improvement project to optimize performance and reduce variation. While implementing the changes, the project team decided to maintain existing limits and monitor performance for 15 to 20 lots to see if the change was successful.

Figure 10 shows data from this process where the change was implemented around lot 58. At around lot 70, the CFT reviewed the data and assessed the change as successful. At lot 110, after a period of time that encompassed additional variance factors, such as equipment maintenance and critical raw materials, the control limits were recalculated and are now considered appropriate for future production.

SUMMARY

CPV is an important initiative for the biopharmaceutical industry. Compliance means that statistical signals revealed from CQAs and CPPs should be addressed appropriately. CPV helps maintain product quality, but it is distinct from batch release. Since CPV's primary purpose is to protect the product from longer-term sources of variation, escalation to the QMS is likely to be rare.

Good practice related to CPV signals involves defining the attributes and parameters to be monitored, along with their associated signal criteria. A set of default responses can be defined, but it is important that signals be reviewed by a CFT familiar with the product and the process. This allows the complexities of the manufacturing process to be considered. Signals may be escalated or de-escalated from their defaults; the rationale for these decisions must be recorded. The review process also provides opportunity for an organization to understand its manufacturing process in greater depth and improve it over time. ‹›

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ESTIMATING PROCESS CAPABILITY IN DEVELOPMENT AND FOR LOW-VOLUME MANUFACTURING

Kimberly Erland Vukovinsky, Fasheng Li, and Dawn Hertz

A contour plot tool that relates the percent out of specification (%OOS) to a quality attribute's average and standard deviation was created to provide an initial or early assessment of process capability based on a limited amount of lot data. This article describes a tool called the process robustness contour plot, its creation, the assumptions, and its application. The article describes how the average %OOS and the upper confidence bound are estimated for a quality attribute of interest, how the tool is used to assess product robustness, and how %OOS relates to process capability. In particular, in a research & development environment where there is limited data, the process robustness contour provides a leading indicator of process and product performance. Details on the computational algorithm are included.

The process capability index (Ppk)[1] is a widely used summary statistic that describes how well a process produces output within specification limits. For these indices to have predictive meaning, contain adequate estimates of the mean and standard deviation, and provide value in process improvement, the process must have demonstrated adequate statistical control with approximately normally distributed data prior to their calculations. This effort requires a sufficient number of lots (*n*), usually equal to or greater than 25.

At the same time, it is advantageous to obtain an estimate of process capability early in a product's life cycle (as soon as a few lots are produced), or an estimate of process capability for those products with infrequent production, as it could otherwise take years to accumulate data for 25 lots.

Within the last decade, quality by design* (QbD) concepts[2–5] and practices have permitted greater process understanding in research and design, and have led in turn to increased knowledge and inherent process capability. This scientific understanding of underlying process and manufacturing conditions enables an assessment of process robustness, even though there may only be a couple of lots produced in development. To differentiate from a formal Ppk capability assessment, a contour-based tool was developed to estimate the percent out of specification (%OOS).

The %OOS contour plot is based on the mean standard deviation and specification of an attribute. Ppk is calculated following manufacture of at least 25 lots of data; several mathematical principles must be demonstrated and the %OOS contours are based on limited direct lot data, along with QbD development experience and fundamental knowledge. Although this experience and knowledge could be substantial, it may not directly translate to a large quantity of lot data during development or in transition to manufacturing.

Additionally, when the contour analysis commences in development, data-driven specifications are often preliminary. The contour tool assesses the fit between experience and the current specification, and helps visualize how well the process meets the specification. In addition, it can be updated as the sample size increases or the specification evolves over time. The contour is a useful visual tool for both small and large number of lots, and for products in development as well as new and marketed products.

THE VALUE OF PROCESS ROBUSTNESS CONTOUR PLOTS

Historically, spreadsheets or similar tabular formats have been used to examine small sets of data. Table A shows an example of such a data set. Examining this spreadsheet may prompt questions such as: How good is the process that produced this data? Do specifications reflect the capability? Can the process be transitioned to manufacturing? What do I expect of the process in the future?

The tabled data indicates that all values are within specifications. Although this is a good start, the process robustness contour plot (Figure 1) visualizes much more information for the six attributes in Table A: content uniformity ICH UDU acceptance value (AV), percent dissolved (at 4 hours), impurity 1, potency, total impurities, and yield (%).

On a process robustness contour plot, the horizontal axis represents the between-lot average and the vertical axis represents the between-lot standard deviation for a quality attribute. An X marks the calculated average and standard deviation for each attribute. The calculated average and 90% confidence bound[6] on the predicted %OOS are shown in a plot footnote.

The contour plots can be partitioned into regions of estimated %OOS

* ***Quality by design*** *(ICH Q8 [R2]): A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.*

Table A: Example Data

Attribute	Content Uniformity (AV)	Dissolution (4 hour)	Impurity 1	Potency	Total Impurities	Yield
Specs	< 15%	35–55%	<0.2%	95–105%	< 1%	> 90%
Data	3.24	52.56	0.09	100.95	0.12	93.39
	7.64	53.96	0.07	96.89	0.16	93.84
	9.57	51.63	0.12	99.71	0.21	94.91
	2.73	47.86	0.11	99.85	0.18	94.49
	8.79	54.60	0.06	98.88	0.19	93.10
	3.98	49.89	0.05	97.85	0.23	94.28

Table B: Summary Statistics for Example Data Set

Attribute	Content Uniformity (AV)	Dissolution (4 hour)	Impurity 1	Potency	Total Impurities	Yield
Average	5.99	51.75	0.08	99.02	0.18	94.00
Standard Deviation	3.02	2.54	0.03	1.47	0.04	0.69

(for given product specifications); they also help compare actual product performance based on estimated product mean and standard deviation across lots. These partitioned contour regions are colored as:

- Green: < 0.27% (good performance)
- Yellow: ≥ 0.27% and < 3% (requires further discussion)
- Red: ≥ 3% (requires attention and further improvement)

The 1% and 3% contours represent estimates in which no more than 1% and 3% of future lots are OOS (on average), respectively. The contour levels of 0.27%, 0.006%, and 6e-5% OOS displayed on the plots are approximately related to Ppk values of 1, 1.33, and 1.67 on average, respectively. Staged goals can be debated; in the case presented here, however, associating the green contour with 0.27% implies a minimum Ppk of about 1 in transition to manufacturing.

Figure 1 shows that for this set of specifications, total impurities, impurity 1, and yield are situated well within the green region; potency and content uniformity approach the yellow region; and dissolution is in the red region. Compared to examining the data spreadsheet, this contour visualization approach offers more and better information for understanding both the data and the process.

Details on the construction, interpretation, and application of the plots will be provided in the next sections.

CONTOUR PLOT CONSTRUCTION

During product development, QbD tools and principles can help develop a well-understood process and an implied a level of process robustness that extends beyond the small sample of available data. Process robustness contour plots can be used to assess the resulting robustness via the following steps:

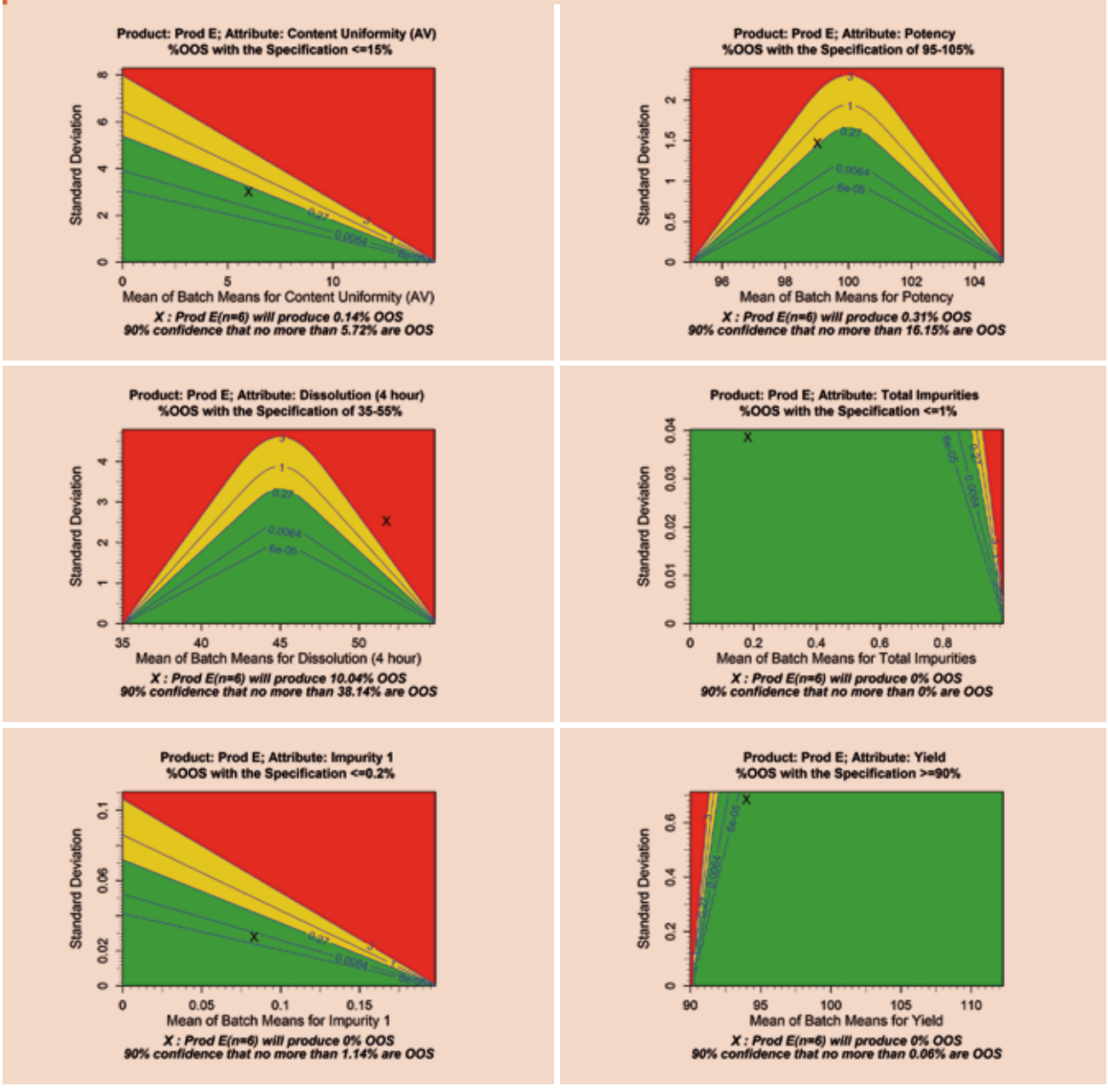
1. Identify product quality attributes to be assessed, as well as their units and specifications. The attributes could be identified via a cause-and-effect matrix, the product risk assessment, their criticality, or by other means. For the example, ICH UDU content uniformity acceptance value (AV), % dissolved (4 hours), impurity 1 (%), potency (%), total impurities (%), and yield (%) were identified.
2. Collect relevant product data, then calculate the between-lot average and standard deviation. Table B shows calculation for the Figure 1 example. It's important that the subject matter expert and statistician understand and discuss the data. A discussion around potency, for example, might include:
   a. As lot release is based on the average potency value, and while multiple tablets might be combined to create a potency value for the lot, only the lot average value is used in the calculation; this summary value represents a sample size of one (lot).
   b. It may not be possible to check between-lot consistency and lot data normality due to the small sample size. It is suggested, however, to study the data as appropriately as possible by applying statistical tools such as box plots, dot plots, and normal probability plots through data distribution fitting and control charting. Here, prior knowledge about a quality attribute's distribution may be used to appropriately transform the data to satisfy assumptions.
   c. Do the data summarized by the product average and standard deviation represent process behavior for the future? Is this the best understanding of combined experimental efforts and theoretical fundamentals? Do the data-driven specifications reflect experience?
3. Create a process robustness contour plot for each attribute using the specifications and the summary statistics (average, standard deviation). Each contour plot is based on the specifications provided; once it has been constructed, average and standard deviation for the sample size of n are added to the contour and marked with an X. More details on plot construction are provided in the sections that follow.
4. Compare the location of the X on the contour plot to the predetermined product goal. Based on the location, evaluate the perceived robustness of the product and determine if process-improvement opportunities are appropriate, or if specification revision is an option.

   The best-case scenario and ultimate manufacturing goal is to be "comfortably" within the green region. If a product lies within the green region but close to the yellow edge, the process may need to shift its mean, reduce variation, or modify its specification. If the product lies within the yellow or red region, more serious discussions around process improvements (e.g., shifting the average, reducing variability) or specification revision are warranted.

   In these cases, data should be reexamined for completeness, special causes assessed for relevance, measurement system variability addressed, and any fundamental or experimental understanding reassessed.

   In the Figure 1 example plots, the criteria were differentiated as follows:
   a. The green region ends at a contour value of 0.27% OOS—a Ppk value of roughly 1. A product with a Ppk of at least 1, presuming this is combined with good process understanding, could typically be transitioned to manufacturing; this would best position manufacturing to make improvements where appropriate and achieve even higher capability levels with experience.
   b. The yellow region boundary maximum is 3% OOS. With this boundary, there is 90% confidence that for 10 lots the true percent OOS is not worse than 12.6%. The decision as to whether this is

Figure 1: %OOS contour plots for various specification types



acceptable for early manufacturing can be discussed by the team, followed by appropriate actions.

c. Beyond the 3% boundary is the red region, where judgment might dictate that the product should not be transitioned to manufacturing without improvement or rationale for modifying the specification.

5. Continue to monitor the data, depending upon manufacturing frequency and the number of available lots. When the number of lots is more than 25, the more rigorous standard process control chart methodology should be employed and process capability indices calculated. However, even as the number of lots increases, the %OOS contour plot still provides a nice visual tool to assess process robustness.

CONTOUR PLOT INTERPRETATION

Once a process robustness contour plot has been constructed, experts should discuss data validity and distribution (if it is of adequate quantity), measurement system capability, and the current specification, followed by the relative location of the X within the colored contour to assess the product performance.

In this assessment, it's important that the location of the attribute of interest and the ultimate goal for the product be emphasized, not simply if the X falls within one specific color zone. Its relative location can indicate, for example, how sensitive the attribute may be to a sample mean change and sample standard deviation; this can indicate potential product performance improvements or a need to modify the data-driven specifications.

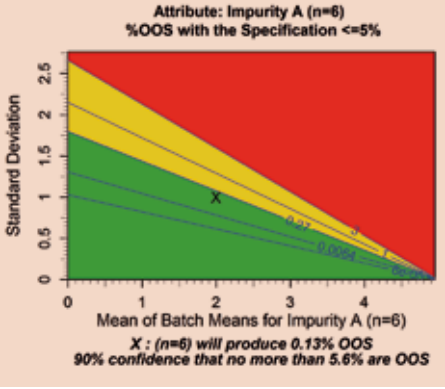
As shown in Figure 1, the X is in the green region for total impurities, impurity 1, and yield. The X is closer to the green/yellow boundary for potency and content uniformity, and is in the red region for dissolution.

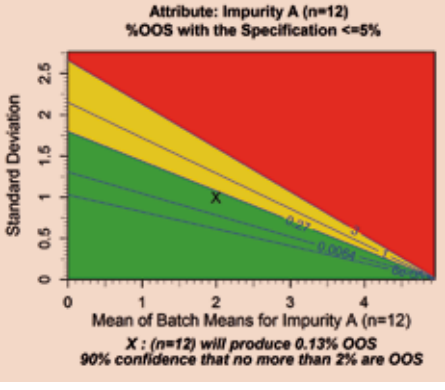
Once constructed, the plots should support an active cross-functional group discussion about product performance, which may progress as:

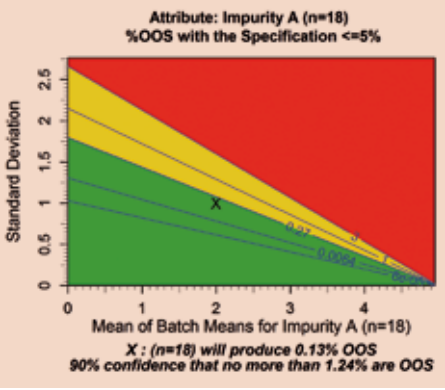
- If the X is in the green, the discussion should focus on the representativeness of the data that contributed to the estimated mean and standard deviation, and expectations around the representativeness of the data to the future process.
- For attributes close to the yellow/green boundary, an increase in the standard deviation or shift in product mean will move the X toward the yellow zone. A decrease in the standard deviation or a shift in the average would move it to a location confidently within the green.
- For an attribute in the red region (such as dissolution), where the predicted %OOS is 10%, something needs to change. If the specifications are preliminary, there may be some flexibility to modify the specifications in development while still ensuring safety and efficacy. In this case either the specification or the process targeting should change.

If the specifications are correct, the assumptions hold, and the variability estimate appears to be reasonable compared to historic estimates (e.g., other similar products) or variance component analysis (e.g., analytical method development data), the %OOS improvement is achieved through adjusting the mean. In other cases, the standard deviation might need to

Figure 2: 90% upper confidence bound decreases as n increases (all else constant)







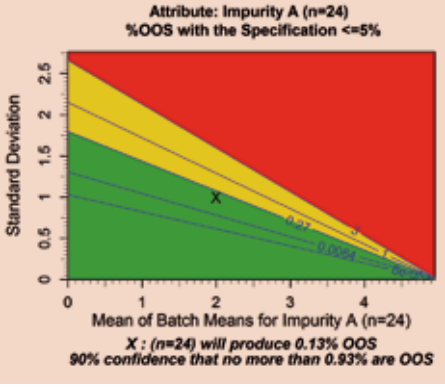
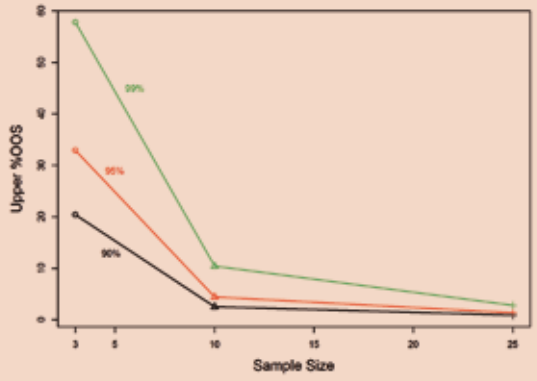


Figure 3: Effect of sample size and confidence level on upper estimated %OOS



be reduced, or the underlying process behavior may not produce normally distributed data, so the calculation assumptions should change.

It is important to recognize the uniqueness of data driven-specifications. In some instances, acceptance criteria may be based on fundamental understanding of the impact on safety and efficacy along with quantification of lot data. In this case, for data-driven attributes whose specifications are established during development (e.g., impurities), the process robustness assessment may help evaluate specifications. For final data-driven specifications and those with pharmacopoeial precedent (e.g., potency), the process robustness assessment will help determine how well positioned the product is to meet those specifications in the future. As needed for all attributes, other data sources can be used in the decision-making process. This could include estimates of variability components from methods and process, knowledge from modeling efforts or other relevant data. The team discussion will vary depending on the stage of specification setting and the type of specification.

Contour levels of 3%, 1%, 0.27%, 0.006%, and 6e-5% OOS are displayed on the plots. As with any summary statistic, there is variability in the %OOS estimates. This variability is represented in the plot footnote by an upper confidence estimate on the %OOS.

Figure 2 illustrates the effect of the number of lots on the confidence bound. For this example, the average and standard deviations were engineered to remain constant, hence in all cases the average %OOS is estimated as 0.13% even as the number of lots increases. For a sample of six lots, there is 90% confidence that the %OOS will be no more than 5.6%, given the specification and an expectation that the process will operate as it did in development.

As the number of lots increases to 12, 18, and then 24, more direct information on the process expectations is collected, and the upper bound estimates decrease to 2%, 1.24%, and 0.943%, respectively. Note that there is not consideration in the upper bound for any information external to the sample size of 6, 12, 18, or 24 alone. This example illustrates that if the process average and standard deviation remain the same and only the number of lots change, then the average %OOS will not change. Both the %OOS confidence bound along with the average %OOS should therefore be examined.

Using the estimated average and standard deviation from Figure 2, Figure 3 illustrates the change in the estimated %OOS confidence bound as the sample size and confidence level vary. The change in the estimated %OOS bound transitions rapidly with an increase in sample size, especially when estimating the 95% and 99% bounds.

Statistically, small numbers of lots provide a particular challenge due to the uncertainty in estimating the process average and process standard deviation, particularly the between-lot process standard deviation. This challenge decreases when the number of lots increases to 10, and essentially is removed at 30 lots, assuming that by then a sufficient amount of process variability has been demonstrated.

Alternatively, external estimates of analytical, material, and process variability can aid decision making for the small number of lots, as mentioned previously. As the tool was developed to include the small numbers of lots (3–10), the 90% confidence bound indicates the most reasonable choice to reflect the larger uncertainty in the variability at these sample sizes, and is used to estimate an upper bound.

COMPUTATIONAL CONSTRUCTION

Ranges for the contour plot x and y axes are based on the specification limits and the value of the X to be placed on the plot. If only the lower specification limit (LSL) or upper specification limit (USL) is provided, the lower (or upper) range of the x axis is generally set as the LSL (or USL). Ranges for the two-sided specification are based on the LSL and USL provided. If only one *x* axis endpoint is based on the specification provided, the other *x* axis endpoint is based on the value of the marked X. The lower value of the *y* axis is generally set at 0, with the upper range based on the *y* axis value of the marked X.

Once the contour ranges are determined, the two-dimensional region is partitioned by dividing each axis into 100 equally spaced intervals (101 × 101 set points), forming 10,000 equal-sized rectangles within the plot region. The OOS% is then computed for each set point (on average), under the assumption that the process is normally distributed with the associated mean and standard deviation at the set point.

Generally speaking, there are three cases associated with the three specification-setting options (LSL only, USL only, two-sided):

1. The process has only an LSL [e.g., dissolution (Y) with lower limit or Q value of 80%]. For a set point of (90%, 3%) or 90% average dissolution with a standard deviation 3%, the average %OOS is equal to the probability $P(Y \le LSL) = P(Y \le 90\%) = P(Z \le -3.33) \approx 0.0004$, where Z is the standard normal distribution.
2. The process has only a USL [e.g., impurity A (Y) with an upper limit of 5%]. For a set point at (2%, 1%), then the average %OOS is equal to the probability $P(Y \le LSL \text{ or } Y \ge USL) = P(Y$ 95% or $Y \ge 105\%) = P(Z \le -2.5$ or $Z \ge 2.5) \approx 0.0124$ where Z is again the standard normal distribution.
3. The process has both a lower and an upper specification [e.g., assay (Y) with specifications of 95%–105%]. For a set point at (100%, 2%), the average %OOS is equal to the probability $P(Y \le LSL \text{ or } Y \ge USL) = P(Y \le 95\% \text{ or } Y \ge 105\%) = P(Z \le -2.5 \text{ or } Z \ge 2.5) \approx 0.0124$, where Z is again the standard normal distribution.

%OOS CONFIDENCE LIMIT

The preceding section provided examples on the calculation of the %OOS, which then is used to place the X on the contour plot. The footnote of the

contour plot contains the estimated upper confidence limit on the %OOS. The 100 (1 - α)% upper bound on the probability of being OOS is calculated according to the small sample tail area confidence bound algorithm provided in Owen and Hua.[4] This section briefly summarizes that calculation.

For a given specification [one-sided lower, i.e., $Y \geq LSL$, or upper, i.e., $Y \leq USL$ or two-sided, i.e., $LSL \leq Y$ and $Y \leq USL$], an upper and a lower confidence bound on the %OOS can be calculated. However, only the two upper confidence bounds are potentially of interest: upper confidence bound for the probability of being less than or equal to LSL [i.e., $P(Y \leq LSL)$] and upper confidence bound for the probability of being greater than or equal to USL [i.e., $P(Y \geq USL)$]. In the formulas below, it is denoted that n lots of data have been collected with estimated mean ($\bar{y}$) and standard deviation (s) and that $\Phi(\bullet)$ denotes the standard normal cumulative distribution function.

One-sided lower specification $Y \geq LSL$ to calculate the upper 100 (1 – α)% confidence bound for the probability of $P(Y \leq LSL)$, define $\eta_L = P(Y \geq LSL)$ and $K = \frac{\bar{y} - LSL}{s}$.

- The lower confidence bound η_L^- of η_L can be solved numerically from the following equations:
  - $P\left(t_{n-1,ncp=\sqrt{n}K_{\eta_L^-}} \leq K\sqrt{n}\right) = 100(1-\alpha)\%$
  - $\eta_L^- = \Phi(K_{\eta_L^-})$
- The upper 100 (1 – α)% confidence bound for the probability of $P(Y \leq LSL)$ is $(1 - \eta_L^-)$

One-sided upper specification ($Y \leq USL$) to calculate the upper 100 (1 – α)% confidence bound for the probability of $P(Y \geq USL)$, define $\eta_L = P(Y \geq USL)$ and $K = -\frac{\bar{y} - LSL}{s}$.

- The upper confidence bound (η_L^+) of η_L can be solved numerically from the following equations:
  - $P\left(t_{n-1,ncp=\sqrt{n}K_{\eta_L^+}} \leq K\sqrt{n}\right) = 100(1-\alpha)\%$
  - $\eta_L^+ = \Phi(K_{\eta_L^+})$
- The upper 100 (1 – α)% confidence bound for the probability of $P(Y \geq USL)$ is η_L^+ .

Two-sided specification is the sum of η_L^- and η_L^+, using $\alpha/2$ in place of α.

SUMMARY

The %OOS contour plot provides a tool to express product robustness and to provide an insight into process capability for processes with fewer than 25 lots where traditional process capability indices such as Ppk are not meaningful. The plot is superior to examining data in a spreadsheet and can also be applied to greater than 25 lots of data to aid visualization.

To be fully meaningful, the tool assumes product knowledge and confidence in operation beyond the lot data available for calculation. Both average %OOS and the corresponding confidence bound are important to assess product robustness. The relative location of the X in the colored zones on the contour plot provides information on product performance and guidance toward process improvement.

Team discussion on the product/process may take the form of whether the process is currently on track/acceptable, if the process needs further attention and investigation, and which improvement actions should be initiated. Additional statistical calculations and modeling could and should be performed to support discussions and decisions.

In all, this tool and the associated process provide a structure to summarize and visually predict process capability. ‹›

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WHERE WILL NEW ANTIBIOTICS COME FROM?

William Fenical is frustrated that the pharmaceutical industry hasn't developed new antibiotics for more than 20 years. Without them, it will be impossible to check the surge of superbugs—antibiotic-resistant infectious agents such as methicillin-resistant *Staphylococcus aureus* (MRSA)—that result in over two million infections in the United States annually, with more than 23,000 fatalities.

"The industry is no longer interested in antibiotic development," says Fenical. "Some pharmaceutical companies are manufacturing antibiotics profitably, but the R&D side is nonexistent and the industry doesn't have the personnel with deep experience." Fenical is a professor at the Center for Marine Biotechnology and Biomedicine at the Scripps Institution of Oceanography in San Diego, California. "The price of antibiotics is so low that there isn't massive profit in treatments. Industry decided to get out of this field and instead work on areas that are more lucrative, like drugs for blood pressure, hepatitis, and cancer."

The job of finding candidates has fallen to academics like him. Their preferred method is bioprospecting, which is the discovery and commercialization of drugs found in plants, animals, and microbes. Almost all of the 120 antibiotics that are currently approved—from penicillin to vancomycin—were found in soil microbes this way.

"More than 60% of all small-molecule drugs were found by bioprospecting," says Eduardo Esquenazi, founder and CEO of Sirenas LLC, a company that screens marine microbes for novel antibiotics and cancer drugs.

These days, researchers like Esquenazi are taking a fresh approach: looking in the world's oceans. At the time the current arsenal of drugs was being discovered, nobody thought to look in the sea. Sirenas, which partners with the Bill & Melinda Gates Foundation, has discovered an antimalarial in an algae living in a salt pond in the Chilean desert.

THE PRICE OF ANTIBIOTICS IS SO LOW THAT THERE ISN'T MASSIVE PROFIT IN TREATMENTS. INDUSTRY DECIDED TO GET OUT OF THIS FIELD

"There's never been a better time to bioprospect," says David Sherman, professor at the Life Sciences Institute at the University of Michigan. "Methods are getting cheaper, faster, and better every year."

Sherman's lab gathers marine sediments from coral reefs and habitats that are high in biodiversity and that can contain as many as a billion microbes in every cubic centimeter. Samples come only from countries, like Costa Rica, that provide legal access and permission to take samples back to the United States. Divers bring back collections of spores that are isolated and screened for activity against pathogens to identify candidates, then isolate and characterize bioactive compounds. These scaffold molecules are then chemically modified to optimize their antimicrobial activity.

"Once we identify the compound's target, we hope to make it more potent through biochemical modifications," says Sherman. "We use sequencing technology to bring in genomics and bioinformatics to determine which molecules from which organisms contain biological activity."

One exciting development in Sherman's lab is the discovery of a molecule that inhibits the formation of biofilms, which are produced by some bacteria, and are a source of hospital-acquired infections. The lab, along with its pharmaceutical partner company, will then engineer the strain to make more of the bioactive compound.

"I'm finding the industry much more open-minded about getting back into natural products," says Sherman. "Big pharma got out of it 20 years ago and now they're realizing that that was a big mistake. It's becoming a much more favorable atmosphere for discovering new natural product molecules."

Antibiotic discovery may be happening, but getting these compounds to market is another matter. Esquenazi points out that while nature is the best source of antibiotics, it is costly and time consuming to cast a wide enough net to find them. This is the main reason that big pharma exited antibiotic discovery in the early 1990s. And Fenical doesn't see governments doing much to solve this pressing problem.

"Beginning in the 1970s, government agencies in the United States and Canada accelerated funding for cancer research and now we have successful treatments," says Fenical. "Despite the massive threat of infectious diseases, they haven't created similar programs for antibiotic research."

His lab at Scripps has discovered six antibiotics, one of which, anthracimycin, is potent against MRSA. "We've shown that it works in animals, we know the chemical structure, and we've proved the mechanism of action," says Fenical. Yet the lab can't find an avenue to develop it. "Nobody is out there with the kind of preclinical money to get it into Phase I. We've had to publish its structure and mechanism of action and hope that someone will pick it up."

He cautions that time is of the essence: "We're in crisis mode."

If we don't do something soon, more people will die of infectious diseases than cancer by 2025." ‹›

Scott Fotheringham, PhD

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