PHARMACEUTICAL ENGINEERING®

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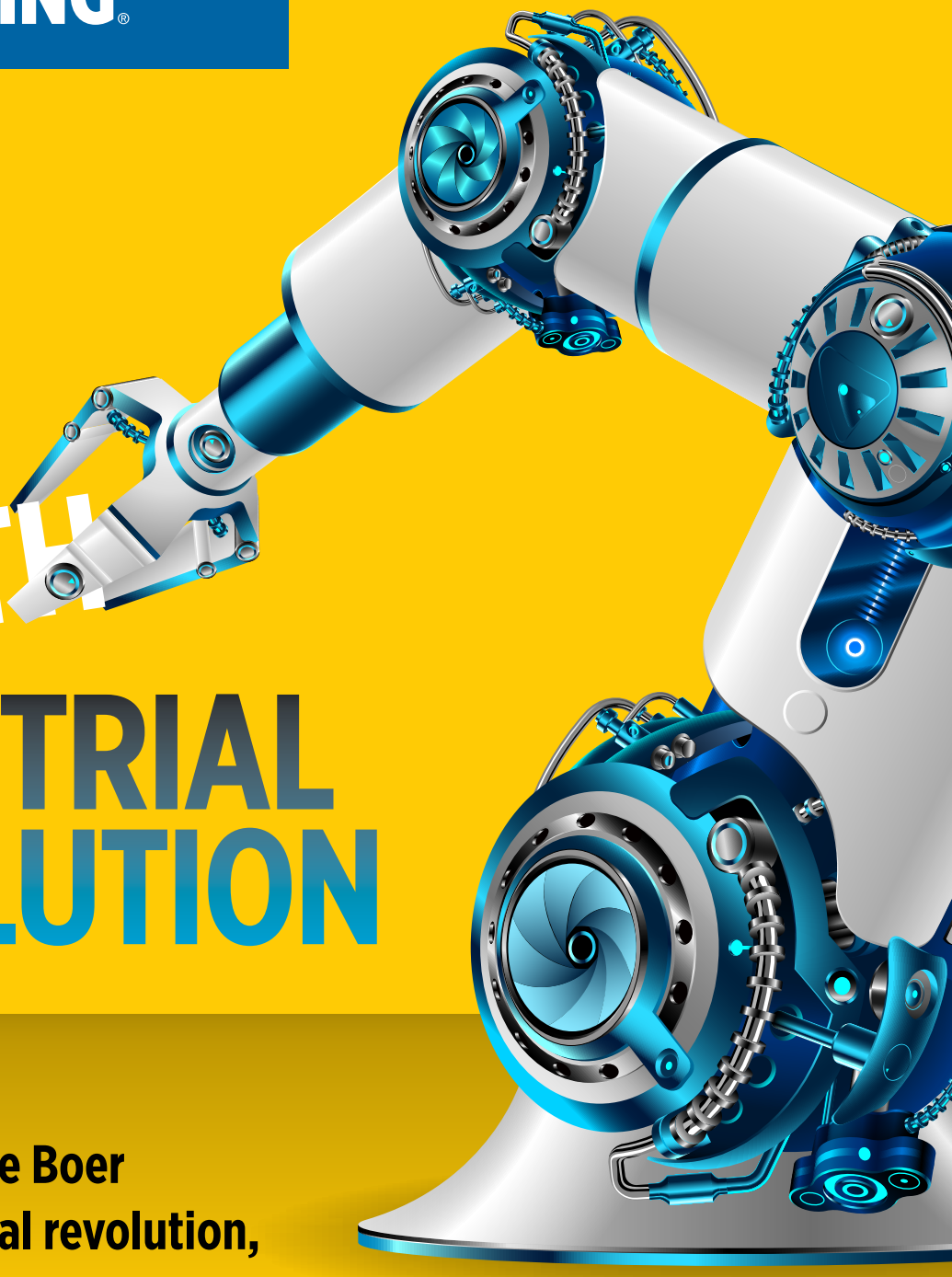

THE FOURTH INDUSTRIAL REVOLUTION

McKinsey's Enno de Boer discusses the digital revolution, deep learning, pilot purgatory, and the road ahead

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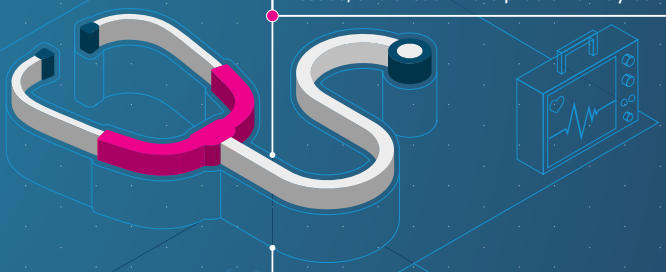

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PE VOICE

PREPARING THE WORKFORCE OF THE FUTURE

Dr. Ferdinando Aspesi
Chair, Pharmaceutical Engineering Committee

In our industry, as in many others, the most important goal is developing and delivering a product that satisfies our customers. In our industry, the end customer is the patient.

A product that satisfies our patients should prevent, stabilize, or cure a specific disease like a simple cold or a very serious disease such as cancer or multiple sclerosis. To do this requires well-characterized materials, proper equipment, adequate facilities, and clear methodologies—and a well-educated workforce both in pharmaceutical development and manufacturing departments around the world.

There is a boom of new treatments based on therapeutic proteins, monoclonal antibodies, cell and gene therapies, combined with the development of the digitized economy where mathematical models, artificial intelligence, and virtual reality will be part of daily efforts and operations. We need to develop a workforce capable of operating in this environment.

Members of the Global Pharmaceutical Manufacturing Leadership Forum (GPMLF) have identified three populations for focus to prepare and develop this future workforce.

Middle and high school students: A focus on this population will ensure a constant interest in science and technology as well as a continuous flow of students interested in pursuing a career in the pharmaceutical industry.

University students: Those who want to pursue a master's degree in the critical innovation disciplines described above are the focus here. The industry is working with academia to provide university deans and professors with the inputs to develop the knowledge and the capabilities for these areas of innovation. Internships and capstone projects will help to develop these capabilities for students that want to pursue careers in the pharmaceutical industry.

Young professionals already working in our industry: Even though they have completed their formal education, young professionals (YPs) will need to expand their understanding, knowledge, and skills to be successful in the innovation areas described above.

Another area to consider, although not yet part of the GPMLF effort, is developing the manufacturing and laboratory operators and technicians. They need a similar effort to upgrade their skills to meet the industry's changing needs. We will address this challenge in future issues of *Pharmaceutical Engineering*. Please contact me if you are interested in participating in a GPMLF Workforce of the Future team.

This effort is going to enhance and complement ISPE's commitment to Student Chapters in starting early to build knowledge and networking in the industry through the Student Chapter experience. ISPE has a robust Student Chapter program comprised of 70 Student Chapters in 13 Affiliates and Chapters worldwide. Students in these chapters work closely with faculty and industry advisors and enjoy the benefits of networking and mentorship opportunities with ISPE members around the globe for training and education in our industry.

Speaking of workforces, ISPE's staff has a new addition: *Pharmaceutical Engineering* recently welcomed a new Editorial Director, Susan Sandler. With a new Editorial Director comes the need for new content, so we welcome your article submissions to be considered for an upcoming issue.

To submit an article, start here for information on what to submit and how: https://www.ispe.org/pharmaceutical-engineering-magazine/submit-article. We are especially interested in technical articles from contributors like you. ‹›

Dr. Ferdinando Aspesi is a Senior Partner at Bridge Associates International. He has been an ISPE member since 1992.

ISPE

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Editorial Policy

Pharmaceutical Engineering inspires engineers and regulators around the world with engaging and useful articles. From technical articles that provide practical how-to advice to thought-provoking features on current issues, *Pharmaceutical Engineering* offers readers a global picture of the profession and the industry.

Opinions expressed herein do not necessarily reflect the views of ISPE.

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Pharmaceutical Engineering welcomes readers' comments. Letters must include the writer's full name, address, organization, and years of ISPE membership. If published, letters may be edited for length and clarity. Send correspondence to Susan Sandler, Editorial Director, at ssandler@ispe.org.

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TIME FLIES
A Look Back—and Ahead

Tim Howard

I am pleased to have another opportunity to share some thoughts and provide a quick update about the progress of ISPE. It is hard to fathom that we are halfway through 2018, and summer is upon us (at least those of us in the Northern Hemisphere). ISPE had a very busy first half of the year, with three major conferences in North America, a very successful Europe Annual Meeting in Rome, and dozens of training courses convened around the globe.

YOUNG PROFESSIONALS: WE ARE IN GOOD HANDS

While attending the Europe annual meeting I had the opportunity to judge the second annual ISPE Young Professionals (YPs) Hackathon. The Hackathon challenges YPs to solve a manufacturing innovation challenge in less than a day and a half and present their solution along with a viable business case. The quality of the presentations by each of the three participating groups was impressive. To all involved with this session, including those who sponsored their YPs, I applaud and appreciate your support of such a successful event. Our industry is in good hands if these sessions are any sort of litmus test. (See more on page 46.)

CONTINUED SUCCESSFUL COLLABORATIONS WITH AFFILIATES

The success of our European conferences is in large part a product of the collaborative work of our European staff, European Leadership Team, and European Affiliate leaders and volunteers. This successful cooperation reflects the effective trans-Atlantic work being carried out with ISPE headquarters. Our headquarters manages the marketing, accounting, and educational support that has contributed to these robust events.

As with the ISPE 2018 Europe Annual Meeting in Rome, our conferences later this year in Lyon, France (Biotech), and Vienna, Austria (Aseptic Manufacturing) are being produced in partnership with the local Affiliates. The high level of collaboration has resulted in great programming and increased attendance numbers year on year. We have already started to plan for 2019 events using the same collaborative model and expect our attendance to continue to grow.

MARK YOUR CALENDARS

In North America we are looking forward to returning to Philadelphia for our ISPE Annual Meeting & Expo. In 2015, we had a record-setting meeting in Philadelphia; we expect 2018 to surpass the metrics of all previous annual meetings. I am very excited about the quality and diversity of speakers we have lined up for our keynote sessions as well as our content-packed conference tracks. Mark your calendars now to be part of this fantastic conference. Here's where to find out more: www.ispe.org/am18

WE CONTINUE TO LOOK FOR OPPORTUNITIES TO COLLABORATE WITH OTHER ORGANIZATIONS

STRATEGIC PLAN UPDATE: OPERATIONAL STRENGTH

"Execute with excellence and a sustainable business approach" is a component of our strategic plan that is fundamental to our continued success. In his presentation at the 2017 Annual Meeting, Mike Arnold, Past Chair of ISPE, provided several data points about where we made great progress last year in improving the operational strength of ISPE. We continue to improve in this area.

Our staff has added key resources to support ISPE operations and has fully implemented a staff training program for professional development. Our board is implementing changes to drive better governance of the society. Some of the changes we are implementing include modifying our board agendas to make sure we address long-term planning each time we meet, and adding a board self-assessment process to our annual agenda. We will continue to look for changes like these that improve our operational strength.

Finally, we continue to look for opportunities to collaborate with other organizations. We signed a memorandum of understanding with the Parenteral Drug Association to collaborate on the topics of quality metrics and quality culture. Our society is as strong as it has been in quite some time, and our strategic objective to continually improve the strength of our operation is ever present and evident in much that we do. ‹›

Timothy P. Howard, CPIP, PE, Vice President at Commissioning Agents, Inc., and President of its wholly owned subsidiary Coactive, Inc., is Chair of the ISPE International Board of Directors. He has been an ISPE member since 1993.

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MORE ADVICE FROM THE TOP

Caroline Rocks

My conversation with six members of ISPE's Board of Directors continues this month. They provided advice on how to develop as a Young Professional (YP), and shared suggestions about how to make the most of ISPE membership. The first half of our conversation was published in the May-June issue of *Pharmaceutical Engineering*.

- Alice Redmond, Vice President, European Operations, Commissioning Agents
- Flemming Dahl, Senior Vice President, Novo Nordisk A/S
- Joanne Barrick, Advisor in Global Validation Support, Eli Lilly and Company
- Jörg Zimmermann, Vice President, Vetter Development Services
- Tom Hartman, Vice President, GMP Operations, GlaxoSmithKline
- Kelly Keen, Project Portfolio Management, BPM, F. Hoffman-La Roche, Ltd.

WHAT WAS THE BEST ADVICE YOU RECEIVED AS A YP?

Alice: Be open-minded, observe team leaders and managers, look for practices (management, communications, etc.) that work, and adapt them to your job and style. Learn from the best, but always make it your own. From the technical perspective, expand your horizons, think, and look beyond your remit to get a full understanding.

Flemming: Be knowledgeable. Find areas that mean a lot to you, both technically and from your heart.

Joanne: Whatever job you are doing, do it really well. Don't ignore the value of networking. Be open to roles and opportunities you hadn't thought about. Be aware you may be able to combine your passions—for example, if you love to travel you may seek a role that includes travel.

Jörg: "Find a job you really like, and you will never have to 'work' again." Sounds good, doesn't it?

Tom: Work hard, do the right thing when faced with decisions, embrace change, be accountable for your performance, and take ownership of your career.

Kelly: My best advice is to stay with ISPE and be present at events. My first event was attended by a group of older men, and I felt very out of place. But I met one person at that first conference. At the next conference, he introduced me to some of his colleagues. The time after that, I met more members through them. The more events I attended, the bigger my network became. That first man I met, Mark Hannon, is now retired, still active in ISPE, and is a very good friend. Listen to presentations and ask questions—and remember that there are no dumb questions. Learn the acronyms and do not be afraid to ask for clarifications. Know your skills, and sell yourself, but don't over-sell.

WHAT SKILLS SHOULD YPS DEVELOP?

Alice: Communication, listening, troubleshooting, project management, and risk management.

Flemming: The ability to oversee a process from the early stages to the end by combining knowledge from various disciplines is key. It's also important that you be able to cooperate with people who work in areas very different from yours.

Joanne: Curiosity. Make sure you are always asking why and probing for deep understanding. Communication and interpersonal skills are important, too. If you have great ideas, you must be able to articulate them well to gain support. You will always have to find common interests to work effectively with others.

Jörg: Try to get as much experience in different fields as possible, and try to build a good network, both in your company and outside. And there is no better place to build a network than ISPE.

Tom: Show ownership and personal commitment to what you are doing. Deliver results, even if they seem small. Small successes build to large successes.

Kelly: Be computer or tech savvy, network, meet people, and have fun while doing it. Get involved: Being present both physically and mentally is a skill few people achieve.

WHAT FUTURE PHARMACEUTICAL INDUSTRY CHALLENGES DO YOU THINK YPS WILL HAVE TO SOLVE?

Alice: The industry will need to become more innovative and embrace change. YPs will have a huge part to play in pushing innovation to maximize the utilization of technology.

Flemming: YPs will need to set an agenda of simplicity in a complex world with new regulations and stakeholders.

Joanne: Cost pressures are challenges that will persist. We must be able to innovate faster and at lower cost while maintaining quality and providing reliable supply.

Tom: Enhancements to supply chain and more patient access to quality medicines, reducing drug development cycles and time lines, and the application of advanced technologies that will improve the cost of goods, reduce capital investment, and improve efficiencies.

Kelly: Insurance companies will have a big influence on medicine in the future. Cost-cutting will continue and biosimilars will become common. Technology will create change, too. Imagine if instead of seeing a doctor, your smart phone analyzed a saliva sample and sent the results to a lab. An ePrescription for the medication you need could be sent to a pharmacy or delivered to you.

The game is changing quickly—it's just a matter of time. ‹›

How did you get involved in ISPE? Join the conversation on the YP Community page: http://cop.ispe.org/yp. To join the YP Community, select it during registration or update your account on ispe.org.

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AN OPEN-ARMS ORGANIZATION

ISPE San Diego Chapter

Chapter President Nicki Lange is cultivating an enthusiastic membership and building a professional community.

Nicki Lange, Director of Business Development for CRB and ISPE San Diego Chapter President, loves her community. "San Diego is the best place in the world. We're people-oriented with a flavor of fun. Our chapter captures that." Lange attributes much of her chapter's success to enthusiastic board leadership and a continuous emphasis on collegiality. With four of its five Gold Sponsors represented on the board, the San Diego Chapter has a strong connection with its membership. "We work hard to welcome everyone," she said, describing an inclusive organization with a "culture of synergy."

In a conversation with *Pharmaceutical Engineering,* Lange was joined by Chapter Vice President Deborah Neatherlin, Account Executive, Siemens Building Technologies, and Chapter Manager Kimberly Syre, Principal, Attention to Detail. All three focused on a strong network of professional relationships. "Any organization is only as strong as its people," said Syre. "Our meetings are genuinely productive, and much of that is driven by the personality of the board members." The close ties among chapter members reveal a genuine community. "It's very unique," she continued. "We really are a family. We go to each other's weddings and important events. We thoroughly enjoy each other's company—we're friends outside of work."

Apparently, this people-first approach is working, with San Diego boasting 348 members—an 8% increase over the past year, versus the standard benchmark of 1% growth for ISPE chapters. According to Syre, this can be attributed to a full slate of events, including periodic "lunch and learns" at local pharmaceutical companies. These provide a friendly, relaxed introduction to ISPE and outline the benefits of membership.

Sustained growth has been a constant since 1992, when a group of engineers in the nascent San Diego pharmaceutical industry established the chapter. "At that time," said Syre, "business connections were kept on a Rolodex." An inaugural meeting featuring a talk by James Stumpf from the US Food and Drug Administration drew over 140 attendees, and growth took off from there. Members met quarterly and held the first vendor night within a year. Twenty-six years later, monthly meetings are the norm, and the annual vendor night is an unbroken tradition. Chapter members also look forward to the annual golf tournament.

INNOVATIVE PLANNING

While its emphasis on inclusivity goes a long way toward building good relationships, the San Diego Chapter couples that collegial spirit with effective practicality. This year, the chapter has embraced a new approach to its annual strategic planning meeting by inviting the advisory council to participate directly alongside the board. Syre described the difference: "We've had strategic planning meetings for many years. Typically at the end of meeting we 'd have ideas, but then we'd need to act on them, and there wasn't always an action plan. Nicki changed that by bringing the advisory board into the meeting."

It was a game changer, the women said, and so successful that it "might be a new best practice" for ISPE chapters and affiliates. As Neatherlin explained, "Our advisory board is made up of executives from leading life science companies in San Diego. They are able to help us understand the training needs of their staff, open their doors for facility tours, and host our dinner meetings at no charge. Their support and insight has been so invaluable to our chapter." Lange emphasized gratitude, commenting, "We're especially thankful to Abzena, Inovio, and Genentech for being such valuable resources."

Inclusivity isn't the only benefit to this approach, however—it has yielded specific practical advantages. Syre mentioned that including the advisory board led to both more effective strategies for implementing plans and a more complete year-ahead calendar. "The earlier our calendar is in place, the more effectively we can seek sponsorship dollars … we can offer companies the entire chapter calendar up front, and we can solicit an annual sponsorship instead of a shorter-term or iterative one. This greatly reduces work to coordinate through the year. It means better cash flow, which in turn allows us to focus more on engagement than money."

REWARDING PROFESSIONAL EXPERIENCE

Neatherlin encouraged industry organizations to join the chapter. "People should join to network, pursue career advancements, find speaking engagements, and discover educational opportunities."

Lange summarized the positive impact the San Diego Chapter has had on her career. "ISPE has never been 'work' for me. It's been the opportunity to be a part of a team of like-minded and like-spirited people. Not only have I learned all the aspects of running a nonprofit business, but I have gained so much knowledge, and have been able to stay current in industry trends. I am truly thankful for the experiences and memories."

With an 8% increase in membership in this, its 26th year, the San Diego Chapter is a growing, forward-thinking, people-focused organization that showcases the advantages of ISPE membership. ‹›

—Paul J. Cumbo, MLitt, MS

Recent and Upcoming Events

2017 ISPE Annual Meeting

San Diego was an ideal venue for the ISPE 2017 Annual Meeting. Along with facility tours at Genentech, Gilead, and Illumina, there were plenty of opportunities to enjoy the city. Past Chapter President John Wammes sponsored lunch and organized a tour of San Diego's popular craft breweries. The chapter also hosted one of its signature events, a golf tournament at La Costa. Local companies held parties for conference participants at rooftop venues with views of the marina, ballpark, and Gaslamp District.

Single-use meeting

In January 2018, over 100 attendees and 13 sponsors gathered for a full-day educational meeting on single-use technologies. The event was organized by Chapter Secretary Juliana Ipuz and Margaret Stava, a board member from the ISPE Los Angeles Chapter. Thanks to the success of the meeting, the San Francisco Chapter is planning a similar event.

YP networking

Young Professionals networking events, a new initiative for the chapter, are held several times per year.

Technical education sessions

The chapter holds an average of four technical education sessions and at least two tours per year. For 2018, these include:

17 May	5th Annual Get to Know Your San Diego Market: A Perspective from the Owner, Architect, Broker, and Land Developer at DPR Construction
28 June	Utilities and Renewable Plan for Life Science Industry in San Diego
12 July	Vertex facility tour
21 August	Educational event at Inovio
13 September	Vendor Night: Life science resource fair at Illumina i3 campus
14 September	Golf tournament at Encinitas Ranch Golf Course

Quick Facts

Founded	1992
Region	San Diego County, California
Membership	348
President	Nicole Lange, CRB (Gold Sponsor)
Vice President	Deborah Neatherlin, Siemens (Platinum Sponsor)
Treasurer	Jeff Landgraf, Cannon Building (Gold Sponsor)
Secretary and Programs Chair	Juliana Ipuz, Charter Medical, Ltd.
Golf Committee Co-Chairs	Laura Ellery, Industrial Commercial Systems, Inc. Annalisa Evans, Evans Consulting
Vendor Night Chair	Kelly Michajlenko, GLUMAC
Social Media Chair	Geoff Parker, Sequoia Consulting
Social Events Chair	Chad Hawk, Pacific Rim Mechanical (Gold Sponsor)
Membership Chair	Lisa Yargeau, Sani-Tech West
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Chapter Manager	Kimberly Syre, Attention to Detail

THE FOURTH INDUSTRIAL REVOLUTION

Dr. Enno de Boer says rapid, major changes are on the horizon for just about everything—including manufacturing.

We are entering the Fourth Industrial Revolution."

Dr. Enno de Boer, McKinsey & Company Partner and Leader of Digital Manufacturing, made this intriguing declaration during his keynote presentation at the 2017 ISPE Annual Meeting & Expo in San Diego, California. Focusing on three principal elements—intelligence, connectivity, and flexible automation—de Boer invited attendees to consider the future of manufacturing across a range of industries, including pharmaceuticals. The opportunities surfacing in this transformative era of technological evolution fueled tangible excitement surrounding his presentation.

De Boer expanded on the game-changing implications of this Fourth Industrial Revolution for the factory of the future in a follow-up interview with *Pharmaceutical Engineering*. Using the advancements of robotics and artificial intelligence (AI), he predicted that manufacturing centers will "eliminate dull, dangerous, and dirty work" and become "much more human-centric, bringing the best that humanity can bring: creativity, problem solving, and the entrepreneurial spirit. These workplaces will attract the best and the brightest."

DIGITAL REVOLUTION

These improvements in manufacturing will also provide direct benefits to the consumer. In the pharmaceutical industry, de Boer explained, "there are a couple of dimensions. We are able to have a much more agile and reliable supply chain, so if demand patterns change, production systems can adjust more quickly. If there's any kind of epidemic, a more agile, flexible production system can produce the needed medication in a shorter time. Innovations are translated to product scale more quickly. In terms of mass personalization, we have the chance to do it at lower cost, in smaller batches, even to the production unit of one. We can tailor products to customers. And lastly, we see a productivity increase in management functions, quality, logistics, maintenance, and on the production line itself."

Describing this progress in his keynote, de Boer explained, "Technology is advancing faster than ever. The Internet of Things (IoT) will make us even more connected than we are now. Connectivity and artificial intelligence, along with flexible automation, will allow us to move from a reactive shop floor to an autonomous, self-organizing factory." Consider this: With over 8.4 billion connected devices worldwide, there are already more connected devices than people. Fifteen percent of production assets are connected today. The over 700 IoT platforms on the market all aim to change this in the coming years. We are poised to see rapid, major changes to the way just about everything works, de Boer said—and that includes manufacturing.

MOORE'S LAW

Evidence of this accelerating innovation is visible all around us. We might consider Moore's Law, attributed to Intel cofounder Gordon Moore, who asserted in a 1965 *Electronics*[1] magazine article that computer processing power would double every year. Ten years later, Moore revised his projection to every two years, and in 2015 suggested that the rate of progress would slow in the coming decade.[2] Nonetheless, according to a 2015 essay in *Scientific American*,[3] Moore's prediction has largely held true over the years.

De Boer underscored this rapid development, emphasizing that the last 36 months have seen incredible leaps in computing power. "During this time, we have become able to train our AI models 60 times faster at less than 1% of the previous cost. Our models are constantly improving, and AI speech recognition is already at the level of the human brain." De Boer explained that in 2010, the error rate for computerized speech recognition systems was 27%, versus only 5% for humans. Three years later, the error rate for computers had dropped to 20%. By 2015, the rate was down to less than 6%, nearly matching that of humans. When it comes to image recognition, the advancement has been even more rapid. While the human error rate has held steady at 5%, the error rate for computerized systems has dropped quickly, from 28% in 2010, to 11% in 2013, to less than 5% in 2015—actually surpassing human performance.

Talking with *Pharmaceutical Engineering*, however, de Boer noted the difference between the existing potential for automation in manufacturing and how little has actually been realized. To explain the gap between the exponential growth in computing power and the more incremental growth we've seen in robotic systems, he offered this insight: "Moore's Law applies to computer power, but robotics are much more physical systems. I'm still bullish on how robotics and automation will grow; the business case is sound. Up to 60% of tasks in manufacturing today can be automated. We have automated only a small fraction of that. There will be a race to close that gap."

That race may be played out on an innovation superhighway, according to de Boer—a technology infrastructure "autobahn" that is ready to be traveled at remarkable speeds. The obstacles to realizing this potential aren't a matter of physical or computing infrastructure; rather, they lie with "people and systems." The figurative autobahn is there, he explained. Manufacturers just need to learn to drive on it.

PILOT PURGATORY

Unfortunately, de Boer continued, "the majority of companies are in 'pilot purgatory,'" a concept detailed in "The Next Economic Growth Engine: Scaling Fourth Industrial Revolution Technologies in Production," a January 2018 World Economic Forum white paper[4] he coauthored with Helena Leurent, a member of the World Economic Forum's executive committee. In that report, the authors present challenges to adoption of technology, focusing on matters of "people and systems" as well as issues such as "lack of knowledge," "lack of trust in scalability," and "lack of leadership support." The list is conspicuously devoid of problems related to any lack of available technology infrastructure, de Boer confirmed.

And so the problem isn't that the potential isn't there, de Boer said—it's that companies get hamstrung in the pilot phase and struggle to scale. "If you stay incremental, you'll never get exponential growth. To get to Moore's Law, you need to put the right scale-up engine behind it—scalable in terms of your data models. You need a scalable analytics model, a scalable people model—then you literally have the autobahn. Keep in mind this is the Fourth Industrial Revolution. It's really about change management."

DEEP LEARNING

"Deep learning" is another broad technological breakthrough that started with machine learning in the mid-20th century. But deep learning is something radically different, said de Boer. "It involves learning based on pattern recognition rather than task-specific algorithms. With that, you train the model. The more data the model looks at, the more accurate the data; the more data the models ingest, the more they drive up accuracy. Keeping in mind that 90% of all data has been generated since 2015, it becomes clear why machine learning algorithms have become so much better." Given this training, the algorithms actually improve themselves over time—assuming they have a steady stream of sufficient data. "That's why it's so interesting in manufacturing," he added. "In terms of sectors, manufacturing is sitting on the biggest amount of data."

Rapid as it may be, this processing power can't come soon enough. Humanity has amassed a mind-boggling quantity of stored digital data, and the cloud is growing at a blistering rate. According to the Cisco Global Cloud Index,[5] "globally, the data stored in data centers will nearly quintuple by 2021" from 2016 levels.

De Boer's keynote presentation emphasized the disparity between the vast (and growing) accumulations of production data and the tiny percentage used effectively in decision-making. Using an offshore oil rig example to illustrate this gap, he explained that of all the data captured by the rig's various systems, only 40% is stored using storage infrastructure. Certainly, that's a rapid drop-off, but the plunge is even more precipitous considering his explanation that only 1% of the data is streamed onshore through data management. Thus, only approximately 1% is monitored post hoc in the form of key performance indicators, and even less is sent back to the rig in the form of analytical insights. So how much is that, ultimately? "It's one-half of 1% of all data that's really helpful," de Boer emphasized in his follow-up interview. "That will change dramatically with artificial intelligence."

Future factory workers will focus on creative problem solving, data evaluation, and planning, rather than routine, unsafe tasks. *(Photo courtesy McKinsey & Co.)*

Augmented reality helps operators view instructions, safety information, and data in real time. *(Photo courtesy McKinsey & Co.)*

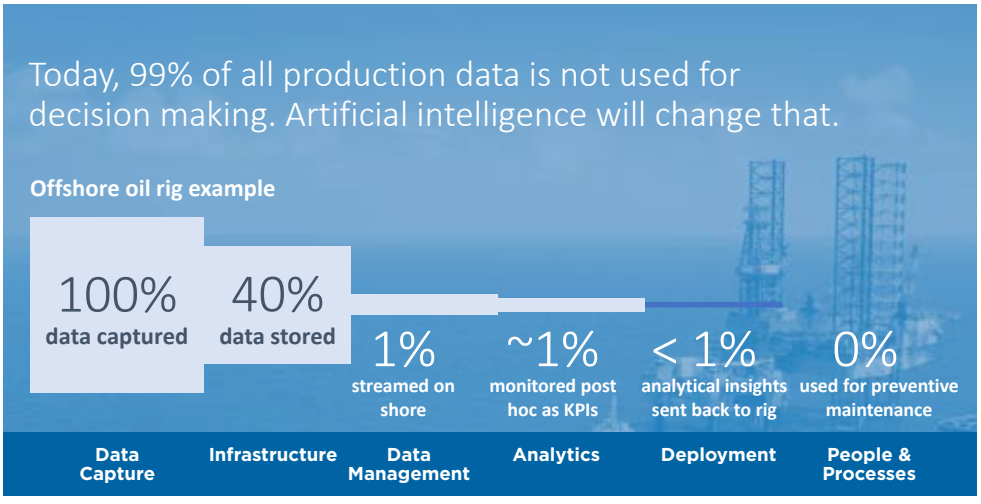
THE ROBOTS ARE COMING

All signs point to a paradigm shift in manufacturing. De Boer explained that more than half (51%) of all tasks globally can now be automated, and in the manufacturing sector the figure is higher, at 60%. To illustrate just how well the stage is set for robotic automation, de Boer offered a breakdown of how time is spent on various aspects of the manufacturing process, and then indicated to what degree each could be automated using current technology.

His numbers, drawn from a McKinsey Global Institute Analysis, are striking. "Predictable physical" tasks comprise 34% of the manufacturing process, and de Boer stated that fully 87% of those tasks could be automated with today's technology. Nearly 78% of data collection, which represents 22% of the manufacturing process, could be automated; likewise, 60% of data-processing tasks, which comprise 11% of the manufacturing process, could be automated. Of course, some elements are less adaptable: managerial aspects, expertise, interface, and unpredictable physical applications will see less automation. Nonetheless, the aggregated data suggest that more than half of the entire manufacturing process—fully 60%—could be automated now, according to de Boer. And that's just based on current technology, which means, for all the reasons laid out above, that those potentialities will continue to increase—likely exponentially. The good news is that only 1% of all jobs can be *fully* automated, while the majority of today's jobs will be augmented by automation.

Despite this substantial potential for automation, industrial robots currently have a surprisingly low penetration rate—less than 5%—in global manufacturing. According to the same aggregated data, only 180 industrial robots are at work per 10,000 manufacturing workers in the United States. That figure nearly doubles in Germany and Japan, where the ratio is 300 robots per 10,000 workers; in South Korea, it's nearly triple—over 600 industrial robots for every 10,000. Given the anticipated rapidity of technological

ONLY ONE-HALF OF 1% OF ALL DATA IS HELPFUL



Enno de Boer speaks at the ISPE 2017 Annual Meeting, San Diego, California

Source: McKinsey Global Institute. Reprinted with permission.

development, it stands to reason that these numbers will increase quickly.

This won't come without consequence, of course, and it's important to consider the potential difficulties inherent in this adaptation process. In a LinkedIn piece titled "How Technology Can Unlock Manufacturing's Potential and $3.7 Trillion in Global GDP,"[6] de Boer offered perspective on some inevitable effects of automation: "Let's be frank: Turning factories into high-tech platforms will displace a significant number of workers. We cannot ignore the social and humanitarian consequences of automation. Governments, businesses, and civil society must take the lead in easing the transitions of workers by upholding social compacts and equipping current and future workers with the training and education they need. All sectors will have to reinvest in local economies and in new areas of growth."

THE ROAD AHEAD

So where is manufacturing headed? "The future of manufacturing will be fundamentally different from what we have today. At the core we will have autonomous manufacturing—similar to autonomous or self-driving cars: a manufacturing shop floor that is self-organizing, self-optimizing, and self-healing. We will see the convergence of products and services. New value-added services and business models will be enabled," said de Boer.

Some of the technologies that have become highly relevant for making manufacturing autonomous are already in use and have matured at scale in cars, he noted.

It is interesting to see how cars have become more and more autonomous over time. Early in the millennium (c. 2005), the automotive industry started introducing "assist systems" using technologies such as GPS/location services, sensors, video recognition, and connected control systems. By 2015, "automation" functionality was introduced, leveraging 4K video, pattern-recognition machine learning, predictive algorithms, augmented reality (AR) displays, and IoT-based vehicle-to-vehicle communication. The next phase, which started with semi-autonomous cars and is currently moving toward fully autonomous cars, involves big-data analytics, deep-learning algorithms, and vision systems that have been further improved.

How will this Fourth Industrial Revolution play out? According to de Boer, the innovation will be realized through a series of paradigm shifts, each interwoven with the others amid an interplay of digital systems. With regard to manufacturing, he explained that technology will transform the future of production through four shifts:

1. Autonomous manufacturing, embedded into an ...
2. End-to-end value chain, embedded into a ...
3. Supplier ecosystem, which enables ...
4. Value-added services and business-model innovations.

The key to this evolution, then, lies in the development of autonomous manufacturing. According to de Boer, this involves an interplay of connectivity, intelligence, and flexible automation.

NEW INTELLIGENCE LANDSCAPE

Connectivity will enable a new level of performance management and radically more efficient assembly operations. Through AR-guided assembly operations and real-time IoT-based performance management, manufacturing systems will see massively enhanced scale and speed. To illustrate this, de Boer offered data from successful deployments of intelligent factory systems: While the current performance-management systems enable the capture of one billion data points per day, fewer than 1% are able to be analyzed. By contrast, with real-time IoT-based performance management in place, systems can capture 10 billion data points daily, with the capacity to analyze 100% of it. Likewise, in terms of speed, data accessibility in current systems is measured in hours and days, whereas IoT-based functionality will measure this accessibility in minutes and seconds.

This connectivity will enable a new intelligence landscape, enabling predictive forecasting and digital supplier collaboration. Considering the immediacy of the "digital thread" that connects all aspects of the manufacturing process—from suppliers through manufacturing to dealers and on to customers—real-time analytics will transform any number of industries and provide notable benefits. Among these are reduced inventory and lead

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time at all steps, improved production planning (one example yielded a 33% better forecast accuracy), and step-change improvement in collaboration. All of this, according to de Boer, will significantly increase customer satisfaction.

Ultimately, manufacturing will exist in a radically transformed end-to-end value chain, in which real-time data access enables intelligent, responsive performance management with substantially reduced waste and highly improved efficiencies. "Ecosystem" is an apt description for the potential reality de Boer describes: an interwoven, interdependent, highly evolved environment wherein each element of the end-to-end chain is connected efficiently and thus able to respond to changes organically and in real time. "This is where the value creation is happening," de Boer said. "And how will we get there? The same way as the automotive industry. We have identified 40 digital applications that are ready for deployment. These are the stepping stones toward an autonomous production system."

This reality is already emerging, and de Boer referenced two unnamed electronics manufacturers to illustrate the impact of these systems. One of these companies, located in China, saw issue resolution go from weeks and months to hours upon deployment of real-time IoT-based performance management. The other company, by implementing an almost fully automated assembly line, has realized a 200% increase in output and a 50% reduction in quality issues. With these improvements also came the ability to move production nearer to the consumer.

RADICAL SYSTEM REDESIGN

Of course, while this Fourth Industrial Revolution is rooted in technological innovation, its implementation hinges on human leadership. Commitment to organizational change is an altogether human enterprise and requires a purposeful and collaborative effort from industry leaders and workers alike, from senior management to the shop floor. "It's very important to not just exchange technology, but radically redesign the system," commented de Boer. Achieving this "digital transformation" requires an intentional approach, which McKinsey has developed in collaboration with the World Economic Forum. Steps include:

1. Mobilizing the organization
2. Strategizing—setting the vision
3. Sparking innovation by demonstrating the value
4. Scaling up to achieve a full-value capture

Considering the rapid pace of technological development, time is of the essence. Organizations must respond to this changing landscape, de Boer added. "Technology fusion must happen quickly."

To facilitate this, a great deal of learning is required. "For this we need training," he continued. "Over the last 12 months we have invested heavily in setting up capability centers—smart model factories that allow you to jump into a manufacturing environment." He described the five newly opened McKinsey Digital Capability Centers, which, like the one in Chicago operated in collaboration with the Digital Manufacturing and Design Innovation Institute, offer "digital immersion workshops." The workshops enable participants to explore experiential learning modules based on the production line. Meanwhile, they empower organizations with access to "an ecosystem of 50-plus technology partners, providing innovating solutions across the value chain." In addition, the McKinsey "digital blueprint"[7] helps management understand how to start, scale, and sustain the digital journey.

PREPARING FOR THE FUTURE

While de Boer's keynote presentation addressed digital technology across the manufacturing spectrum, he shared insights on the unique context of the pharmaceutical industry during our conversation. A significant factor at work in pharmaceuticals, he said, is the degree to which innovation needs to go hand in hand with regulatory compliance. Therefore, he noted, "It's important to work in consortiums like [ISPE] to determine what you want to change in the processes and bring the regulators along with you. The disruption will happen—probably from the outside. So you have to be prepared for the future."

Explaining further, de Boer stressed that for innovation to proceed optimally, manufacturers and regulators must "travel together on the innovation journey." A partnership approach will facilitate travel on that figurative autobahn. "Technology will only unfold if we innovate the processes. We need collaboration. It's not one or the other." Referring to the interest in innovation that he's seen among regulatory bodies, de Boer claimed, "Actually, regulators are for innovation. I see a lot of willingness on all sides of the table."

Digital innovation is constantly accelerating. We need only consider the fascinating technologies at work in our lives today on even the most pedestrian level—smart speakers and appliances, predictive advertising, voice recognition, intelligent and integrated navigation services, mobile boarding passes, and digital wallets. These are realities we now take for granted, and it's easy to forget that they weren't widely available—or, in some cases, available at all—just a few years ago. This same dynamic evolution is at work in the industrial sector, and if de Boer's vision of the Fourth Industrial Revolution plays out as he's described, the future of manufacturing is upon us.

As we concluded our interview, de Boer reiterated his enthusiasm about the near future of manufacturing: "I think the one thing I would really like to emphasize is this 'facility of the future,' which is an exciting workplace. There is a new workforce coming in, and we can make the work in the factories very attractive. Where else in the world will all these systems come together to drive change? We need to—and we will be able to—attract the best and the brightest of the next generation."

While de Boer's vision certainly implies new challenges for the pharmaceutical industry, it also points to potentially groundbreaking levels of efficiency and innovation. Ultimately, we can hope, this evolution in manufacturing will yield radical advances that benefit both patients and workers. ‹›

—Paul J. Cumbo, MLitt, MS

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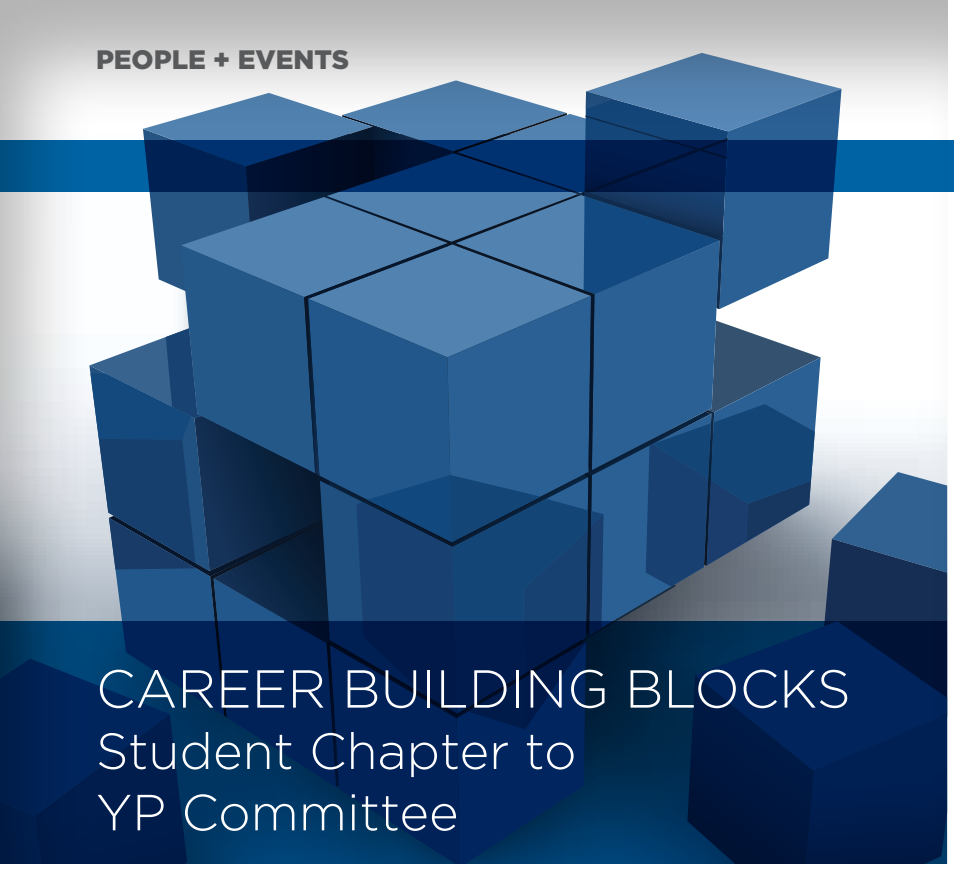

CAREER BUILDING BLOCKS Student Chapter to YP Committee

Also in this section

Some people are born leaders. They take initiative, become pioneers, start new groups, and develop new ways of doing things, all while motivating others along the way. Young professional Evan Siebenmorgen certainly appears to be one of them. At age 24, Siebenmorgen has jump-started an ISPE student chapter at his alma mater, and has recently became the youngest ever Board member of ISPE's Rocky Mountain Chapter. These successes are in addition to a myriad of other accomplishments centered around his personal mission of positively impacting as many people as possible.

Born and raised on a cattle farm in the small town of Scranton, Arkansas, Siebenmorgen knew from a young age that he had an interest in medicine and pharmaceuticals. "Having family in the medical field and with my mother being a biology and chemistry teacher, I was always curious how the medical world worked" he said. "Growing up on a farm definitely fed this curiosity. Constantly working on equipment and solving complex problems with my father created an internal problem-solving attitude. I have always had an interest in the mechanical side of things, and through a conversation with my aunt, I found I could merge the two together through biomedical engineering."

SERENDIPITY HAPPENS

Siebenmorgen moved to Colorado in 2011 to study at Colorado State University (CSU), where he pursued a dual degree in biomedical and mechanical engineering. During his sophomore year, he met ISPE Rocky Mountain member Deanna Scott. "Deanna introduced me to ISPE and approached me to help run a CSU student chapter," he said. "I relaunched the chapter, because all of the student members had graduated the year before. I literally started with nothing and built the chapter back up. By the end of my presidency, we had around 30 student members."

During his later years at CSU, he pursued internships at medical device company Medtronic, and so Siebenmorgen became less involved in ISPE. He graduated from CSU in 2016 and began working full time as an associate technical services specialist at Medtronic. It was not too long before a voice from his ISPE past came calling.

"Aside from Deanna Scott, Paul Trunzo was one of my first contacts within ISPE, and he has mentored me throughout," said Siebenmorgen. Trunzo, a past president of the Rocky Mountain Chapter, approached Siebenmorgen to join him at Tru-Flow, a manufacturer's representative and distributor for the biotech and pharmaceutical industries in the Midwest and Rocky Mountain regions. Siebenmorgen joined the team in March 2017 as a sales engineer.

"I like the communications perspective of sales," he says. "Being able to communicate about very technical pieces and equipment and finding ways that equipment can be used to make the pharmaceutical industry more efficient is a passion. One day I may be working with animal health products, the next day I'm working with a new cancer treatment, and the next day I'm working with diabetes and insulin products. It's great to have a hand in all these amazing technologies and to play a direct role with how they're manufactured. That's the exciting part for me in this job and how I feel that I can give back to others in the world."

The Tru-Flow position also led him back to ISPE. He has become active in the Rocky Mountain Chapter and is currently starting the Chapter's Young Professionals committee. In January 2018, he also became the youngest member of the Rocky Mountain Chapter, taking over Deanna Scott's seat. "It is very serendipitous how it has come full circle," he says. "She is the one who introduced me to ISPE, and now I am taking her spot on the board."

SERVANT LEADERSHIP

A recurring theme throughout Siebenmorgen's education and his young

career so far has been pioneering. His class was the first to graduate from CSU with the ABET-accredited BSc biomedical engineering and BSc mechanical engineering dual degrees. He was a founding member of the Phi Kappa Theta Fraternity at CSU and relaunched the ISPE Student Chapter at the university. His role at the Rocky Mountain Chapter involves starting and chairing the Young Professionals committee, and his job at Tru-Flow is building a sales team for the organization.

"I love the feeling of starting things up and bringing others to organizations," he said. "In my day-to-day life, I'm always looking for ways to grow and to help others grow as well. Servant leadership is something that I learned through my faith, family, and fraternity. Our fraternity's motto from St. Thomas Aquinas is 'Give, expecting nothing thereof.' This has always stuck with me. I want to be able to give to others when I meet them, and hopefully, they're a better person by the end of our meetings or experiences."

Siebenmorgen was recently married and currently lives close to Denver, Colorado, with his wife. They enjoy hunting, fishing, and home renovation projects, but most of all, any activity that gets them outdoors to appreciate the Rocky Mountains. ‹›

—Mike McGrath

Student Chapter to Chapter President

Wendy Haines, PhD, ASQ, CQA

My road to becoming an ISPE chapter president started by joining a student chapter. In 1995, ISPE's Carolina–South Atlantic (CaSA) Chapter started student chapters at Campbell University and North Carolina State University (NCSU). These universities were perfect for new ISPE student chapters. Campbell had started a new pharmaceutical sciences degree program with instructors from the pharmaceutical/biotechnology industry. NCSU had an engineering program and many CaSA alumni.

I was a member of the charter class of the pharmaceutical sciences program at Campbell and was vice president of the ISPE Student Chapter during my last two years there. I liked attending our student chapter education events, but the tours of pharmaceutical/biotech companies were my favorite events. We were able to see "up close and personal"

I FEEL BLESSED TO BE A PART OF AN INDUSTRY THAT PRODUCES LIFESAVING MEDICINE FOR PATIENTS.

what each site did and speak with people who had different roles and responsibilities. Through attending educational sessions, I met people in our industry who I still know today.

After graduation, I worked on the genome project of the US Environmental Protection Agency (EPA) and the National Institute of Environmental Health Sciences, part of the National Institutes of Health. I thought it was important to stay involved in ISPE to continue learning more about the pharmaceutical/biotech industry and to maintain my network. I decided to pursue a PhD in toxicology at the University of North Carolina, Chapel Hill (UNC-CH) and conducted my research at the EPA. UNC-CH didn't have an ISPE chapter, although I knew a lot of scientific PhD students wanted careers in our industry.

COMMITTEES AND CONNECTIONS

With the help of Jane Brown, we started one of the first ISPE student chapters with PhD candidates at UNC-CH. We had typical student chapter events, including speakers and tours. One of our largest events focused on resume writing and interviewing techniques. We partnered with several other on-campus organizations to bring in human resource representatives and hiring managers from small and large pharmaceutical/biotech companies. The most helpful part of the event involved students being interviewed on stage with a critique from the panel of HR and hiring professionals.

While I was a student in 1999, I entered the student poster competition that ISPE started that year. Chapters conducted local poster competitions and the winners competed at the first International Student Poster competition at the ISPE Annual Meeting in 2000. I competed with about 15 other students from our chapter. The winner was one of my classmates in the PhD toxicology program, who went on to win the International Poster competition. I reentered the next year and won in both the local and international competition in 2001 at the Annual Meeting in Las Vegas—the first one I'd ever attended.

After 2001, I attended several ISPE Annual Meetings as a student, where I continued to expand my network and learn more about our industry. Since I had attended the Annual Meeting and was on my local student board, I asked if I could be on the Student Development Task Team (which later became the International YP Committee). I believe that I was the first student on this international group, which was named Best Committee/Task Team in 2002. I stayed active on the International Student Committee for many years, and later chaired the International Young Professionals (YP) Committee, which comprises both YPs and students. I later joined the *Pharmaceutical Engineering* Committee because of my interest in writing and editing.

FEELING OF FAMILY

As a student, one of the things that I loved about ISPE was its feeling of family. People were so willing to speak to me and answer my questions about our industry. I felt that they really cared and wanted to get to know me even as a student; this was not the feeling that I had gotten with other professional societies. Because of this family feel and the knowledge that I gained, I continued to be involved in my local chapter. While I was earning my postdoctoral degree, I served as co-chair for the Student Affairs Committee and became the chair of that committee for two years.

I was hired by a past president of the CaSA Chapter for a position at a small environmental firm. I also started teaching anatomy/physiology labs and became a lecturer at a community college. Later, I became a study director and research toxicologist at a contract laboratory organization with biotech and federal clients.

At the ISPE Annual Meeting in 2012, I reconnected with Bruce Craven, who had been the industry advisor to our Clemson University student chapter when I was the CaSA Student Affairs chair. I went to work for Bruce at Mangan Biopharm conducting computer-system validations. I also started a toxicological assessment service for clients, which involved literature review, risk assessment, and calculations to assist with cleaning validation and protect worker safety.

MOVING ON UP

For the CaSA Chapter, I later became an at-large board member and then the chair of the Communication/Newsletter committee. I was asked to join the executive board as secretary in 2014. (CaSA rotates executive board positions so that each member serves all five positions from Secretary to Past President.) I am serving as President of the CaSA Chapter this year. I'm now the Associate Director of Technical and Scientific Services for PharmEng and Bruce Craven is my boss. My focus is on toxicological assessments and bringing in new clients.

I have attended the Joint Affiliate Council (JAC) and NASAC meetings at the ISPE Annual Meeting for several years. Chapter and affiliate leaders meet at these events to discuss what is working and what needs to improve for our members. It is a great way to learn and help others for ISPE.

My career and leadership skills have been enhanced by my involvement with ISPE. I have learned so much from the leadership opportunities that I have been given and my involvement in the organization. I truly feel that the connections that I have made are like an extended family—people who are there for me and will be there for me if I need anything. I have also learned so much about our industry and all the different facets it takes to get a drug to market that impact lives. At the end of the day, I feel blessed to be a part of an industry that produces lifesaving medicine for patients. ‹›

Wendy Haines, PhD, is Associate Director of Technical & Scientific Services at PharmEng Technology. She has over 20 years of experience in research and the biopharmaceutical industry. She has been an ISPE member since 1996.

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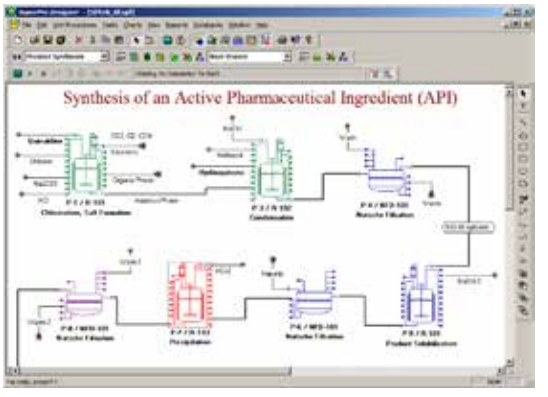
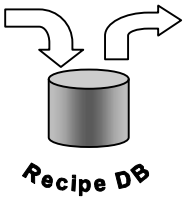
The Market-Leading Engineering Suite for Modeling, Evaluation, Scheduling, and Debottlenecking of Multi-Product Facilities

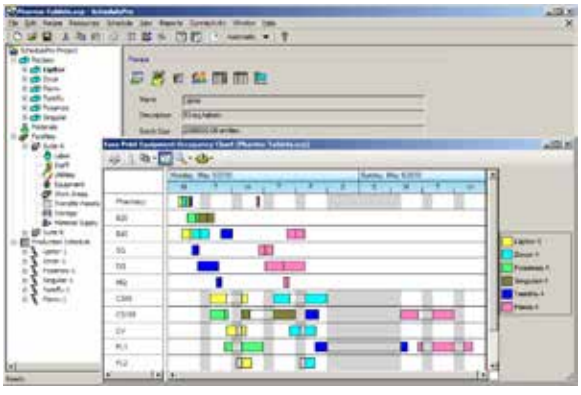
SuperPro®



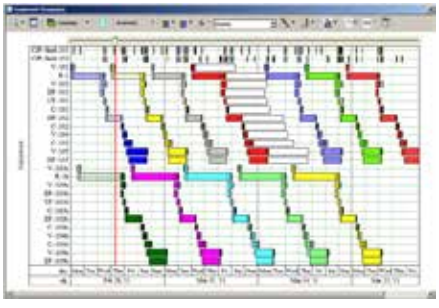
Use SuperPro Designer to model, evaluate, and optimize batch and continuous processes



SchedulePro®

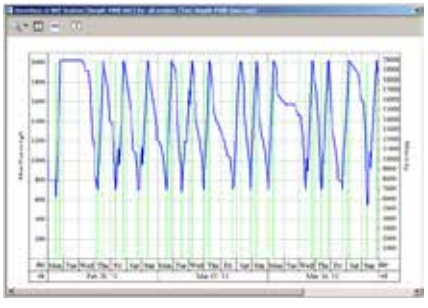


Migrate to SchedulePro to model, schedule, and debottleneck multi-product facilities



Easy production tracking, conflict resolution and rescheduling

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



Managing inventories for input, intermediate, and output materials

SuperPro Designer is a comprehensive process simulator that facilitates modeling, cost analysis, debottlenecking, cycle time reduction, and environmental impact assessment of integrated biochemical, bio-fuel, fine chemical, pharmaceutical (bulk & fine), food, consumer product, mineral processing, water purification, wastewater treatment, and related processes. Its development was initiated at the Massachusetts Institute of Technology (MIT). SuperPro is already in use at more than 500 companies and 900 universities around the globe (including 18 of the top 20 pharmaceutical companies and 9 of the top 10 biopharmaceutical companies).

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

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BLOCKCHAIN: THE NEXT BIG DISRUPTOR IN CLINICAL TRIALS?

Sujay Jadhav

The digital revolution is driving change across all industries. With its ability to increase transparency and trust between parties, the recent innovation called blockchain has the potential to significantly disrupt the clinical trials industry.

Blockchain was invented in 2008 with the creation of the cryptocurrency known as bitcoin.[1] Finance was the first sector to utilize this new technology, which helped foster trust and transparency in financial transactions.

As blockchain technology has steadily matured, its potential to reduce costs, increase efficiency, and improve trust have made it attractive to other industries as well: A recent study from IBM, for example, revealed that 16% of health care executives had solid plans to implement a commercial blockchain solution this year, while 56% expected to do so by 2020.[2]

BLOCKCHAIN TECHNOLOGY, DEFINED

Blockchain technology uses a distributed computer network to create a digital ledger or database that stores time-stamped transaction records. Each server or node in the network verifies each data entry, and every node archives all transactions that have been recorded to the network.

Transaction data stored in a blockchain cannot be stolen or hacked, since it is not kept in a central repository; the data is distributed across dozens or even thousands of geographically dispersed nodes. The distributed nature of the network, time-stamped records, and verification requirements ensure that the stored data remains intact and immutable, since it is write once and read only.

By utilizing established cryptographic techniques to allow "trustless" peer-to-peer interactions between network participants, blockchain enables effective collaboration and an immutable audit trail. Participants can store, exchange, and view information in the database without the need for preexisting trust between parties. In fact, trust is coded into the blockchain protocol via a complex cryptographic algorithm. Rather than relying on a centralized, trusted third party to facilitate transactions, blockchain technology effectively eliminates the need for the "middleman," thereby reducing costs.

Blockchain is not a substitute for an enterprise database that is optimized for high-volume data and instantaneous access within a single organization. Instead, blockchain solutions are ideal for data records that are meant to be shared across a network of partners where transparency and collaboration are important.

BLOCKCHAIN TECHNOLOGY IN CLINICAL TRIALS

Researchers face numerous challenges concerning trust and transparency in clinical data. The enormous amounts of data generated in clinical trials, along with trends toward globalization and increasing regulatory constraints, are outstripping the ability of legacy data-management platforms to manage the competing needs of data sharing, patient privacy, and data integrity. The dearth of platforms that are both secure and transparent enough for effective, trustworthy data distribution is having detrimental effects on many aspects of clinical research.

Reproducibility, regulatory approval, data integrity, data sharing, privacy concerns, and patient enrollment are significant challenges for modern clinical trials. How could blockchain technologies help?

Patient recruitment

The traditional method of recruiting patients at investigative sites is less than ideal. Some estimates calculate that patient enrollment takes up 30% of the time required to conduct a clinical trial, with some sites never enrolling even a single patient.[3] Blockchain databases have the potential to dramatically improve the recruitment process. A blockchain-enabled solution could share patient information with pharmaceutical or contract research organizations (CROs) without divulging the patient's identity; this could provide more information about potential participants who are likely to be motivated to join a study.[4]

Medical data sharing and privacy

Unfortunately, most clinical trials results are not reported, and investigators often do not share their study results.[5] In fact, around 90% of trials on ClinicalTrials.gov currently lack results.[6] This creates knowledge gaps for researchers and safety issues for patients. Blockchain technology could create a secure tracking system for any data generated from patient-physician interactions. Blockchain anonymity allows electronic health record (EHR) data to be stored

BLOCKCHAIN IS IDEAL FOR DATA RECORDS THAT ARE SHARED ACROSS A NETWORK WHERE TRANSPARENCY AND COLLABORATION ARE IMPORTANT

and shared transparently, yet still maintain patient privacy. This could free enormous amounts of data for clinical research, and open clinical trials to secondary or meta-analysis.[7]

Data integrity

Good quality data from clinical trials requires security, proper content (metadata), and an immutable audit trail. Blockchain data integrity is ensured by cryptographic validation of each interaction or transaction. When there is a data integrity issue in a blockchain, it is possible to immediately identify where and when the problem happened, along with the last person to touch the data. These immutable, time-stamped records could reduce fraud and error in clinical trial records by eliminating the potential for outcome switching, selective reporting, and data snooping.

Protocol and traceability of consent

In clinical research, tracking patient consent for the approved protocol (including revisions) is an important aspect of good clinical practice compliance. According to the US Food and Drug Administration (FDA), nearly 10% of studies have issues related to patient consent, including unapproved forms, failure to obtain written informed consent, invalid consent documents, and failures to obtain reconsent to a revised protocol.[8]

In a recent proof-of-concept study,[4,9] researchers from the University of Paris and Columbia University applied cryptographic validation to transactions related to patient consent and the clinical research protocol for a fake experimental study. Each patient consent was time-stamped on the blockchain, as were consent renewals for protocol revisions. The resulting master data collection traced each consent to a version of the revised protocol. The result was a cryptographic representation of the real consent and protocol document data that can be verified on the web.

Blockchain as a service

Organizations looking to utilize blockchain technology to record, track, and share clinical data securely must first decide how to build the application. Public blockchains have thousands of computer nodes distributed randomly worldwide to verify and archive the records. Private blockchains distribute nodes only among stakeholders, who can then access the data-management solution that is built on the network.

To reduce the time and cost associated with building a private blockchain network, consortia are working to develop and adapt blockchain technologies for health care. One such group, Hashed Health (a collection of health care companies) provides value-added technology support services for blockchain solutions.[10]

Other companies have created private blockchains that are anchored to a public blockchain. Tierion, for example, has created an application programming interface that anchors data to the bitcoin public blockchain and provides a cryptographically verifiable audit trail for each record. This technology provides seamless data and process tracking.[11–12]

DELIVERING TRANSPARENCY WITH PRIVACY

From a global perspective, applying blockchain technologies to clinical research has wide-ranging promise and promotes data integrity while increasing the availability of granular patient information. Health care companies and regulatory agencies alike are excited about these new possibilities; both the FDA and Centers for Disease Control have announced partnerships with IBM to pilot blockchain technology for patient data exchange and medical data management solutions.[13–14] Ultimately, blockchain technologies offer the possibility to not only further clinical research, but to improve patient safety while bolstering data privacy. ‹›

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DIGITAL LABELS REVOLUTIONIZE IMPs

Labeling is an important part of the supply chain. This is especially true for investigational medicinal products (IMPs), which must be labeled with clear expiry dates and other mandated information. IMP shelf life is notoriously difficult to quantify, however, and new findings on their stability frequently emerge during clinical trials. This often requires companies to relabel IMPs with revised expiry dates and other information. It's an expensive and time-consuming process that affects the entire supply chain.

"Whenever stability data change, we typically initiate a relabeling process where IMPs receive new labels that carry revised expiry dates," Rocco Barone, Associate Director, Operations, at Merck & Co., Inc., told *Pharmaceutical Engineering.* "Relabeling takes time and can lead to supply chain delays and budget extensions. IMPs may need to be shipped from the trial site to the depot, where they are relabeled, before being returned to the site. The complete relabeling process not only means time and cost. Compliance requirements for manual relabeling are also high," he said.

According to a study conducted by the Tufts Center for the Study of Drug Development, the US Food and Drug Administration (FDA) approved 225 new biopharmaceutical products from 2006 through 2016, accounting for 35% of all new drug approvals during that period. And the pace is increasing: The FDA approved 13 new biotech products annually during the first eight years of the study, but that figure climbed to more than 20 per year between 2014 and 2016, with a market value of $68 billion in the final year.

It's no surprise that the share of biopharmaceutical IMPs in clinical trials is rising steadily. Over the next two decades, 70% of traditional medications will be replaced with biopharmaceuticals, making IMP labeling methods critical to their predicted growth. "Biopharmaceuticals are complicated and expensive to manufacture," Barone noted. "In addition, their stability data are often so limited that it is sometimes impossible to conduct any trial at all."

PAPER LABELS, MANUAL UPDATES

While smart labels with radio frequency identification (RFID) tags have become a fixture in pharmaceutical manufacturing, the IMP labels used in clinical trials have not been able to adopt the technology as readily. As clinical trials become more complex and costly, however, finding ways to be make IMP materials more efficient and cost effective is imperative.

Traditional paper IMP labels, for example, must include multiple regulatory elements. To meet these requirements and fit the information into the small space available (on a syringe or vial, for example), providers are often forced to resort to very small, nearly illegible font sizes. And when expiry data change—an especially frequent occurrence with biopharmaceuticals—each package must be manually relabeled, a costly and time-consuming process.

"The current method for updating reevaluation dates on clinical labels involves a manual process that leads to inefficient use of resources and capacity, with long cycle times," Barone told attendees at the ISPE 2017 Annual Meeting & Expo in San Diego, California. "Total time is approximately three to five weeks."

Digital technology, however, is helping clinical trials find new ways to incorporate faster and lower-cost labeling options for IMPs. Electronic labels (e-labels) can contain a regulatory-compliant IMP label, and they may also decrease or even eliminate deviations caused by extension relabeling, sterility breaches, tamper-evident seal removal, product mix-up, and temperature excursions. In addition, IMP changes that affect label content can be communicated quickly.

THE EVOLUTION OF SMART LABELS

Unlikely as it may seem, the first e-label was patented in 1952. While functional, it remained too expensive for large-scale implementation for over 20 years. IBM adapted the technology in 1973, and the result was the ubiquitous one-dimensional bar code we now know as the Universal Product Code, or UPC (Figure 1). By 1980, the symbols and their scanning systems were being adopted by 8,000 stores per year.

FIGURE 1: A ONE-DIMENSIONAL BAR CODE.

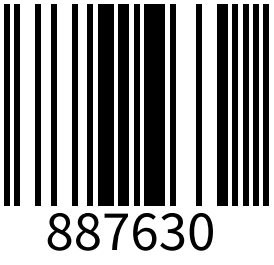

FIGURE 2: QR CODE, A KIND OF 2D BAR CODE.

FIGURE 3: MED LABEL ON AN IMP CONTAINER.

Source: Faubel press photo

DIGITAL TECHNOLOGY IS HELPING CLINICAL TRIALS FIND NEW WAYS TO INCORPORATE FASTER AND LOWER-COST LABELING OPTIONS FOR IMPS

Since their debut in grocery stores, bar codes have found a broad range of uses in the pharmaceutical industry, including drug manufacturing, security, identification, traceability, and expiry information.

Two-dimensional (2D) bar codes were introduced in 1990. These images, which hold significantly more information than their one-dimensional predecessors, can be read vertically and horizontally (Figure 2). They are used on primary and secondary pharmaceutical packaging as part of global serialization initiatives and other health authority guidances. Since January 2011, for example, 2D data matrix codes have been part of European pharmaceutical regulatory mandates.

By the mid-2010s, "smart labels" included RFID technology. RFID tags can hold significantly more information than standard bar codes and can be read inside or outside of the package. Within a year, near-field communication (NFC) labels carried even more information than a 2D bar code and could be read on a smartphone or tablet.

E-PAPER LABEL SYSTEM

Merck & Co., Inc., in partnership with Faubel & Co. Nachf. GmbH, have co-developed Med Label, a semi-electronic label system that replaces the manual IMP label updating process with a time-saving, cost-effective alternative (Figure 3).

Software reads an RFID tag attached to a standard IMP booklet label. Each RFID tag contains a transponder (a microchip with an antenna or coil), an analog circuit for receiving and transmitting (transceiver), a digital circuit,

* E-paper devices have easy-to-read displays that reflect light to simulate the appearance of natural ink on paper. They consume just 1% of the power required for an LCD display and can be read in direct sunlight.

RFID TAGS CAN HOLD SIGNIFICANTLY MORE INFORMATION THAN STANDARD BAR CODES AND CAN BE READ INSIDE OR OUTSIDE OF THE PACKAGE

and a permanent memory. Since RFID tags cannot display information, smart labels are equipped with battery-free e-paper* displays linked to the tags. If the transponder is within range of a reader, connection is triggered through electromagnetic induction. Each RFID tag also carries a unique identification number (UID).

RFID UID and GPS location data can be combined to monitor labeled packages across the entire value chain (track and trace). "This kind of monitoring is the key to seamless traceability in clinical trials," Barone noted. "It also helps control material and product flows in inventory management."

US PILOT

To evaluate the technology and eliminate regulatory conflicts, Merck conducted US-only trials in September 2016. (The United States does not require reevaluation dates on labels.) Demonstration videos and user manuals helped the studies run smoothly.

"There are a few pharma companies working on these smart technologies in clinical trials," Meinrad Kopp, Head External Networks Management, Merck, told *Clinical Trials Arena* in June 2016. "However, I [have] yet to see a company that has run a larger trial with such smart technology for their patients."

In the trial, each container received a fully compliant paper label plus a Med Label. Merck then ran two extension updates: one within Merck and one at a clinical trial site.

"Compared to conventional relabeling, which often takes months, the label can cut updating time to just one day if everything is well thought through," Barone explained to *Pharmaceutical Engineering*. "By eliminating a whole range of work steps, such as filling out documentation by hand, daily work went faster without jeopardizing the quality of work in any way."

Participants completed and returned questionnaires at the end of studies. Results were positive and contained few suggestions for improvement. Following these successful tests, Faubel launched Med Label in 2017.

In an April 2018 press release, Konrad Zachman, Head of Production for New Technologies at Faubel, said that the label "… is a breakthrough product that makes the handling of investigational medicinal products in clinical trial supply chains so much easier."

ADVANTAGES

Temperature

For many cold-chain IMPs, temperature fluctuations of 2°–8°C can cause quality problems, as can high temperature and humidity levels in the supply chain. Smart labels with integrated RFID temperature sensors can withstand a wide range of temperatures. The update device is rated to –5°C, and the e-paper display can function at –20°C. Depending on the requirements, booklet labels can be made of special paper, foil, adhesives, and inks for temperature and moisture resistance.

Regulatory compliance

Neither the EU guidelines nor the US Code of Federal Regulations Title 21 state that labels must be made exclusively of analog materials such as paper. No requirements prohibit RFID technology in labels, nor are individual components, such as antennas or sensors, covered by these guidelines.

"In the past, authorities had no objection to innovative labeling as long as requirements on contents, durability, and legibility were met," Barone explained. "A smart label with an RFID tag, e-paper display, and booklet label complies fully with Annex XIII," he said. Implementing Annex VI may pose a challenge to the pharmaceutical industry.

Tracking and documentation

Because the software stores the UID of each RFID tag, multiple expiry dates and counters inside the kit can be updated in a single operation. As soon as the tag starts to exchange data with the update device, data on individual packages is received in real time.

Data for each labeled container is automatically stored in the software before being merged into batch documentation. This can serve as a source of information for inventory management whenever logistical product flows are to be controlled and monitored.

If an allocation error occurs when the container is shipped from the depot, for example, it can be identified if data transfer is performed using an update device. Wrongly addressed containers can then be withdrawn from the shipment.

Automatic updates

Key takeaways, Barone noted, were the elimination of labor- and resource-intensive activities—such as writing batch records, printing and shipping labels,

and physically applying labels in depots/sites—as well as vastly improved cycle times.

"Another potential benefit of e-labels," Kopp told *Clinical Trials Arena* in his 2016 interview, "is you can start a trial with a very short initial shelf life. Whenever new stability data becomes available, new retest dates can be assigned and an update can be performed, because it is so simple and so quick. It is a matter of minutes."

NEXT STEPS

Merck is currently focusing on Phase 1 and 2 studies, Barone said, but hopes to focus on larger Phase 3 studies in the future, and will also explore additional options such as new label formats, study pooling, and full electronic display of a clinical label.

"I can imagine over the next few years we will start to see real trials being conducted with the help of these technologies," Kopp concluded. "What's more, I am personally convinced this is the future. Over time, the use of paper labels will gradually fade and we'll start to see more electronic technology being used in clinical trials." ‹›

—Amy R. Loerch, Publications Manager

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NEW JOB SUCCESS STRATEGIES

I finally landed a great job. How can I get started on the right foot?

David G. Smith

Congratulations on accepting a new position! Your first days in your new role will go a long way to shaping your career with the new organization. Here are some ideas for a successful transition.

BEFORE YOUR FIRST DAY

Do your homework. Complete any required forms and find the required documents before day one. Review the benefits summaries and other information so you can ask questions during orientation.

Revisit the job description and your interview notes, including position responsibilities and interview key points. Prepare a checklist of key learning areas to prioritize for your specific job function and the organization. Bring a portfolio so you can keep your checklists, agenda, and other items organized and handy.

Plan how you will present yourself on your first day. Get a good night's sleep so you can start your first day refreshed and ready. Plan for a little extra commuting time. Make sure you review any dress code (especially for manufacturing-related roles).

ORIENTATION

A formal new employee orientation (NEO) for new hires can provide a consistent new-hire experience and key information about employment with the company. If your new organization offers an NEO, you'll receive an agenda and a list of items you will need to bring with you on your first day.

In addition to the usual paperwork related to benefits enrollment, tax forms, proof of work authorization, and company compliance documents, you'll set up your phone and computer to access required systems and information. Capture the names and contact information that you may need to follow up with later.

Get a tour of the facility and orient yourself with the major department locations, including those you will work with and key support functions such as IT, finance, and HR. Also ask to see areas for lunch, company amenities, and parking.

TIPS FOR EARLY SUCCESS

Take ownership of your development and establish how you will work with your new team. Here are some focus areas:

Understand the business. It is critical to thoroughly understand the company's products and/or services, goals, and structure. This will help you learn the interdependencies and value of your responsibilities, which should help you communicate with key stakeholders and prioritize your work.

Learn how to work with your boss. Make sure you understand your boss's communication preferences (in person, phone, IM, and emails). Establish what you need to report or inform about and how often. Communicate what you need, your best learning methods, where you would like to develop your skills and contributions, and your own communication style.

Learn and train. Look for learning that fits your personal learning style: For visual learners, seeing an activity firsthand is best, audio learners might learn best in a classroom, and others may gain the most from reading. Be sure to take breaks from learning activities and vary your day to ensure you stay fresh and attentive.

Seek understanding before you suggest change. Process improvements are always a goal, and as a new employee, you will be eager to make a quick impact. Take time to understand before you suggest or act. Credibility is based on knowledge and trust, so be sure to see the larger picture, ask questions, and solicit stakeholder feedback.

Build relationships with your team. Good relationships are essential. Learn how your team communicates, and determine their interests and strengths. Understand how your role intersects with the rest of the team and how others depend on your work. Establish credibility by meeting deadlines, keeping your commitments, and seeking feedback to ensure you are delivering what is needed. You probably will ask a great deal from others during your early days, so look for ways to reciprocate.

Immerse yourself in the company culture. Your manager will likely review and provide expectations related to the company culture as part of your performance plan, and you will need to look for ways to adopt them into your daily interactions.

Seek balance. The urgency of getting up to speed and the burden of performing in your new role can take a toll if you're not careful. Get proper sleep, exercise, and fulfill non-work priorities—these are key to keeping motivated and engaged. Many companies provide on-site wellness programs and other benefits that can help. While you will learn best practices and become more efficient over time, make sure you are reviewing your workload with your manager and request help before you find yourself in a pinch.

Congratulations on the new opportunity, and I wish you the best of luck. ‹›

Do you have other career questions? Feel free to email me at david.g.smith@biogen.com

David G. Smith is Talent Acquisition Lead, PO&T North America, Biogen.

THE MAGIC OF DISCOVERY

Genentech's Futurelab changes education in South San Francisco

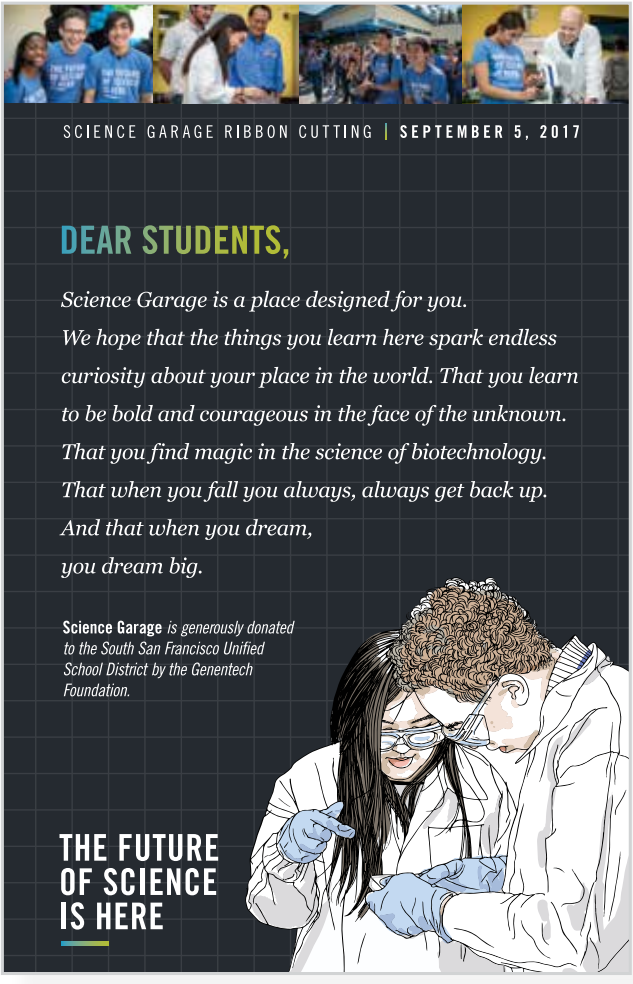
For the jobs of tomorrow, STEM fields—science, technology, engineering, and mathematics—are powerful economic competitiveness drivers: 80% of the fastest-growing occupations depend upon mastery of math and science, and 92% of traditional STEM jobs require at least some post-secondary education and training. But in the United States, almost 50% of students have lost interest in the sciences by eighth grade, and only 6% of high school students ultimately choose a STEM degree in college.

While these issues exist nationwide, they are particularly pressing in California. South San Francisco faces even greater challenges. Once known as the "Industrial City" for its steel mills and paint factories, South San Francisco has become a thriving biotech hub. This transformation is often lost on local students, however. More than 30% are English-language learners and 40% come from low-income families. Only one in three goes on to college. Until recently, most couldn't even dream of a fulfilling and productive career in the sciences.

With its well-known support for education, Genentech (a member of the Roche group) saw this as an opportunity to help and invest in its local community. The biotechnology firm partnered with the South San Francisco Unified School District (SSFUSD) to launch "Futurelab": a science-education program for all students in grades K–12, designed to create a pipeline of future scientific talent in the Bay Area.

By promoting hands-on learning, mentorship, and healthy doses of teamwork, Genentech hopes to ignite "the magic of discovery" in children's natural desire to learn and solve problems. The company's goal is to spark a love of exploration and innovation in the fascinating world of science.[1]

Futurelab's groundbreaking curriculum was showcased in a keynote address by Carla Boragno, Vice President Site Services, Genentech, at the ISPE Facilities of the Future Conference, 20 February 2018, in Arlington, Virginia.



"Science starts with students," she said. "It can take years for our scientists to develop a new medicine. And in that time, a student can develop into a scientist—just in time to start work on the next medicine.

"We designed our Futurelab programs with the goal of inspiring students to pursue careers that are needed for the jobs of today and tomorrow, right in their own backyard," she said. "These students are the future of science, and we want to arm them with the skills needed to solve some of the greatest unmet needs in medicine and beyond. Through Futurelab, our mission is to develop a center of science education excellence in South San Francisco for all students in kindergarten through 12th grade, and create a pipeline for future talent."

THREEFOLD STRUCTURE

Futurelab has three distinct programs for students of different ages. They are designed to bring science to life by progressing from "excite" to "engage" and finally, "equip."

Gene Academy

Excite

Begun in 2008, Gene Academy is a program focused on elementary school students in SSFUSD that promotes hands-on science activities. Students come to the company's campus once a week, where they are each paired with two mentors who help with science projects, homework, and other creative learning activities.[2] Since the program's inception almost 10 years ago, nearly 1,300 students have been mentored. "We want to teach them that science can be fun and people who work in science come from different backgrounds," Boragno said.

Helix Cup

Engage

For middle school students, Helix Cup is an annual science competition for all SSFUSD eighth graders. "It's hands-on science engagement," said Boragno. "It

gets kids thinking they can do science, and teaches teamwork and resiliency."

Helix Cup begins as student teams challenge each other within their classroom. Top teams go on to compete against other classes in their school and then move on to compete with other middle schools across South San Francisco. The finale is a full-day event held at Genentech headquarters. This competition not only exposes students to the world of science; it helps them learn problem-solving skills like teamwork, resilience, and perseverance—skills that are valuable inside and outside of the lab.[3]

Science Garage

Equip

Science Garage is a University of California/California State University–approved biotech curriculum for high school students. To house the curriculum, Genentech designed and built a 7,000-square-foot $7.8-million classroom and state-of-the-art biotech lab at South San Francisco High School—the only one of its kind for SSFUSD. "Our scientists were amazed when they first saw Science Garage; they remarked that they only had these kinds of labs in graduate school," said Boragno.

Science Garage is designed help high school students explore biotechnology and kindle interest in STEM careers. Classes are hands-on and lab-focused; each lab is an example of what has been tested in university and industry labs.

Genentech also awards two four-year scholarships of $50,000 per year for outstanding students who plan to pursue a degree in the sciences.[1]

Teacher benefits

Futurelab equips science teachers and expands the SSFUSD curriculum with professional development training, Genentech employee volunteers, and other resources to present engaging science lessons of their own.[4]

"Futurelab will better equip teachers in our local community to nurture scientific curiosity in kids at every grade level," said Genentech CEO and head of North American commercial operations Bill Anderson.[2]

OUR MISSION IS TO DEVELOP A CENTER OF SCIENCE EDUCATION EXCELLENCE AND CREATE A PIPELINE FOR FUTURE TALENT

BENCHMARK RESULTS

The Futurelab program has set a benchmark in science education. It's been so successful that it was awarded a US2020 STEM Mentoring Award in 2016 for excellence in public-private partnerships,[5] and was recently named on *Fast Company's* list of the World's Most Innovative Companies for 2018.[6]

Boragno identified the unique characteristics that make it successful.

- *Focus.* Futurelab's "hyper-local" approach is aimed at a single school district that allows Genentech to continually build on its effectiveness, working closely and in partnership with SSFUSD.
- *Mentoring.* By connecting Genentech employee mentors with students, children can learn about what people do at Genentech and biotech careers in general. Genentech believes this will enable more kids to think about career paths they might not otherwise envision.
- *Hands-on STEM activities.* Students love learning when they're engaged in something meaningful and fun.
- *Engage all students.* "This is for all kids—not just the top of the class," Boragno said.

The results for students and teachers has been nothing short of extraordinary:

- *Excite:* 73% of students reported an increased interest in science and biotech
- *Engage:* 76% of students discovered that they can learn and understand new science concepts
- *Equip:* 77% of students were "very" or "extremely" interested in attending college after taking our biotech course and 48% of students are more interested in pursuing a career at a company like Genentech as a result of the biotech course
- 100% of teachers report that they have or will incorporate content from Futurelab into their everyday teaching
- 83% of teachers increased their confidence in teaching science
- 67% of teachers reported renewed enthusiasm for teaching

But students aren't the only ones who benefit. "The program also gives our employees the chance to get involved through volunteering and mentoring," Boragno said.

- 100% of volunteers reported they were able to effectively support students' in-classroom learning
- 95% of volunteers reported that volunteering contributes to Genentech being a great place to work
- 91% of volunteers reported they were able to strengthen or build new skills as the result of volunteering with a Futurelab program

BUT WAIT—THERE'S MORE

Futurelab teaches more than science, Boragno said. "What we see is that hands-on work activates students who were previously 'checked out,' and that real-world relevance helps all students get interested, not just the best and brightest. On our side, this human-centered approach also allows our employees to experience, first-hand, the impact of their work and allows them to grow and develop themselves."

Boragno encouraged her listeners to look for similar opportunities in their cities. "There's a need for companies to engage," she said. "Many of your current assets will be valuable, and time spent volunteering benefits business. Think about the role that you can play in developing future talent."

In closing, Boragno thanked the audience for "sharing a journey that Genentech has taken to cultivate talent. We hope it inspires you to do something about this as well." ‹›

—Amy R. Loerch, Publications Manager

Photos and infographic courtesy of Genentech. Reprinted with permission.

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2018 ANNUAL MEETING & EXPO

VISION TO REALITY: DELIVERING NEXT GENERATION THERAPIES

4–7 NOVEMBER | PHILADELPHIA, PA | PHILADELPHIA CONVENTION CENTER

The 2018 ISPE Annual Meeting & Expo is where ISPE's worldwide membership gathers to discuss the latest developments in pharmaceutical science and manufacturing. This member-driven event draws professionals from all segments of the industry, with attendees that range from young professionals to senior executives to members of global regulatory authorities.

The program, crafted from proposals submitted by ISPE members, provides education and technical sessions on the latest developments in:

- Supply chain
- Facilities and equipment
- Information systems
- Product development and production systems
- Quality systems and regulatory oversight
- Cutting-edge innovations

The meeting also features a large exhibition hall where members can discover latest technologies and services for the pharmaceutical industry.

Keynote Presenters

From Vision to Reality: Delivering Next-Generation Diabetes Treatment

Lars Fruergaard Jørgensen
President and CEO, Novo Nordisk, A/S Honorary Conference Chair

Manufacturing and Supply: Vision Becomes Reality

Kirsten Lund-Jurgensen, PhD
Executive Vice President and President, Pfizer Inc.

Gene Therapy: Bringing It to Life

Nick Leschly, MBA
CEO, bluebird bio

The Impact of the Industry's Work: A Patient's Perspective

Becky Furata
Ambassador, Team Novo Nordisk Diabetes Cycling Team and Health Care Policy Consultant

REGISTER BEFORE 28 AUGUST TO SAVE! LEARN MORE AT WWW.ISPE.ORG/AM18

CONFERENCE SCHEDULE

Sunday, 4 November

1100–1245

Young Professionals Brunch and Orientation

1300–1515

FOYA Category Winner Presentations

1300–1500

Technical Workshops

- Building a Framework for Success: A Tale of Two Site Master Plans
- Equipment Reliability and Preserving Functional Requirements
- Data Integrity Strategy and Implementation
- The Use of Descriptive Statistics in the Pharma Industry
- Lifecycle Process Validation: How Are We Still Getting This Wrong?

1530–1730

Opening Plenary Session - Keynote Presenters

Lars Fruergaard Jørgensen, CEO, Novo Nordisk A/S

Kirsten Lund-Jurgensen, PhD, Executive Vice President and President, Pfizer Global Supply, Pfizer Inc.

1730–1900

Welcome Reception – Expo Hall Open

Becky Furata, Ambassador, Team Novo Nordisk Diabetes Cycling Team and Health Care Policy Consultant

1900–2200

Facility of the Year Awards Banquet
(Separate Registration Required)

Monday, 5 November

0630–0800

5K Charity Run/Walk
(Separate Registration Required)

0700–0815

New Member/First Time Attendee Orientation

0830–1000

Plenary Session - Keynote Presenter

Nick Leschly, MBA, CEO, bluebird bio

1100–1230

Concurrent Sessions

- Manufacturing and Supply Chain Capacity Planning Using Discrete Simulation
- Renovating an Existing Biotech Plant
- Next Generation Manufacturing Control
- Challenges in Bioprocessing of Emerging Biological Classes
- Technology Transfer Acceleration
- Regulatory Affairs before and after a Natural Disaster

1345–1515

Concurrent Sessions

- Robust, Resilient, Reliable Facilities: Lessons Learned from Hurricane Maria
- Implementing a Sterile Oncology Facility in China
- CyberSecurity in Life Sciences
- Digital Innovation in an Evolving Manufacturing Paradigm
- From Industry 4.0 to Pharma 4.0: A Holistic Concept
- Accelerated Product Development through Inspection and Launch: Part 1

1600–1730

Concurrent Sessions

- Improving Supply Chain Performance through Human Performance
- State of the Sterile Products Industry: 2018 Survey Results
- Cloud Computing in a Regulated Environment
- Dynamic Modeling for Sustainable Manufacturing Facilities
- Pharma 4.0 - Plug and Produce
- Accelerated Product Development through Inspection and Launch – Part 2

1900–2030

Women in Pharma® Networking Dinners
(Separate Registration Required)

1900–2200

Young Professionals Event at Yards Brewing Company
(Separate Registration Required)

Tuesday, 6 November

0800–1000

Membership and Awards Breakfast

1100–1230

Concurrent Sessions

- Sustainable Serialization Solutions
- Emerging Technology Approvals: Lessons Learned
- Digital Personal Medicines
- Opportunities and Challenges in PAT: Considerations for ICHQ12
- Streamlined Manufacturing: Continuous Manufacturing and Other Design Challenges in a Changing Landscape
- Drug-Device Combination Products: Hot Topics and Trends

1345–1515

Global Regulatory Town Hall

Accelerating Global Acceptance of Emerging Technology and Novel Therapies

1600–1730

Concurrent Sessions

- Strategies for Deterministic Container Closure Integrity
- Advancements in Commissioning and Qualification
- Lessons from Global Data Integrity Case Studies
- Building Facilities to Deliver on the Promise of Cell and Gene Therapy
- Data Analytics and Security in an Integrated Manufacturing Environment
- Regulatory Considerations for New Manufacturing Technologies

1900–2200

Tuesday Night Party – Reading Terminal Market

Wednesday, 7 November

0800-0930

Concurrent Sessions

- CAR-T Supply Chain: Challenging, Achievable, Realistic, and Transformational
- The Right Maintenance Strategy for Your Operation
- Transformative DATA: Aggregation and Analytics with Integrity
- Green and Sustainable Technologies
- Data Science Solutions for Accelerating Time to Market

0945-1115

Concurrent Sessions

- Advancing Pharmaceutical Quality
- Industry 4.0: What's Next?
- Applying and Qualifying a PAT System for Life Science Manufacturing
- eClinical: Clinical Trial Data and GAMP® Compliance
- Analytical Method Lifecycle: An Industry Perspective

1145–1700

Facility Tour

Adaptimmune
(Separate Registration Required)

Please note that sessions and presenters are subject to change. Visit www.ispe.org/AM18 for the most up-to-date information.

SOLD-OUT EUROPE ANNUAL CONFERENCE DRAWS RECORD ATTENDANCE

In March 2018, more than 640 attendees met in Rome for the 2018 Europe Annual Conference. The record attendance and roster of 70 speakers made it the largest ISPE Europe meeting to date. Sessions covered the paradigm shift driven by digitalization as well as factors such as mass serialization and the need for data integrity.

Participants included more than 30 international regulators from Denmark, Germany, Italy, Jordan, Turkey, Russia, and the United Kingdom. ISPE's Young Professionals delivered great content at a weekend Hackathon, which also featured a keynote speaker and interactive Pharma 4.0 session.

Here are highlights from some key sessions and events at the conference.

EXECUTIVE FORUM

The Executive Forum set the stage for the conference with its focus on Industry 4.0. The next industrial revolution is being triggered by digitalization* —and the survivors will be those who adapt to change most readily.

In his report on electronic industry production, Dr. Gunter Beitinger, Site Head for Siemens, Amberg, Germany, discussed single-batch production and the transition from Five Sigma to Six Sigma. Process understanding education for managers will be key, since the ability to make decisions is a counterpart to technical abilities.

Dr Thomas Usländer, Research Manager for Fraunhofer IOSB**,** added an academic perspective on Industry 4.0 with his presentation on the trends that are driving the change and its effect on value chains. A key managerial factor in successfully implementing new industrial concepts is alignment of expectations, interpretation, and definitions among functions, roles, and responsibilities. System interoperability is the leading success factor on the technical side. In the pharmaceutical industry, for example, mass packaging serialization is an effective measure against infiltration of counterfeit medicines into the legitimate supply chain.

Dr. Roman Hipp from Porsche Consulting addressed two main industry trends: individualization and customized products, and changing corporate role models. Porsche, for instance, is moving from producing cars to becoming a "mobility" provider, mainly via self-driven and electric vehicles. This is supported by predictive analytics and new key performance indicators such as error frequency forecasts.

Pharmaceutical industry boundaries were discussed in the second part of the executive forum. Former EMA Regulator Arielle North reported on the potential effects of Brexit, including significant legal implications when agreements cannot be realized.

Seven years after the Falsified Medicines Directive, the mass serialization deadline is posing a challenge for the industry: Prescription drugs must be protected by safety features and a 2D barcode by May 2019. Reporting on Merck Darmstadt's successful serialization efforts, Andre Overmeyer identified three key factors: (1) portfolio pruning to eliminate "sleeping" stock keeping unit numbers, (2) good data management, including master data management, and (3) a process efficiency program. With this kind of preparation, he said, mass serialization could be implemented one year before the legal due date.

Andreas Walter from the European Medicines Verification Organisation provided an overview of the complex global regulatory landscape. Almost all first- and second-world countries have regulation in place, and some emerging economies are beginning to catch up. The challenge for the industry will be harmonizing these regulations in the decades to come. Industry 4.0 will be enormously helpful this effort.

KEYNOTES

Philippe Luscan, Executive Vice President, Global Industrial Affairs, Sanofi, addressed global trends that are creating a paradigm shift for the pharmaceutical industry: longer life expectancies, the health economy agenda, digital revolution, and empowered patients. Innovation in technical operations is focused on core technology platforms, a value chain continuum, and excellence in manufacturing. All of these rely on R&D breakthroughs for product development.

The portfolio of the future will be increasingly diversified, he noted, and manufacturers must adapt capacity to reflect the parameters of network, volume, supply chain agility, partnerships, and costs of goods. Important enablers are quality standards for the global supply chain, ONE standard, and standardization based on best practices. Regulatory partners are essential to achieving these goals. Current challenges such as supply chain integrity, anti-counterfeiting, and mass serialization must be mastered. A seamless

* Digitalization is the use of digital technologies to provide new revenue- and value-producing opportunities. It enables change across organizations and along the complete value chain network. Its evolution is comparable with the development of the World Wide Web.

FOYA 2018 Category Winners

Facility Integration: Shire

Facility of the Future: Vetter Pharma-Fertigung GmbH & Co. KG

Operational Excellence: Shire

Project Execution: BioMarin Pharmaceutical Inc.

Sustainability: Wyeth Pharmaceuticals Co., a Pfizer Company

Honorable Mention: Emergent BioSolutions, Inc.

Honorable Mention: The Government Pharmaceutical Organization (GPO)

Conference attendees enjoyed the exhibit floor

connection between people, ecosystems, and Pharma 4.0 are essential, he said.

Developing future talent requires partnerships between universities and industry. To move toward optimized, digitally enabled operations, companies will need integrated industrialization, connected plants, and connected teams working on smart quality and real-time, data-driven supply chains.

Christian Wölbeling, Senior Director Global Accounts, WERUM IT Solutions, explained how common Industry 4.0 concepts could be applied to the highly regulated pharmaceutical industry. Starting with the defined value network for Industry 4.0, he presented a pharmaceutical operating model.

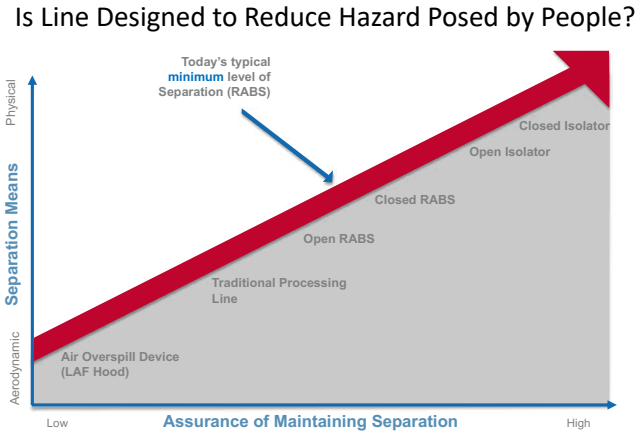
This model is the basis for developing road maps and maturity models for main processes. One focus is also on the completion of ICH Q10, the new quality system, with additional enablers such as data integrity by design and digital maturity as well as new elements (see Figure 2 on page 42). The outcome will be a holistic control strategy, which considers all aspects from the control strategy in product development and including all elements of process flow, data flow, automation, and environmental control in manufacturing over the full product life cycle. Another important topic on the agenda of the SIG Pharma 4.0 is the establishment of a plug-and-produce concept.

Brendan Cuddy, Head of Manufacturing and Quality Compliance, EMA, discussed the four pillars of the 2018 European Regulatory Strategy:

1. Mutual recognition agreements are in place between the United States and many EU member states, with more to come in 2019. As of July 2019, all member states are expected to be recognized under the MRAs, following a revision of all individual states' oversight systems. The main tasks are to maximize inspection resources by focusing on sites with the highest risk, minimize duplication of inspections, and broaden inspection coverage.
2. Legislative changes are numerous, but one is of particular importance: the new investigational draft "Guideline on Safety and Efficacy Follow-Up and Risk Management of Advanced Therapy Medicinal Products."
3. Because drug shortages due to manufacturing or quality issues are a continuing problem, availability of authorized medicines is another focus, as is preventing the penetration of counterfeit medicines into the legitimate supply chain.
4. Preparation for Brexit and the relocation of EMA offices to Amsterdam will involve some activities and energy at EMA.

Andy Hopkins, Expert Inspector, MHRA, presented the status of European Commission GMP Guide Annex 1, "Manufacture of Sterile Medicinal Products." Following a development process launched in August 2014, the revised draft

FIGURE 1: TECHNOLOGY RANKING FOR ASEPTIC PROCESSING



Source: Adapted from G. Farquharson, "ISO 14644 ... Part 7: Separative Devices." Presented at the 8th Pharmaceutical Isolator Conference, Warwick, UK, December 2004.

was published in December 2017, followed by a comment period that ended 20 March 2018.

Important topics covered in the revised annex are quality risk management, the need to ensure protection and control of product and employees, contamination control strategy (air supply in grade A is requested), and a documented risk assessment and sterilization should be used wherever possible after reassembly. A new chapter, "Utilities," has been added, plus a requirement to include trending in environmental monitoring.

A question and answer panel discussion was a highlight of the conference. Andy Hopkins, MHRA; Rick Friedman, FDA; and Vladislav Shestakov, Director of Institute for GXP at the Moscow Ministry of Trade and Industry, fielded questions and comments from among the 500 submitted by participants.

Rick Friedman addressed FDA's view on sterile manufacturing. A life cycle–oriented quality risk management system is seen as necessary. Some inspection findings showed the need for facilities modernization. FDA provides incentives for adopting today's technology (Figure 1) and less capable manufacturing operations receive increased scrutiny. Quality risk management and knowledge management should be applied throughout the facility life cycle by iterative learning and leveraging technology, which facilitates good decision-making.

FOYA CATEGORY WINNERS

The session was closed by Jim Breen, VP Project Lead Biologics Expansion, Janssen Pharmaceuticals and current ISPE International Board of Directors Vice-Chair, and Tim Howard, President at Commissioning Agents and current ISPE Board Chair, who announced the winners of 2018 Facility of the Year Awards (see page 39).

Next year's ISPE Europe Annual Conference will be held in Dublin, 1–3 April 2019. ‹›

—Thomas Zimmer, Vice President, European Operations

An earlier version of this article was published in *CHEManager International*, March 2018. Information is reprinted here with permission.

PHARMA 4.0 Hype or Reality?

Lorenz Binggeli, Hans Heesakkers, Christian Wölbeling, and Thomas Zimmer, PhD

The smart factory, the factory of the future, the Industrial Internet of Things (IIoT), and Industry 4.0. These are buzzwords that populate a new manufacturing world triggered by digitalization. "Pharma 4.0" is a holistic operating model for pharmaceutical factories and supply chains of the future based on Industry 4.0 capabilities, digital maturity, and data integrity by design[1] (Figure 1). Created by ISPE's Pharma 4.0 Special Interest Group (SIG), it is fueled by trends such as big data, interconnectivity, collaborative robotics, artificial intelligence, and distributed cloud-based architectures to develop next-generation therapies that may enable lab-to-patient or even patient-to-patient value chains. Pharma 4.0 is the digitalized operations model of a pharmaceutical organization.

What are the roots of this evolution? What are its philosophies, and how will they influence the future of pharmaceuticals manufacturing?

ROOTS OF THE EVOLUTION

In 2005 Dr. Janet Woodcock verbalized the US Food and Drug Administration (FDA) vision on pharmaceutical risk-based cGMPs for the 21st century as: "A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drugs without extensive regulatory oversight."[2]

Additionally, the International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), which supports this vision, pointed out the need for a life cycle approach in ICH Q12.[1]

PROBLEM STATEMENT

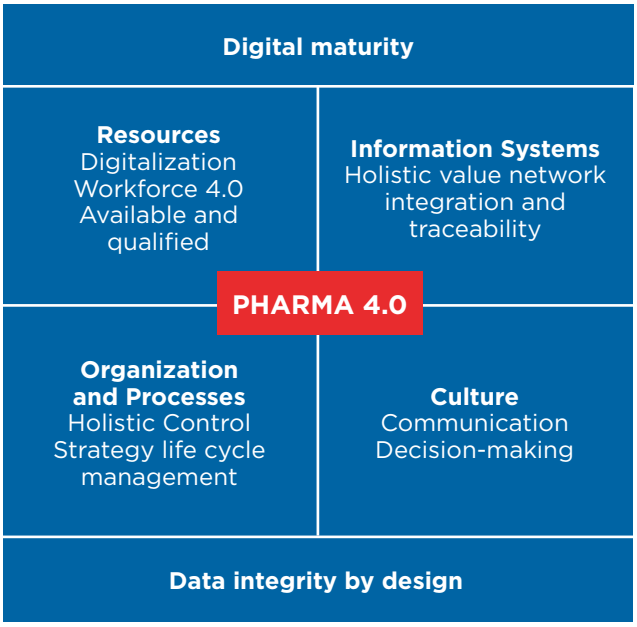
The current single-submission-based control strategy (SSCS) plays a key role in ensuring that critical quality attributes (CQAs) are met and the quality target product profile is realized. This does not, however, enable production-specific changes related to GMP, facilities, utilities, or equipment to mitigate process variability. The effect of unknown process parameters, material attributes, and impurities are often not addressed in the SSCS. Furthermore, it is difficult to foresee these variations over the complete product life cycle during the development phase.

When process and product understanding require a change, this must be communicated to regulatory authorities. It's also important to refine the control strategy that comes out of development and to enhance it into one that can be executed in manufacturing. Data integrity is still an issue along the pharmaceutical value chain, since repeatable, robust, and right-first-time-based pharmaceutical business processes are not yet fully implemented.

PHARMA 4.0 = DIGITALIZATION + ICH Q10

The quality management process in Pharma 4.0 is based on ICH Q10: "Pharmaceutical Quality Systems" (PQS).[1] In 2017, the Pharma 4.0 SIG published an award-winning article in *Pharmaceutical Engineering* showing

FIGURE 1: PHARMA 4.0 OPERATING MODEL



how ICH Q10 can be enriched with "elements and enablers" to benefit from new technologies.[3]

The four "elements" of the operating model and the "enablers" data integrity by design and digital maturity are shown in Figure 2. This model combines the submission-based and manufacturing control strategies to create a PQS and control strategy that covers the complete product life cycle.

ICH Q10 elements and enablers are shown in grey. New elements made possible by digitalization are shown in blue. When combined with the new enablers digital maturity and data integrity by design, they form a holistic control strategy for the complete product life cycle. This requires information exchange into the decision hierarchy, along the value chain, and across the value network.

ICH-DEFINED ENABLERS

Knowledge management and quality risk management

ICH Q10 defines CQAs, critical process parameters (CPPs), and critical material attributes (CMAs) as key elements of product and design. ICH Q12 adds key process parameters (KPPs); these are elements of the manufacturing process that may not be linked directly to CQAs but should be monitored in the move toward a Six Sigma–capable process.

KPPs, CPPs, CQAs, and CMAs are identified by ICH Q12 as established conditions (ECs); these are monitored by product quality and process performance systems to detect out-of-trend or out-of-spec results. ICH Q12 also clarifies the communication necessary between regulatory authorities and firms for changes depending on the type of EC (Figure 3).

Holistic process and platform understanding requires cross-organizational interdisciplinary knowledge management of all suborganizations (internal and external) and integration of all GxP-related information technology (IT) systems. This enables data integrity of all relevant (big) data as well as enhanced analytical approaches that will become the bases for decision-making. Process analytical technology (PAT),[7] essential in highly automated environments, further enables advanced technologies like continuous manufacturing.

NEW PHARMA 4.0 ENABLERS

Digital maturity

The four quadrants of an operating model have been common to all stages of industry, but the ways in which they were implemented differed. An organization's digital maturity defines its capability to operate within the parameters of Industry or Pharma 4.0. The Pharma 4.0 SIG has designed a pharma-specific model that allows organizations to assess where they are, which holistic control strategy capabilities are possible, and what the road to future capabilities looks like. Digital maturity is the first enabler in the change to a data-driven, agile organization.

Table A shows that computerization and connectivity are prerequisites for Pharma 3.0. To move toward Pharma 4.0, an organization needs data visibility, data transparency, predictive capacity, and adaptability. New technologies like paperless execution systems, virtual reality (VR), augmented reality, collaborative robotics, 3D printing, blockchain, and other technologies can empower resources, but will only render value if all four quadrants, which are the Pharma 4.0 operating model elements, are equally mature.

Data integrity by design

Data integrity was essential to patient safety even in paper-based eras, so it has always been a focus of regulatory agencies. In Pharma 4.0, data will travel in all directions of the value network; governing its integrity will pose new challenges. The data pedigree must be transparent, with data flow charts linked to process flow charts.

In the Pharma 4.0 environment, the performance of business processes along the product life cycle depends on structural capabilities. If an organization is trapped in silos, for example, the chance is high that sociotechnical information systems are designed for and governed by a culture in which each element defends its own "island." If a holistic control strategy (a "red thread" in popular terminology) is to perform throughout the product life cycle, the structural capabilities that connect to that red thread should be considered during the design, implementation, and operation of the control strategy.

In many organizations business processes are not well defined or documented. But if you want to bring IT into an organization, you must have defined processes and data flows. This starts with the implementation of the enterprise resource planning (ERP) system. Each system that controls the manufacturing process must also be based on a well-structured, documented, and validated software system.

Data integrity is much more than ensuring a good audit trail. It is about data quality, the right content, the data life cycle, and upholding ALCOA+ principles. Excipients, for example, should have just one name and one reference number across the company's global network to avoid mix-ups and misunderstandings. Data integrity requires well-defined, robust, and

FIGURE 2: HOLISTIC PRODUCT LIFE CYCLE CONTROL STRATEGY

ICH Q10 elements and enablers are shown in grey. New elements made possible by digitalization are shown in blue. When combined with the new enablers digital maturity and data integrity by design, they form a holistic control strategy for the complete product life cycle. This requires information exchange into the decision hierarchy, along the value chain, and across the value network.

repeatable (but flexible) processes, risk-management principles, and critical thinking. It includes thorough data science approaches and architectures. When establishing a quality risk map using ICH Q9, one of the most important steps is risk identification, which requires extensive experience, a balanced view on risk, and foresight on what can go wrong. For this reason, prior knowledge should be available in a structured form.

NEW PHARMA 4.0 ELEMENTS

Resources

> *"Resources" refer to tangible, physical resources. These include a company's workforce (human resources), machinery and equipment, tools, materials, and the final product.*[4]

Physical assets in Pharma 4.0 will be fast and adaptive, able to produce diverse products with the efficiency of mass production. Smart "plug and produce" equipment will adapt to multiple configurations. PAT will monitor KPPs and communicate through a digital infrastructure with different partners in the value network. New process validation methods will empower continuous improvement.

Each product-quality and process-performance monitoring system can be explained with the RAMI 4.0 cube (Figure 4). The integration layer acts as the task-based interface between the digital and the physical worlds (i.e., the human-machine interface). The communication and information layers enable the traceability and visibility of information, which can be pushed to the manufacturer for predictive maintenance through VR and artificial intelligence. Each layer communicates with the whole value chain network, across one site or throughout the entire company. The mature design, implementation, and operation of all axes will reduce latency, enhance the quality and the availability of products, and raise the business benefit.

To excel in this adaptive, information-rich environment, a new breed of human-machine interfaces will ensure flawless data acquisition and information reporting.

FIGURE 3: ESTABLISHED CONDITIONS

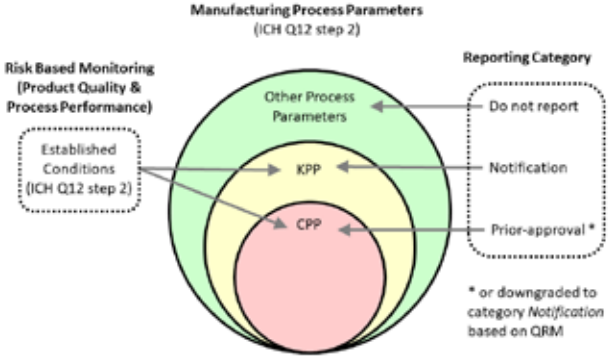
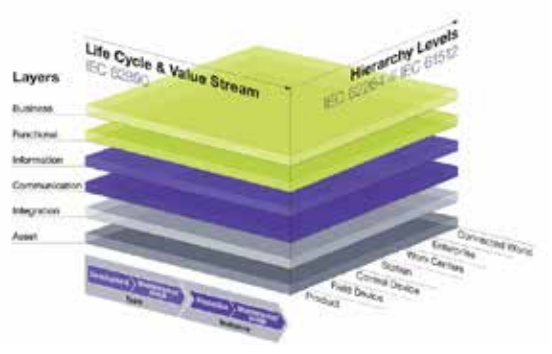


FIGURE 4: INDUSTRY 4.0 RAMI ARCHITECTURE



Source: DIN SPEC 91345:2016-04 Reference Architecture Model Industrie 4.0 (RAMI 4.0)

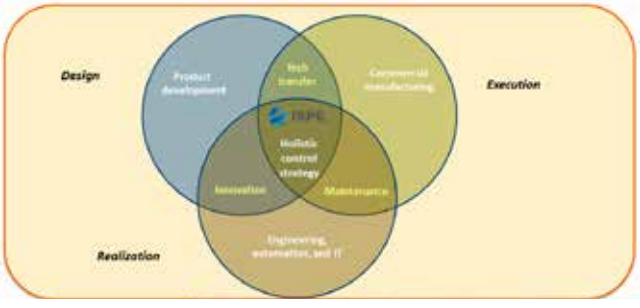
TABLE A: DIGITAL MATURITY MODELS

Industry	1.0	2.0	3.0	4.0
Resources	Mechanical	Electrical	Digitalization	Visibility
Information systems	Unit operation	Production process	Computerization	Transparency
Organization and processes	Craft shop	Taylorism*	Connectivity	Predictive
Culture	Internal focus, adaptive behavior	Internal focus, stabilizing behavior	External focus, stabilizing behavior	External focus, adaptive behavior

* A 19th-century management system that broke down steps in a manufacturing process into repetitive tasks

FIGURE 5: PYRAMID OF WISDOM

FIGURE 6: DESIGN, EXECUTION, REALIZATION: THE COLLABORATIVE VALUE CHAIN



Information systems

> *Information systems are socio-technical systems in which information is provided based on economic criteria by both people and information and communication technology. They prepare, process, store, and transfer data and information.*[4]

This is the basis for the integration of all supporting computerized systems in Pharma 4.0, vertically and horizontally across systems, the product life cycle, and the value chain network. This includes data interfaces, process automation to support continuous process verification (CPV) by applying technologies like PAT, and predictive process controls to establish real-time release testing. Recognizing this need, some big pharma companies have established a "data lake" that also serves as "one source" for system integration as well as fast real-time and ad hoc reporting.

Areas for system integration include preventive maintenance, environmental monitoring, energy management, automation, CPV, mass serialization, real-time release, batch release, and track and trace.[3] ERP systems and equipment must also be integrated. Integration concepts must adhere to global technical standards such as GAMP® and ISO. Product development must be oriented toward "manufacturability" in automated processes. Most importantly, good decision-making needs a thorough understanding of data and information, a broad knowledge base, and solid experience (Figure 5).

Organization and processes

> *Organisational structure refers to both a company's internal organization (structure and operational processes) and its position within the value network. In contrast to area of "culture," the "organisational structure" establishes mandatory rules that organize collaboration both within the company and externally.*[4]

In the pharmaceutical industry, which is driven by meeting and complying with regulatory expectations, a holistic control strategy is the key element for life cycle management, followed by a risk-based approach based on well-defined business and pharmaceutical processes.

Process validation guidelines from the ICH[1] and FDA[5–6] recommend flexible production processes, including continued and ongoing process verification, which enables close monitoring of CQAs and CPPs to ensure high product quality.

In Pharma 4.0, however, the concept of quality assurance must be adapted to cross-functional business processes. In addition, the tasks and responsibilities of systems, cross-functional process owners, and content owners must be redefined.

There is a lot of work ahead of us, and it must be based on a step-by-step approach consistent with other structural capabilities such as culture. If, for example, people need paper documents such as standard operating procedures or working instructions to master the complexity of integration, it becomes obvious that the approach took more than one step, which puts the holistic control strategy at risk.

The long decision chains typical of pharmaceutical organizations should be mitigated through fast, specialized communities, which are created and disbanded depending on the needs of the value chain network. As the network moves toward the Internet of Things or Industry 4.0, pharmaceutical companies should establish cross-functional communities to design the step-by-step approach and ensure the integrity and performance of the holistic control strategy.

Figure 2 shows that Pharma 4.0 enhances the ICH Q10 PQS with structural organization and processes, creating a new quality by design element in the product life cycle.

Culture

> *"Culture" covers the value system within the company and thus describes the soft factors of collaboration. Nevertheless, both [organization and culture] structural areas are mutually dependent and must be coherent with each other.*[4]

Implementing Pharma 4.0 and the holistic control strategy uses the holistic approach to design and execute the business processes and to bring automation and paperless execution to the shop floor. This requires a culture of collaboration for all business units (Figure 6) responsible for the production process, technology, and quality. Some regulatory authorities have started to request control strategy digitalization. This request absolutely makes sense considering that the holistic control strategy implementation uses more and more IIoT and Industry 4.0 solutions.

Organizational culture should be geared toward understanding the importance of each element in the control strategy:

- Audit trails along critical information flows are designed to detect design-space changes—not to control human beings.
- If one department does not produce risk-based evidence for some human activities, the integrity of the holistic control strategy is jeopardized.
- Stakeholders should not wait to request improvements in their organizational culture, the use of sociotechnical information systems, and greater automation of resources.

It is management's responsibility, according to ICH Q10, to ensure compliance with the holistic control strategy.

SUMMARY

There is a huge potential for improving safety, quality, transparency, agility, flexibility, and productivity by implementing the Pharma 4.0 holistic control strategy across the pharmaceutical value network. The regulatory framework defined in ICH and FDA guidance is a prerequisite to ensure patient safety and stakeholder benefit.

Once this has been established, all that is needed is the entrepreneurial courage to start and the guidance to change with a controlled road map. ‹›

Acknowledgments

The Pharma 4.0 SIG of the ISPE Germany, Austria, and Switzerland (DACH) Affiliate would like to thank the following Pharma 4.0 leaders and subgroup leaders: Christian Wölbeling, Werum (Chair); Hans Heesakkers, Circuition (Co-Chair); Jennifer Baughman, MilliporeSigma; Lorenz Binggeli, B. Braun Medical; Wolfgang Dedden, Bayer; Uli Kuchenbrod, Vetter Pharma-Fertigung; Volker Roeder, Arcondis; Klaus Sauermann, Werum; and Thomas Zimmer, ISPE.

The Pharma 4.0 SIG and its subgroups aim to provide industry-wide implementation methodologies, approaches, and case studies on how to evolve life science organizations to Pharma 4.0. The group is currently focusing on the first step required to implement digital maturity into a pharma organization: Make it think and act in well-defined, best practice business process, and follow a data integrity by design approach.

They will post progress reports on a regular basis.

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About the authors

Lorenz Binggeli has been working in quality management for computerized systems (CS) at B. Braun Medical AG, Switzerland since 2003. He was previously working as an IT / SAP consultant for the same and other companies. Binggeli has experience based on numerous GxP projects for CS from enterprise to manufacturing levels. As of 2012 he worked for two years as a CS compliance subject matter expert for a manufacturing site at the company headquarters at Melsungen. He is owner of the Swiss quality system processes for the life cycle of computerized systems, documentation, and data. The risk-based control of information flows is among the key elements in those processes. He has been an ISPE member since 2003.

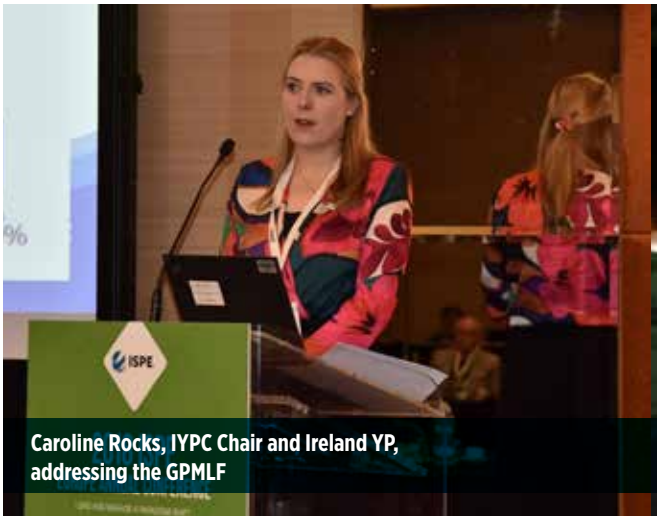
Hans Heesakers is Managing Director of Circuition Life Science Consultants and Co-Chair of the ISPE Pharma 4.0 SIG. He has 30 years' experience in the life sciences industry, 20 in business process reengineering and IT projects, 15 in manufacturing and supply chain management, and 15 in the areas of clinical development and investigational products. He has been an ISPE member since 2004.

Christian Wölbeling is Senior Director, Global Accounts, at Werum IT Solutions based in Lüneburg, Germany, part of the Körber Medipak Systems Group. Werum is the market leader in manufacturing execution systems solutions for the life science industries, working for 17 out of the global top 30 pharma companies with more than 800 installations. He holds a master's degree in mechanical engineering. With more than 25 years' experience working in life sciences manufacturing IT, Christian has had significant experience in all GMP-related processes. He has broad involvement with ISPE as Pharma 4.0 SIG Chair, GAMP® MES SIG Co-Chair, ISPE GAMP member at large of the European Steering Committee, Knowledge Network Council Co-Chair, PAT & Lifecycle Control Strategy CoP Steering Committee member, and DACH Affiliate board member. He has been an ISPE member since 2001.

Thomas Zimmer, PhD, held numerous positions at Boehringer Ingelheim between 1981 and 2013: pharmaceutical development, pharmaceutical production, international production, quality management, quality standards, corporate lead auditor GMP, implementation production alliance Europe, product transfers, transition management from national to international supply, plant manager/directeur industriel of pharmaceutical production in France, senior vice president of global quality, qualified person, and senior vice president of environment, health, and safety and sustainability. Since November 2013 he has served as the Vice President of ISPE's European Operations. He has been an ISPE member since 2005.

EUROPE ANNUAL CONFERENCE: YP HIGHLIGHTS

Caroline Rocks, Craig Milner, and Chloe Lang



Caroline Rocks, IYPC Chair and Ireland YP, addressing the GPMLF

Robert Landertinger, IYPC Europe Regional Leader and DACH YP, delivering his keynote speech

BEST-YET YP PARTICIPATION

Young Professionals (YPs) often ask us about the value of attending ISPE's large international conferences. As an answer, we're happy to report that YP participation is going from strength to strength at these events. This year's Europe Annual Meeting in Rome was no exception, featuring YP track leads, YP keynote speakers, and a second successful YP Hackathon. We're already looking forward to the YP events that will be hosted at the ISPE Annual Meeting and Expo later this year in Philadelphia, and at the 2019 Europe Annual Meeting in Dublin.

YP co-chairs

Increased YP participation was an objective set by the International Young Professional Committee (IYPC) for 2018. To accomplish this goal, a new strategy was proposed at the ISPE Pharma 4.0 Conference in Verona last November: Include YPs as education track co-chairs. The format has proved successful, and continued at the Rome meeting.

- Pharma 4.0: Thorsten Böhle, Chair, DACH YPC; Federico Poli, Italy YP
- Factory of the Future and Aseptic Processing: Marick Paris-Cadet, France YP
- Data Integrity: Matteo Pracchia, Italy YP
- Anti-Counterfeiting and Mass Serialisation Challenges: Abdelghani Meqdad, France YP

The YP co-chairs began to work well in advance of the conference with their involvement in the program committee, selecting speakers and choosing track themes. Each YP co-chair also received coaching from his or her track Chair on speaker introductions, audience encouragement, and managing Q & A sessions.

Caroline Rocks, IYPC Chair and Ireland YP, presented the YP perspective on Workforce of the Future to the Global Pharmaceutical Manufacturing Leadership Forum (GPMLF). Her talk included the results of a global survey conducted with over 40 YP leaders, and a live audience poll to gauge agreement between the GPMLF and YPs on future skills and current gaps. She also presented recommendations from the Workforce of the Future Academic subteam, who have partnered with industry and academia to define needed changes in course curricula to address future skill needs.

YP keynote

Robert Landertinger, IYPC Europe Regional Leader and DACH YP, gave a keynote speech on YPs and Pharma 4.0, presenting the next generation's challenge on execution. He recapped the results of the Hackathon and summarized why this will have a significant effect on the medicines of tomorrow.

Current YP status in Europe: 150 active volunteers

2014
First YP Group established in Ireland

2015
Europe Regional Leader appointed to International YP Committee

2016
YP Groups representing 12 countries in Europe

2017
First YP Hackathon at Europe Annual Meeting

2018
YP keynote speakers and track chairs at European conferences

Digitalization, a major factor in Pharma 4.0, is a reality for YPs, Landertinger said. He pointed out that streaming and online communities already dominate their lives. Being familiar with these technologies gives YPs a high "digital maturity" level. In conclusion, he outlined how digitalization is affecting job profiles and how robotics is changing the workspace.

YP networking and acknowledgments

A networking dinner drew over 60 ISPE members including YPs, Board members, GPMLF members, and ISPE staff. Tables were mixed to allow meaningful networking for everyone. Many thanks to Novo Nordisk, who sponsored this large dinner.

The Italy Affiliate, as the host country, sponsored a second YP dinner to allow Hackathon participants, who represented 10 different countries, to meet in advance of the event. Many thanks to Frederico Poli and Matteo Pracchia from the Italy YPs for choosing a wonderful restaurant and treating us to classic pizzas and pastas!

Many thanks also to Thomas Zimmer, Elmarie Herloff-Petersen, the team at EUROKONGRESS GmbH, and the Italy Affiliate for their support. Much appreciation goes also to Sartorius-Stedim Biotech for sponsoring refreshments as the YPs worked late into the night of the Hackathon! Thanks also to the affiliates and corporations who sponsored many of their YPs' participation and travel.

YPs and coaches at the Pharma 4.0 Hackathon

Thorsten Böhle, Chair, DACH YP, presents the Hackathon results

PHARMA 4.0 HACKATHON

The biggest YP event at this year's Europe Annual Meeting was the Hackathon, which was organized by Craig Milner, Senior Project Engineer, Sanofi and UK YP Chair; and Chloe Lang, Senior Data Scientist, Sartorius-Stedim Data Analytics, and DACH YP.

The Hackathon is a 24-hour challenge in which YPs work in groups to explore, strategize, innovate, and overcome future industry challenges. The Pharma 4.0 event was the second of its kind; the inaugural Hackathon was held at the 2017 Europe Annual Meeting in Barcelona.

The YPs, who hailed from 10 different European countries, were supported by four coaches: Damian Greene, Senior Associate, Lachman Consultant Services; Christian Wölbeling, Senior Director Global Accounts, Werum IT; Dr. Michelangelo Canzoneri; Digital Operations Leader, Sanofi; and Davide Smaldone, Corporate IT Demand Manager and Pharmaceutical Track and Trace Expert, Menarini Group.

The first day started with an introduction from each coach on concepts such as ICH Q10, Pharma 4.0, building business cases, and breaking down industry silos. After each YP group chose a topic or challenge as its focus, they selected a starting point from among a variety of options, including biotech allogeneic/autologous therapy, regenerative medicines, personalized/individualized medicines, single-use technology, regulatory challenges, small-molecule factories of the future, process analytical technology (PAT), automation architecture, data integrity, big data, serialization, artificial intelligence, unmanned factories, and many other examples.

Groups of six were divided into two teams. Three members were the "client" and three were the "consultant." The client, who had a $5 billion investment fund, had to consider an area for development over the next five years. The consultant team had to help guide the client to develop the concept, a high-level business case, and charter for design and implementation.

THE HACKATHON IS A 24-HOUR CHALLENGE IN WHICH YPs WORK IN GROUPS TO EXPLORE, STRATEGIZE, INNOVATE, AND OVERCOME FUTURE INDUSTRY CHALLENGES

Having settled on their respective challenges, each YP group chose their own area of focus. Interestingly, all teams selected a personalized medicine concept, but each had a different approach and area of innovation; all included a holistic manufacturing control strategy.

To challenge the YPs to back up their ideas and show value, each group also created a business case that supported their concept. While all partici-

2018 Hackathon Participants

- Niels de Blende, ISPE YP Belgium
- Thorsten Böhle, F. Hoffmann-La Roche AG
- John Clarke, Pfizer
- Christiane Dickel, Werum IT Solutions GmbH
- Anna Emanuelsson, ABB
- Lise Heyninck, Novartis
- Caroline Kustermans, Altran Belgium SA-NV
- Chloe Lang, Sartorius-Stedim Data Analytics
- Martina Laus, Novartis
- Craig Milner, Sanofi
- Fiachra O'Raghallaigh, John Sisk and Son
- Marick Paris-Cadet, Technip
- Margot Pazzaglia, Techniconsult Firenze Srl
- Federico Poli, Italia Automazione Srl
- Matteo Pracchia, CTP System Srl
- Diego Rodriguez Yañez, Eli Lilly and Company
- Thomas Rubow, NNE
- Beatriz Sacristan, Pfizer
- Marta Malo de Molina Solano, Laboratorios Farmacéuticos Rovi
- Jan Wambeke, Pfizer
- Thomas de Vliegere, MSD Heist Operations

pants had strong technical backgrounds, the business case calculations were clearly challenges. This demonstrates that interdisciplinary knowledge is not yet a standard component of education in the sciences.

Concept 1

The first YP group chose the problem of drug shortages caused by increased population. Focusing on a low-volume, high-value product (hormone therapy), they found two areas affected by product loss or wastage in the supply chain. By tailoring the dose to patient need and not overfilling, they developed a concept that charged per patient per year instead of per vial.

Other concepts considered were using an injectable chip to monitor and determine needed dosage, a technology already in the market. Chip data analysis results would be sent directly to the manufacturing site as an order. This could reduce some patient data issues raised by the European Union Data Protection Regulation Act, since only the analysis is sent to the production site; the data is owned by patient. The drug would be validated as one product strength with variable fill volume. In-process control and release testing would be in real time using PAT, and personalized packaging with serialization would track the product. The group proposed that distribution be outsourced (e.g., Amazon) with a quality agreement and tracking.

Concept 2

The second concept considered a disruptive approach by rethinking drug-to-patient supply. The idea originally focused on cholesterol, but the group decided another target might be more appropriate. In this case the YPs chose to locate diagnostic equipment (single use, disposable chip analysis) at a pharmacy. The manufacturing facility would be located at the distribution center with concepts including factory on a truck, plug and play, adaptive formulation with exact quantities, and 3D printing. The product would be delivered to the patient's home, and diagnostic data could be fed back for improved formulation and efficacy.

Concept 3

The final concept took the option of providing a drug that could cure leukemia. This YP Group developed a factory of the future with an automated production process that used augmented reality to train operators, and blockchain for data management (data integrity and security). Since the time to patient delivery is crucial, smart packaging was proposed. The drug product would be packaged and sent to the patient while final release testing was being performed. The package could not be opened until quality had been approved, reducing the need for on-site storage.

At the end of their work, after only a few hours' sleep, the YP groups presented their results to the GPMLF. Each group pitched their concept to the forum members, who acted as potential investors for each project. The key question was always: "Will you trust and invest in our business idea?"

The Hackathon provided a great opportunity for YPs to meet each other, interact with industry leaders and develop their knowledge around current industry guidelines and trends. Results were presented during the Pharma 4.0 track by Thorsten Böhle, DACH YP, showcasing the YPs and their hard work.

And in case you're wondering: The second concept won the challenge. ‹›

Caroline Rocks is IYPC Chair, Ireland YP, and Senior Process Engineer, AbbVie, Inc.

Craig Milner, MEng, is UK Affiliate YP Chair and Senior Project Engineer, Sanofi Genzyme

Chloe Lang, is a DACH Affiliate YP, and Senior Data Scientist, Sartorius Stedim Data Analytics AB

Check out the online YP community page for more photos and information of the YPs at ISPE Europe Annual Meeting. It's easy to join our YP community; just select it during your registration process or update your existing account on www.ISPE.org.

We welcome more volunteers to grow our YP groups globally and to participate in local and international ISPE events. If you are interested in finding out more, email us at ask@ispe.org and put "IYP Chair" in the subject line.

Join the conversation on the YP Community page: http://cop.ispe.org/yp

2018 ISPE TRAINING

TRAINING SCHEDULE

SEPTEMBER

Lyon, France

- Applying Bio Manufacturing Principles, 18–19 September
- Bio Process Validation, 18–19 September
- Risk-Based Commissioning and Qualification, 18–19 September
- Overview Bio Manufacturing Processes, 18–19 September

Bethesda, MD

- GAMP® Data Integrity, 10–12 September
- Quality Assurance for Facilities Management, 13–14 September
- Cleaning Validation Principles, 17–18 September
- Process Validation Lifecycle, 19–21 September
- GAMP®5, Annex 11/Part 11, 24–26 September

OCTOBER

New Brunswick, NJ

- Commissioning and Qualification, 3–4 October
- HVAC, 1–3 October
- Process Validation Lifecycle, 1–3 October
- Sterile Facilities, 1–2 October
- Basic GAMP®, 1–3 October
- Technology Transfer, 3–4 October

Boston, MA

- Water Generation, 15–16 October
- Water Storage, Delivery, and Qualification, 17–18 October
- CIP System Design, 15–16 October
- OSD, 15–16 October
- Basic GAMP® 5, 15–17 October
- GxP Process Control Systems, 17–18 October

NOVEMBER

Philadelphia, PA

- Cleaning Validation, 8–9 November
- Project Management, 8–9 November
- Quality Management Systems, 8–9 November
- Quality Assurance for Facilities Management, 8–9 November

Vienna, Austria

- Cross-Contamination (Risk-MaPP), 26–27 November
- Applied Quality Risk Management, 26–27 November
- Bio Process Validation, 26–27 November
- GxP Process Control Systems, 26–27 November
- Quality Management Systems, 26–27 November

DECEMBER

Bethesda, MD

- GAMP®5, Annex 11/Part 11, 5–7 December
- Quality Management System, 10–11 December

Huntington Beach, CA

- ICH Q7A GMPs for Active Pharmaceutical Ingredients Training Course, 13–14 December
- Applying Bio Manufacturing Principles, 13–14 December
- Overview Bio Manufacturing Processes, 13–14 December
- Quality Assurance for Facilities Management, 13–14 December

MAKING CPV A PROACTIVE COMPONENT OF PROCESS AND PRODUCT IMPROVEMENT

James Crichton and Frederick W. Faltin

Our purpose in this paper is to aid pharmaceutical companies in their CPV journey by sharing the lessons we have learned during our combined 70 years of practical experience. Although the content of this paper is primarily technical, we have added comments to illustrate the merits of this discussion where appropriate. We would have liked to include case studies and discussions of other topics, but that would have required much more material than space allows.

Change often takes years longer in the pharmaceutical industry than in others. Why can we not challenge that paradigm? The auto industry, for example, successfully forced changes to its supplier base within a couple of years. By benchmarking other industries that have dealt with similar problems, we can learn from their experiences.

While continued process verification (CPV) may be relatively new to the pharmaceutical industry, it is not new to most others. The automotive industry and its supplier base, for example, began to implement such programs in the 1980s. One of us wrote a book chapter on this subject in the early 1990s.[1] Building on that base, the current paper focuses on three key points:

1. Monitoring can mean many things, not just control-charting.
2. Process control strategy should be viewed as a living, risk-based business process subject to constant review and potential revision.
3. Industry should focus on the business process side of CPV, constantly improving its efficiency and effectiveness.

POINT 1

Monitoring ≠ control-charting

It is quite clear from our experiences in the pharmaceutical industry that "monitoring = control-charting" is a common mindset. We've seen this in a variety of ways:

- Auditors: "What is being monitored? Show me the control charts."
- The CPV monitoring plan showing variables as either "in" or "out."
- "We are monitoring critical quality attributes and a few critical process parameters."

This is an inadequate way of thinking. Monitoring is not a yes-or-no proposition, but a continuum—a view of the concept that has been utilized in the automotive industry for decades.[2]

As an analogy, imagine going to the hospital and hearing a doctor ask a nurse to begin monitoring the patient's blood pressure. The doctor does not mean the nurse should pull out a control chart. Rather, "monitor" indicates an appropriate level of observation, whether by cuff once an hour, twice a shift, or by automatic continuous monitoring.

The US Food and Drug Administration (FDA) recognizes this distinction. Consider, for example, the agency's guidance for process validation:

> The terms *attribute(s)* ... and *parameter(s)* ... are not categorized with respect to criticality in this guidance. With a lifecycle approach to process validation that employs risk based decision making throughout that lifecycle, **the perception of criticality as a continuum rather than a binary state is more useful.** All attributes and parameters should be evaluated in terms of their roles in the process and impact on the product or in-process material, and reevaluated as new information becomes available. **The degree of control over those attributes or parameters should be commensurate with their risk to the process and process output. In other words, a higher degree of control is appropriate for attributes or parameters that pose a higher risk.** [emphases added]

Later in the document, the FDA states that monitoring levels should be adjusted according to performance, not just in or out of the monitoring program:

> These estimates can provide the basis for **establishing levels** and frequency of routine sampling and **monitoring** for the particular product and process**. Monitoring can then be adjusted** to a statistically appropriate and representative level. Process variability should be periodically assessed and **monitoring adjusted accordingly**. [emphases added][3]

TABLE A: PROCESS MONITORING INTENSITY LEVELS

Level	Process monitoring intensity level
1	Recording data manually or electronically
2	Comparing data to specification limits
3	Plotting run charts
4	Plotting against pre-control or practical alert/action limits
5	Plotting control charts having statistically derived limits
6	Operating an automated controller (feedback or feedforward)

FIGURE 1: INDIVIDUAL CONTROL CHARTS, WITHOUT A (LEFT) AND WITH B (RIGHT) SPECIFICATION LIMITS

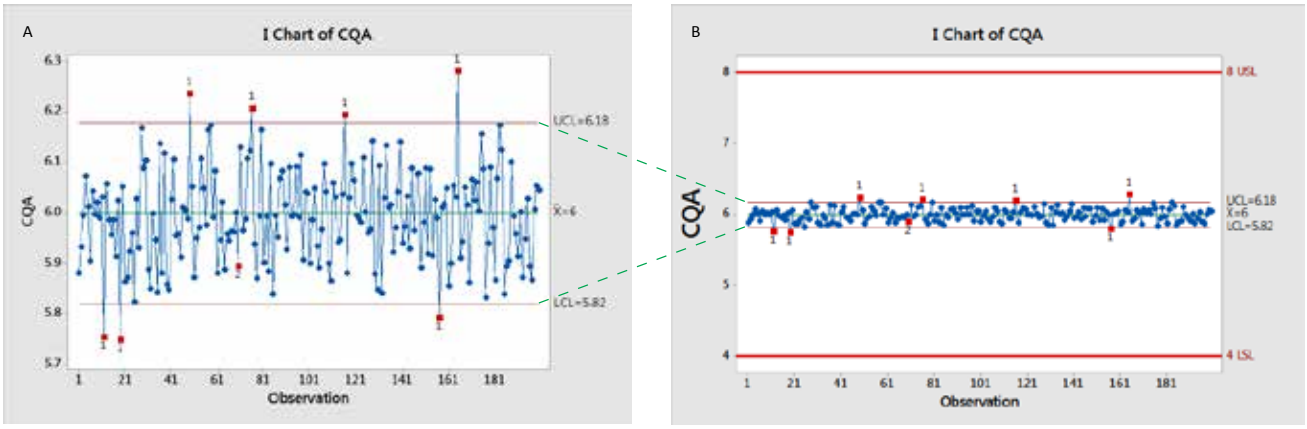
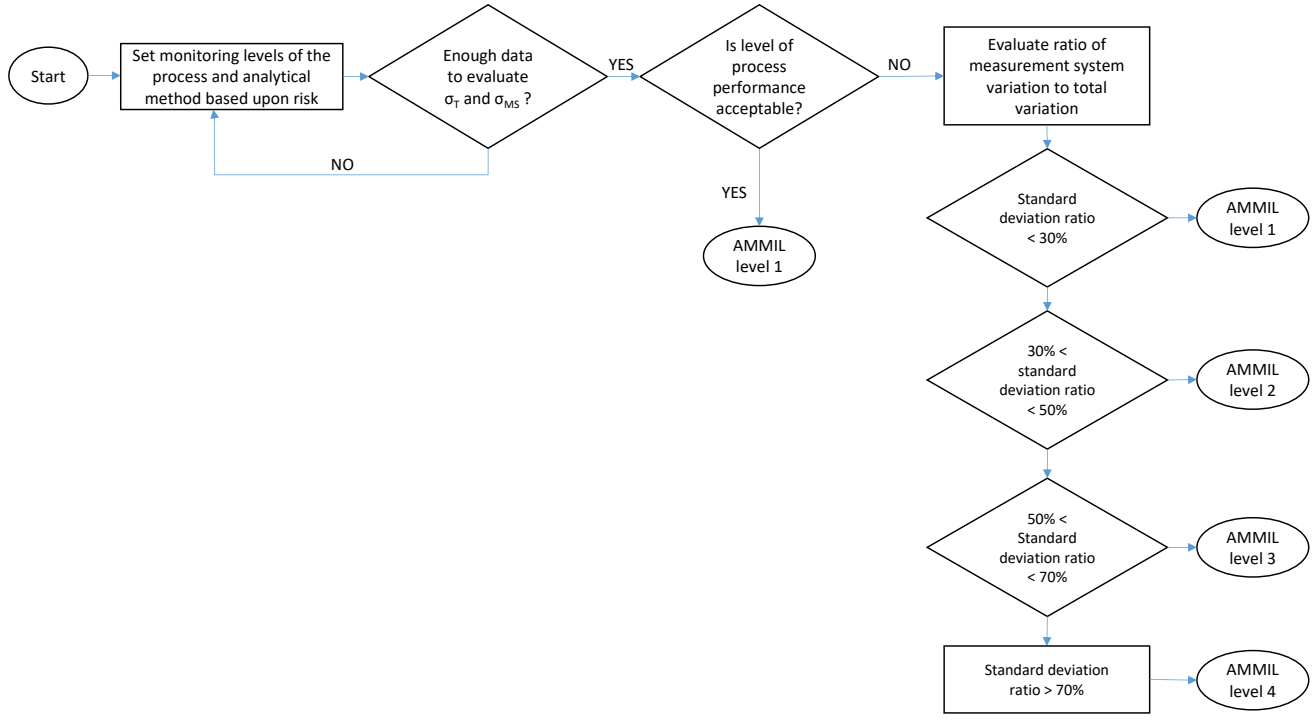


FIGURE 2: PROCESS FOR ANALYTICAL METHOD MONITORING



PMILs

Process monitoring intensity levels (PMILs) should be categorized and applied in specific instances based upon risk (see example in Table A). While the pharma industry certainly uses these control methods, they aren't usually called out and tied to risks.

PMILs are mutually exclusive, so each variable would be assigned to only one level at any point. Over time, a monitored characteristic might move from one level to another, depending on circumstances. Each variable considered would be assigned an appropriate PMIL, based upon risk level.

This is not a question of *what* is being monitored, but *how*. As risks change, the intensity level should change accordingly. We have seen numerous examples of variables—even those with very high performance levels—being control-charted even when they exhibit very high performance levels as measured by a metric such as the process performance index, or Ppk.

TABLE B: ANALYTICAL METHOD MONITORING INTENSITY LEVELS

Level	Variance ratio	Standard deviation ratio	Analytical method monitoring intensity level
1	< 10%	< 30%	Normal system suitability testing and standards testing (with acceptance limits)
2	10% –25%	30%–50%	Precontrol or practical alert/action limits
3	25%–50%	50%–70%	Control-chart system suitability testing/standards data
4	> 50%	> 70%	Investigation or remediation required

Figure 1, for example, shows a control chart of a variable. Taken in isolation, the message conveyed seems alarming (pun intended). When placed into the context of the specifications, however, it's apparent that this variation, whether from special or common causes, is virtually meaningless.

Extremely capable processes have been known in a variety of industries for decades. In cases of "excess capability," statistical process control methods should be adapted to provide meaningful information. Control-charting was developed on the assumption that the process under study was unstable or, at best, stable but marginally capable. Manufacturers needed a way to discover changes quickly to avoid producing nonconforming product.

"Excessively capable" processes represent the opposite of this scenario. Their high Ppks demonstrate that their centerline and variability are unlikely to produce out-of-specification product. We plan to devote further attention to this issue in a subsequent paper.

We've often heard the argument that specifications do not reflect what is clinically relevant. If so, the fault lies with the specifications. They should be changed, even if only internally, thereby creating a new performance (Ppk) value and risk level to drive the level of monitoring assigned. We've also heard the argument that every signal is an opportunity to learn, regardless of the specifications. Imagine doing an Internet search that retrieves millions of results, then sifting carefully through each one, instead of applying the Pareto principle* to determine the appropriate choices. In industry, over-monitoring can produce an essentially infinite number of out-of-control signals, making it impossible to devote equal energy to all of them. (We will address this and related issues below, in the section on efficiency and effectiveness of CPV as a business process.)

These same ideas apply to CPV monitoring of analytical methods. Risk levels should be evaluated by measuring the influence of the measurement system on release data. One way to do this is to calculate the ratio of the measurement system variability $(\sigma_{MS} \text{ or } \sigma_{MS}^2)$ over the total variability $(\sigma_T \text{ or } \sigma_T^2)$ of the release data. In Six Sigma literature, the ratio of standard deviations σ_{MS} or σ_T, when expressed as a percentage (Table B), is called the "percent repeatability and reproducibility," or simply %R&R. An analytical method monitoring intensity level (AMMIL) can then be established, based on performance categories. Table B shows an example of such an approach.

The goal of this risk-based approach is to maximize value-added work, as opposed to much of the non-value-added work that would result from intensely monitoring every analytical method with a control chart. Figure 2 shows a risk-based approach for analytical monitoring.

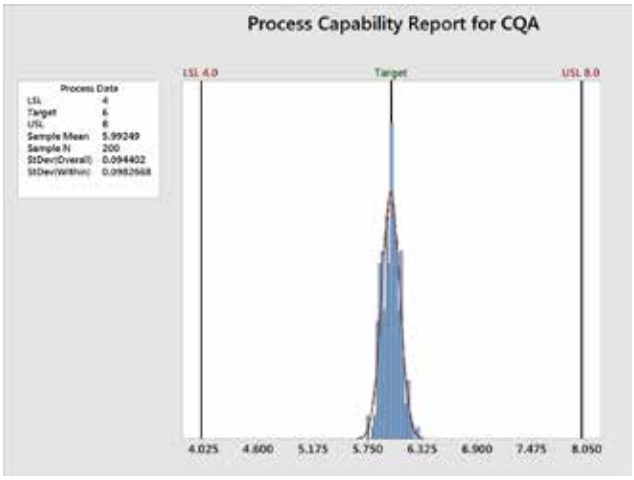
Initially, when only small amounts of data may be available, the AMMIL should be risk-based using all available information from development and validation. Once more data becomes available, then data-driven approaches help refine the AMMIL. Monitoring should remain at level 1 when the process performance of the variable is good, such as when Ppk > 1.0.

Figure 3 shows the historical performance of a variable as an example. The performance is clearly very high, with a Ppk value of around 7. The analytical method is certainly not a concern here, as variation in the measurement system cannot be greater than the total variation. In cases such as this, we do not care if the measurement system contributes 10% or 90% of the total variation. Total variation is acceptable, period. Any further work beyond level 1 AMMIL or periodic revalidation of the method would be non-value added. If the level of process performance is not acceptable, then the AMMIL should

A TYPICAL INVESTIGATION REQUIRED ABOVE 100 MAN-HOURS

* Named for 19th-century Italian economist and philosopher Vilfredo Federico Damaso Pareto, the Pareto principle states that for many events, roughly 80% of the effects come from 20% of the causes.

FIGURE 3: EXAMPLE OF CRITICAL QUALITY ATTRIBUTE PERFORMANCE



be based on a comparison of the method variability to the total variation from the process as depicted in Figure 2.

In summary, increased monitoring or improvement work for analytical methods should focus on low-performing variables where the analytical method variation is also a major contributing factor to total variability.

POINT 2

The control strategy is a living business process

While the pharma industry is focused on risk assessments and control strategies, we believe it also has some weaknesses besides the narrow view of monitoring. One of these is too little use of formal control plans. Figure 4 shows a high-level view of the situation.

Knowledge from research and development, including subject matter expertise, experience, and design of experiments work should initially drive the risk assessment. A tool such as failure modes and effects analysis is a good device for identifying original risks before controls, and residual risks with controls in place. Starting from the original risks, the team should document how the control strategy will mitigate or control the higher risks. (Again, other industries have been doing this for decades, using the formal methodology of a control plan.) While the typical control strategy document contains most of the information, we maintain that an actual control plan document portrays the information in a clearer, more efficient, and more effective manner because it is designed to show the relationship between risks and monitoring intensity—type, location, and frequency of data gathering, with the corresponding PMIL—as well as a reaction/corrective action plan for dealing with deviations.

IN OUR OBSERVATION, THE POTENTIAL FOR FALSE ALARMS (AND THEIR CONSEQUENCES) IS GENERALLY NOT WELL UNDERSTOOD

POINT #3

Efficiency and effectiveness

CPV is not just a compliance program: It is a continuous improvement effort, a business process that should be evaluated as any business process would be for its efficiency and effectiveness (E&E). Companies should understand that their CPV programs add value besides compliance with FDA requirements. The agency has clearly stated that it intends for companies to learn how "[d]ata gathered during this stage might suggest ways to improve and/or optimize the process..."[3] This can be accomplished by investigating signals from control charts and using historical data offline for troubleshooting and correlation studies.

Let's take a look at the E&E of using control charts in pharma. The tendency is to want to control-chart anything and everything (just in case), highlighting signals in the statistical software and forcing many impractical investigations. So, going back to Point 1 and the word "monitor," we need to make sure we are control-charting and reacting appropriately only where this level of intensity is required. The industry is beginning to recognize that not all signals need full investigations.[4] This is a step in the right direction, but pharma needs to change risk and control plans based on performance, as discussed above.

Efficiency

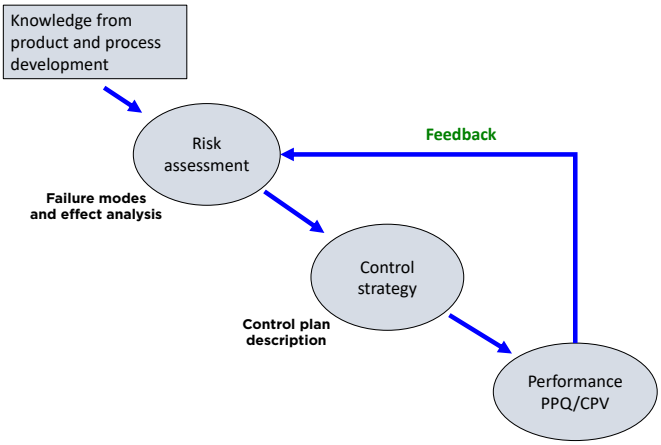
Efficiency is a measure of the time and resources required to support a process and produce an output.

In the CPV context, one area of efficiency involves the amount of time and resources spent on investigations. Think about the various steps involved in a typical signal investigation:

- Record and monitor the event in a tracking system
- Investigate possible issues for this particular measurement
- Search the manufacturer's batch records for discrepancies
- Evaluate past data
- Come up with hypothesis to test
- Declare a root cause
- Write a report that pins the root cause onto something logical
- Include any action items that result
- Send the report for review by numerous people, including quality assurance
- Potential interactions and discussions with regulatory agencies

[†] A process control method to determine whether a variable is out of control (unpredictable versus consistent)

FIGURE 4: INFORMATION FLOW REVOLVING AROUND THE CONTROL STRATEGY



SINCE THE FDA ISSUED ITS 2011 GUIDANCE, THE TENDENCY IN PHARMACEUTICAL MANUFACTURING HAS OFTEN BEEN TO OVER-MONITOR PROCESS AND PRODUCT PARAMETERS

In thinking about efficiency, a key principle is: Every moment spent on one activity is time spent away from something potentially more important. Relating this to the Pareto Principle, it means that every moment spent on the low end of the scale is time away from the high end. Figure 5 shows the Pareto principle as applied to control chart signals. Time spent on false signals is not only costly, but takes time away from analyzing the big practical signals.

Out of curiosity, one us studied the number of false alarms that would be generated just in the tablet compression area of a site if control charts were applied rigorously to tablet weight and hardness monitoring. Given the production volumes, number of lines, etc., a 1% false alarm rate typical of the four Nelson Rules[†6] was calculated to result in around 10 false alarms per day. It's easy to see how expensive this would be.

We collected anecdotal data from knowledgeable people who perform investigations at various sites. Our findings showed that a typical investigation required above 100 man-hours on average per investigation. One site estimated the cost to be around $5,000 per investigation—a figure that we regard as extremely conservative. Now multiply this by the number of potential false alarms, and it's easy to see why this is such an expensive proposition. It's also why we need to focus on the business side of CPV.

In our observation, the potential for false alarms (and their consequences) is generally not well understood. Even in the simplest control-charting scenarios, applying all of the common Western Electric rules,[6] as many practitioners do in statistical software, can lead to false alarm rates of 2% or more. Imagine your control chart giving a false alarm on average every 50, or even every 100, observations. Now imagine *all* of your control charts giving false alarms every 50–100 points. The cost implications are staggering; what's more, consider the harmful effects of making process changes based on the spurious root causes identified for these false signals.

Effectiveness

Effectiveness, on the other hand, measures how well a process achieves its intended purpose.

How would effectiveness be seen in a CPV context, especially in reaction to control chart signals and the resulting investigations? Very simply, how often is a root cause actually found, a solution implemented (to either correct or prevent the cause in the future), and data gathered to demonstrate that the changes are actually working?

Every site has a favorite case study that can be pulled out of the file cabinet to demonstrate that the CPV process of investigation actually did something positive beyond compliance. But that is one out of how many investigations? Did the case study demonstrate improved performance? What effect did it have on the business?

FIGURE 5: PARETO PRINCIPLE APPLIED TO SIGNALS

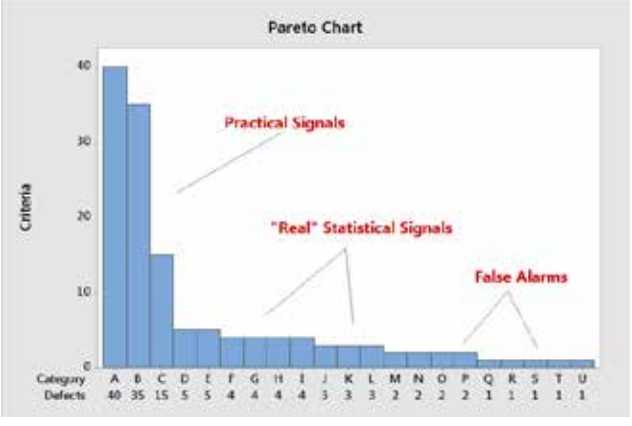
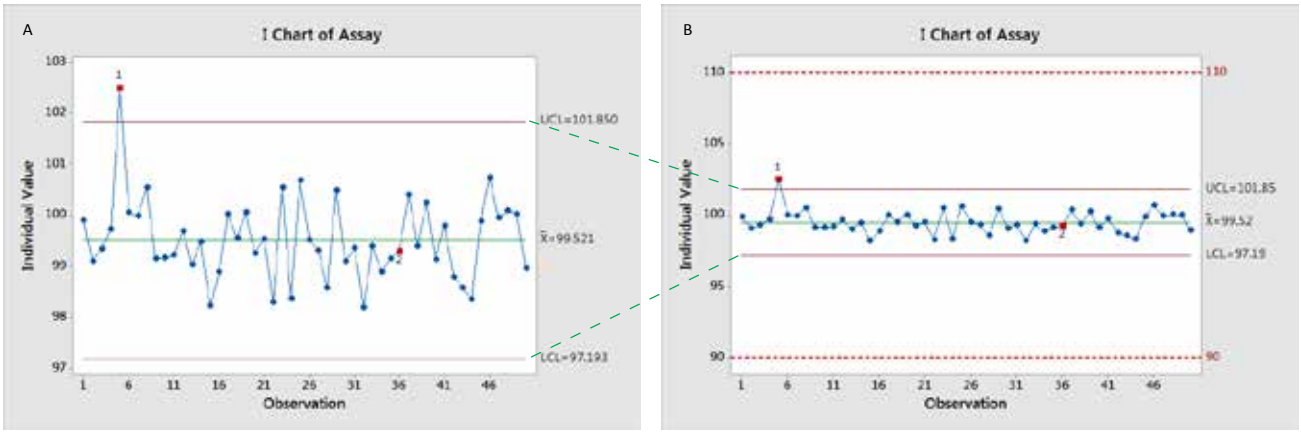


FIGURE 6: CONTROL CHARTS WITHOUT A (LEFT) AND WITH B (RIGHT) SPECIFICATION LIMITS



WE ENCOURAGE INDUSTRY AND REGULATORS TO ADOPT CPV PROCEDURES THAT DRAW ON BEST PRACTICES FROM OTHER INDUSTRIES

In an informal survey of a number of sites, one of us found the effectiveness rate of investigations was estimated to be below 10%. It appears that the real motivation behind these investigational reports is to complete them on time, have a logical "excuse" for the signal, and stay out of trouble with the FDA when asked about them. After all, the cost of this inefficiency and ineffectiveness is passed on to consumers/patients/governments, so what is the incentive to change?

Part of the answer lies in the realization that the ostensible root causes found for false or minor signals are likely to be erroneous. (We can only wonder how likely is it that enacting "corrective" actions will, in fact, do harm rather than good, and inflict unacceptable societal and financial costs in the process.) Another factor that should motivate change is the increased scrutiny pharma is beginning to face from payors, regulators, and even politicians. As pricing comes under greater pressure, continuing to allow costly inefficient/ineffective practices will cease to be viable. We recommend that industry and regulators together study these issues from a more practical, realistic, and cost-conscious perspective, while, of course, maintaining focus on patient risk.

RECOMMENDATIONS

As we mentioned earlier, it's important to stay updated on the PMIL required of variables being monitored. One way to do this is to limit the number of control charts that require reaction plans—designate only those that are truly needed. Second, utilize the Pareto principle to focus response on practical signals, based on risk (Figure 4). Set up systems that will detect the signal as quickly and as close to the source as possible. Finding signals weeks later, when the test results become available and much more production has taken place, makes identifying true root causes extremely difficult. It's not unlike the criminal justice axiom that says if good evidence is not found within 48 hours, the chances of solving the crime fall dramatically. The same logic could be applied here. Other good suggestions for improving effectiveness can be found in Scherder.[5]

Let's look at an example to see what the potential effects of an investigation could be. Figure 6(a) shows a control chart of an assay with two signals of potential special causes. Past thinking would suggest that investigations should be opened for each of them. This is where realism, business sense, and risk-based thinking are needed. Figure 6(b) puts this finding into context by showing it relative to specifications.

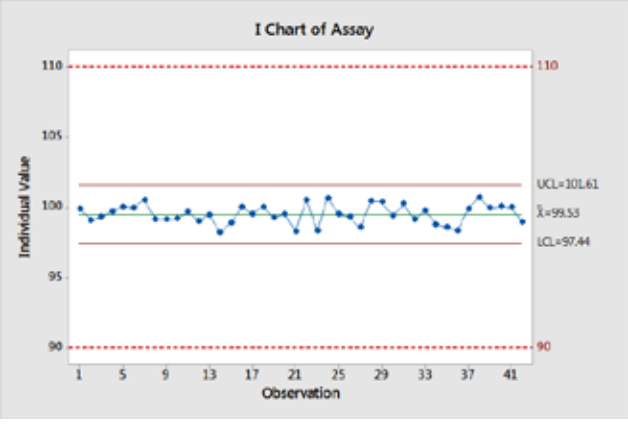
Why is this being control-charted? The performance would suggest that a lower MIL be applied. The Ppk value for this process is around 3.5, with an estimated out-of-specification (OOS) risk of < 0.0000002%, which is the value when Ppk = 2.0.

Let's suppose we actually do find a root cause and implement a successful solution. What would be gained? Figure 7 shows what would happen. We have eliminated the special-cause variation, Ppk has increased to 3.9, and the estimated risk of OOS is now even further < 0.0000002%. Imagine when these results are presented to management to demonstrate that we just spent $10,000 on two investigations to reduce the risk of OOS from << 0.0000002% to <<< 0.0000002%!

CONCLUSION

Companies have choices in approaching CPV. In the US, the FDA has made it clear that companies can and should exercise rational discretion in adapting

FIGURE 7: CONTROL CHART WITHOUT SPECIAL CAUSES



the degree and type of monitoring applied to a given parameter, based on the risk of deviation from required performance. MILs such as those proposed here provide a valid and practical mechanism for implementing such a program, while maintaining focus on the Pareto principle for fundamental process improvement.

Nonetheless, since the FDA issued its 2011 guidance, the tendency in pharmaceutical manufacturing has often been to over-monitor process and product parameters, even when unjustified by any realistic risk of nonconformance to specifications. In many organizations, dogma then requires investigation of any and all signals that arise. Together, these practices squander countless man-hours of effort in pursuit of process deviations that are minor or, in some cases, entirely spurious. This waste not only builds unnecessary cost into all pharma products thus affected, but actually incurs risk by diverting resources from more to less critical opportunities for improvement and by raising the possibility that some of the "fixes" applied may actually result in harm rather than good.

The authors wholeheartedly endorse a risk-based approach to process monitoring that embraces the continuum paradigm the FDA has articulated, and which employs the MIL concept for both processes and analytical methods to implement a "statistically appropriate and representative level"[3] of oversight for each key parameter. Such methods are truly customer-focused and provide the means to maximize efficiency and effectiveness of the business process, while maintaining and improving quality.

We encourage industry and regulators to work more closely to adopt CPV procedures that draw on established research and known best practices from other industries, focusing on substance rather than form, to improve quality, reduce costs, and promote the public good. ‹›

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About the authors

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Frederick W. Faltin is Associate Professor of Practice in the Department of Statistics, and Director of Corporate Partnerships for the College of Science, at Virginia Tech. He is also Cofounder and Managing Director of The Faltin Group, a consulting and training firm providing services in statistics, Six Sigma, economics, and operations research to companies throughout the Americas, Europe, and Asia. Previously, he founded and managed the Strategic Enterprise Technologies laboratory at GE Global Research. Faltin has published books, research papers, and articles on statistics and related topics, including the *Encyclopedia of Statistics in Quality and Reliability* (2007), *Statistical Methods in Healthcare* (2012), and *Analytic Methods in Systems and Software Testing* (2018). He is a Fellow of the American Statistical Association and a recipient of the American Society for Quality's Shewell Prize. Faltin received his SB in mathematics from MIT, and holds MS degrees in both mathematical statistics and operations research from Cornell University.

SURROUNDING AND CONTROLLING UNDERGROUND LEAKS

Double-Wall Containment: An Answer to Unsafe Piping Systems

Bashar Madani

While most in the pharmaceutical industry understand the need for double-wall containment piping systems, our field observations indicate that many companies do not. We frequently see pipes that should be (but are not) double-wall containment systems. This article presents an overview of the topic, so that readers who may not know they have a problem might be motivated to have their piping system upgraded. We also discuss risk management as a multifaceted, nonlinear process to further illustrate the risks of not having a containment system in place.

Leaks cannot always be prevented, but they can be contained. Because leaks in underground fluid pipes can take years to make themselves known, the choices and expenses of containing a toxic, corrosive, and/or hazardous leak present a challenge to decision-makers, especially in the pharmaceutical field, where leaks can pose especially deleterious threats to public health and require urgent solutions.

For underground fluid-transferring systems, one of the best ways to achieve peace of mind and ensure compliance with the US Environmental Protection Agency (EPA), Resource Conservation and Recovery Act, and other guidelines is to use double-wall containment piping systems. EPA regulations[1–3] mandate that underground transportation of hazardous materials must be protected from release into the environment.

DESIGN CONSIDERATIONS

Whether installing a new double-wall containment piping system or altering an existing system, there are several design considerations to address, including pipe materials, fluid temperature and pressure, leak-detection methods, inspection, and testing requirements.

Pipe materials

Double-wall containment pipe is designed as its name suggests. The choice of material for both the carrier or product (inner) pipe and the containment (outer) pipe material depends on the liquid type, temperature, pressure, and corrosive properties. Polypropylene can be the least expensive; stainless steel can be among the most expensive. Fiberglass-reinforced plastic (FRP) pipe is lightweight and strong, and provides a good return on investment for the proper circumstances. Table A compares representative pipe materials and applications.

What the table does not convey are the many choices and tradeoffs available for specific combinations of chemicals, media and fluid temperatures, as well as fluid pressures and system materials, including combinations of carrier and containment pipes with and without internal and external coatings. Neither does it represent all the questions of installation, safety, costs, and ease of use or maintenance. The final cost of the system, including pipe materials, leak detection system, design fees, installation, testing, commissioning, and documentation may have less to do with the pipe materials themselves than with the final configuration necessary to make sure the fluid leak can be contained.

FIGURE 1: STAINLESS STEEL DOUBLE-WALL CONTAINMENT SYSTEM

PHOTO BY BASHAR MADANI

INSTALLATION

Installation time ranges from almost immediate "plug and play" quick socket fusion to multiple hours of on-site welding, depending on the system. When installing a pipe system, it is important to plan for and include leak-detection, inspection, and pressure-testing procedures. The keys to making the right decisions and lowering project risk are: 1) choosing a well-designed system as specified by an experienced engineer; 2) following manufacturer procedures; and 3) using trained installers.

Leak detection

The automatic leak-detection and reporting system can be located between the inner and outer pipe and at the lowest point of the system. Leaks can also be detected and observed through multiple inspection ports located at the lowest level of the pipe system or at a collection double-containment sump. Because electronic systems can fail, to be truly proactive and safe any system design should include frequent visual inspections for leaks as mandated by toxic substance control regulations.

Inspection and pressure testing

A complete visual pipe inspection for both carrier and containment systems should be performed before pressure testing, including welds, joints, cracks, and slopes. Once the visual inspection has been completed, a pressure test can be conducted as follows:

CARRIER PIPE

Once the carrier pipe is installed, it is essential to certify the pipe and to confirm that it can handle the design pressure. For a gravity-flow system, most plumbing codes require a 1/8 inch per foot slope and a working head pressure test for 15 minutes. Other systems may require that the system be certified at a higher pressure rating; this will allow more flexibility for future pipe inspections with higher-pressure media, especially when a suspected leak cannot be located with a borescope. Choosing the correct pipe material will determine the system's ability to handle higher pressure testing.

CONTAINMENT PIPE

When the carrier pipe has passed both the pressure test and an inspection by a certified professional, the containment pipe can be closed and tested. Usually, this requires a lower pressure rating test than the carrier pipe. In some systems, the containment pipe is tested when the carrier pipe is charged.

In general, inspections and testing can be progressive or sectional. This is determined at various project phases.

UNDERGROUND OR ABOVEGROUND?

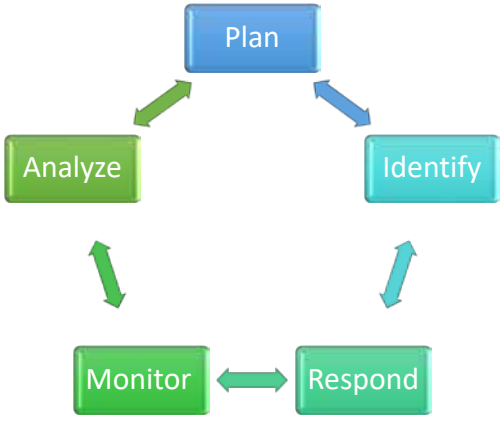
Underground and aboveground containment piping systems both have pros and cons.

Underground

Pro: In some applications, underground fluid-transfer systems rely on gravity flow, avoiding pump and installation costs.

Con: Underground double-walled containment piping in an elongated system can hide a slow leak for a long time before it finds its way to the end or lowest point of the piping system. Pinpointing a particularly small leak's location can be a challenge, especially when it's not detectable via a borescope inspection. Additionally, false alarms can occur when an automatic leak-detection system can't differentiate between a dangerous toxic leak and harmless condensation between the inner and outer pipes. Frequent manual inspection and testing can preclude these false readings, averting unnecessary stress and expense.

FIGURE 2: RISK-MANAGEMENT PROCESS



Aboveground

Pro: Aboveground systems make leak detection simpler, if only because manual observation is straightforward. An inspection leg with a sampling port can be added to the pipe system to collect fluid leaking from the containment system. Additionally, the containment pipe in a polypropylene system can be clear polypropylene; stainless steel pipe can include a dead leg to check for carrier pipe leaks.

Con: A toxic leak in an aboveground system—especially above a building complex—can enter the public water system through a roof drain or site water runoff. Precautions such as a secondary containment pipe or containment pit may be required to prevent accidental damage to the physical plant and mitigate danger to employees.

RISK-MANAGEMENT PROCESS

Piping system selection is subject to space restrictions, fluid pressure, installation, fittings, documentation requirements, susceptibility to cracking—and, of course, cost. There is no one-size-fits-all solution. It is important, therefore, to identify risks and incorporate an overall risk-control methodology.

Surrounding and controlling toxic underground leaks hinges on a commitment to risk management. Risk management is not linear in its execution. It is a multifaceted process that requires simultaneous attention to identifying, analyzing, monitoring, planning, and responding. This may be a difficult position to accept, but we believe it is important.

Negligence and ignorance are expensive, not only in monetary fines that can run into millions of dollars, but more importantly in health problems, employee or community medical costs, equipment damage, lost production, rebuilding costs, environmental issues, and damage to the organization's reputation.

TABLE A: PRODUCT COMPARISON MATRIX

Manufacturer	A	B	C
Material: carrier and containment pipe	Polypropylene	FRP	Stainless steel T316L
Applications	▫ Drainage applications ▫ Chemical resistance ▫ Pressurized transfer line ▫ Underground installation	▫ Acid ▫ Salts ▫ Chemical and industrial processes ▫ Solvents and caustics	▫ Plant chemical distribution lines ▫ Water and wastewater ▫ Acid systems ▫ Pharmaceutical
Maximum temperature (°F)	160	160	700
Carrier pipe diameter (inches)	1–16	1–12	0.5–20
Containment pipe diameter (inches)	3–20	3–16	2–26
Internal corrosive coating	None	Epoxy	None
External corrosive coating	None	Epoxy	None
Wall thickness (inches)	0.280 for 6×8 inch	0.170 for 4–6 inch 0.220 for 10–14 inch	0.28 for 6 inch 0.365 for 10 inch (schedule 40 pipe size)

Compliance decisions rendered against companies will be based on variables that include the fluids' corrosive or hazardous properties, temperature, and conformance to codes such as ASME Process Piping Standard B31.[3]

Selecting the proper materials is an important step. Stainless steel piping and fittings are among the most expensive of the products listed above, but they may be the only options that will contain leaks when operating and testing a pipe under high pressure. Polypropylene or FRP might work for now. But because new materials and science are continually advancing, an annual system review—at a minimum—is prudent. Quarterly and monthly evaluations are recommended. Daily inspection and system evaluation is the best defense against failures.

CONCLUSION

Today's marketplace demands responsibility and responsiveness, but the world's need for proactive attention to containing and preventing toxic leaks cannot be overlooked. Double-wall containment piping systems, when correctly researched, properly installed, and professionally attended will help avert crises, injury, disease, and death. Component choices can be compared objectively with the help of designers and experts, and then certified by a professional engineer before the project is submitted to the appropriate governmental entity for approval.[4–5]

The pharmaceutical industry is fortunate to have an abundance of engineers, suppliers, and designers to discover the best, most effective, lowest risk double-walled containment systems for surrounding and controlling underground toxic pipe leaks. ‹›

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BRINGING CYBERSECURITY TO GXP SYSTEMS

Jason Nathaniel Young and John Patterson

Recent cyberattacks like WannaCry and Petya have affected GxP computerized systems, prompting questions on how to address risk from cyberspace using traditional computerized systems validation according to GAMP® 5. This article explores life cycle management of GxP computerized systems and associated cybersecurity risks that can affect patient safety.

Look at any ISPE conference around the world and you'll see that interest in cybersecurity has increased significantly. Unfortunately, confusion and misinterpretation have also accompanied this growth. To discuss cybersecurity issues properly, let's start with a quick overview of what cybersecurity is and how it is implemented.

Cybersecurity is a set of actions taken by stakeholders to reduce risk to systems and information in cyberspace. These actions combine all aspects of information security to address needs for confidentiality, integrity, and availability (known as the "CIA triad") with critical information infrastructure protections.

In the context of protecting GxP-regulated computerized systems, cybersecurity is a method of applying technical and procedural controls to reduce risk to both systems and patient safety. This is accomplished in two ways: identifying and addressing system vulnerabilities and data integrity threats, and providing traceability to established frameworks and technical controls for computerized systems validation (CSV) and corrective and preventive action (CAPA). These activities are implemented via an information security management system (ISMS),* which operates according to established cybersecurity frameworks as well as internal company policies and procedures.

The ISMS becomes a separate organization, built on standard cyber-security roles and responsibilities, that is tasked with enforcing information security governance. The ISMS includes positions such as:

- Chief information security officer
- Information security officer
- Information security manager
- Information system security office

To ensure proper separation of duties, these positions may be imbedded within information technology (IT) governance, but they must be independent of it, and not part of IT management. This is a crucial element of the ISMS, as the purpose of security—whether it be a management or governance position—is to verify that the security configuration is set as directed by the organization's policies and procedures. These established roles and responsibilities rely on methodologies for the implementation of cybersecurity using concepts like defense in depth to manage cybersecurity centrally from within the enterprise. Simply put, "defense in depth" means that security controls increase with each layer of an organization's architecture that provides security to systems. This basic concept is to be maintained when managing the security aspects of standardization, configuration management, and vulnerability/threat monitoring.

This holistic view can make implementing cybersecurity within GAMP 5 guidelines challenging, because centralized production systems in any industry become problematic due to the individual nature of cybersecurity control requirements.

Because cybersecurity personnel are trained to work in specific ways, corporate cultural differences can create friction between the quality unit and ISMS. GAMP 5 terminology and systems-validation methods can conflict with International Organization for Standardization (ISO) and ISACA† definitions and lead to miscommunication. Quality units in other industries and government organizations use the ISMS to verify technical and cybersecurity controls within their validation process according to ISO and ISACA frameworks. No one from a US government quality unit, for example, would have administrative access to a system that was being qualified within their system. That quality unit would request this from the cybersecurity personnel who were qualifying the system.

Within the life sciences, the quality unit ensures that GAMP 5 security procedures for GxP-regulated systems are followed. This is important because regulators increasingly emphasize how and where cybersecurity controls are implemented for both GxP-regulated systems and their associated infrastructures. Questions also arise about how the quality unit should manage and implement cybersecurity controls with its CSV processes.

Since 2008, GAMP 5 has relied on the US National Institute of Standards and Technology (NIST) and ISO standards. More recent cybersecurity methods, however, are much more complex. We frequently see the confusion that arises from this complexity in discussion groups formed during our cybersecurity training.

Here are some sample questions about the organizational structure of the quality management system (QMS) and how ISMS operations can integrate their processes:

- From a cybersecurity perspective, what is the role of the ISMS representative for crafting policies and procedures on GxP-regulated systems within the QMS?

* A systematic approach that applies risk-management procedures to protect sensitive information, people, processes, and IT systems. Frameworks include ISO/IEC 27001, ISACA's COBIT 5, and NIST 800-53.

† Previously known as the Information Systems Audit and Control Association, ISACA—which now goes by its acronym only—is a nonprofit global association for the development, adoption, and use of globally accepted knowledge and practices for information systems.

- How should duties be divided between the quality unit, ISMS members who perform security-related verifications, and the IT department?
- How should risk to GxP-regulated systems from GAMP category 1 (infrastructure) systems be addressed?
- How should threat and vulnerability management be performed? More specifically, how would common vulnerabilities and exposures be used within the CAPA process to track and resolve high-level threats and vulnerabilities?

Other questions focus on areas within the CSV process that need clarification:

- Considering traditional ways of using GAMP categories 1, 3, 4, and 5, how should the system address impact, security categories, and data classification during the initial risk assessment?
- How should cybersecurity requirements that do and do not affect data integrity be defined?
- When using frameworks like ISO/IEC 27001 or COBIT 5, how can traceability to cybersecurity controls be used against GAMP 5 and regulations like CFR 21 Part 11?
- How can standards for cybersecurity technical controls like the Center for Internet Security‡ benchmarks or the Cloud Security Alliance‡ be used for traceability to technical controls?
- What testing methods or best practices can be used during operational qualification and installation qualification?

These are important areas that need consensus on how to deal with them and their effects on qualifying systems.

COLLABORATION

Fortunately, Chris Reid, a member of the ISPE Leadership Team, has announced a new collaboration between ISPE and ISACA to create cybersecurity guidance for the industry. This effort is supported by the highest levels of ISPE leadership. Discussions are expected to yield guidance from ISACA to the cybersecurity community and from ISPE to the quality unit.

With this in mind, the cybersecurity community for GxP-relevant systems believes that guidance should address roles and responsibilities as well as traceability methods for cybersecurity technical controls. The payment card industry (PCI), for example, uses the PCI Data Security Standard (PCI DSS), which issues guidance for a range of organizations—from Walmart to local restaurants—on their responsibilities for payment-system cybersecurity. One requirement is the need for penetration testing. The PCI provides detailed guidance on testing, methods, scope, time frames, and reporting mechanisms. ISPE may want to consider some of these methods and concepts when crafting its new guidance.

ISMS SUPPORT TO GXP COMPUTERIZED SYSTEMS

To see why clear roles and responsibilities are important, let's look at the responsibilities for one of the roles we identified earlier: the chief information security officer, or CISO.

‡ Center for Internet Security: A nonprofit organization that provides cyber-threat prevention, protection, response, and recovery for US government entities.

‡ Cloud Security Alliance: A nonprofit organization that offers cloud security research, education, certification, events, and products, working in collaboration with industry, higher education, and government on a global basis.

TABLE A: ACRONYMS AND INITIALISMS

CAPA	Corrective and preventive action
CFR	US Code of Federal Regulations
CIA	Confidentiality, integrity and availability
CISO	Chief information security officer
CSV	Computerized systems validation
DAR	Data at rest
EU	European Union
GAMP®	Good automated manufacturing practices
GDPR	General data protection regulation
GxP	Good "x" practices
ISMS	Information security management system
ISO	International Organization for Standardization
ISACA	Previously known as the Information Systems Audit and Control Association
ISPE	International Society for Pharmaceutical Engineering
IT	Information technology
NIST	National Institute for Standards and Technology
PCI	Payment card industry
PCI-DSS	PCI Data Security Standard
PII	Personally identifiable information
QMS	Quality management system
SC	Security category

According to ISACA, the CISO is responsible for the enterprise information security program and, more specifically, for ensuring that the ISMS is established and maintained according to the company's strategic cybersecurity plan. A key component of the CISO role is creating a structure to support the QMS. The CISO must also ensure that the governance portion of the ISMS—which supports the QMS—does not conflict with the information security manager's mandate to enforce company security policies and procedures. The CISO must also balance cybersecurity needs throughout the organization, including infrastructure and GxP-regulated systems. To accomplish all of this, the strategic plan must include separation of duties and be scalable to the size of the organization.

According to ISACA, the ISMS must align, plan, organize, and manage the following areas, some of which play a significant role within the QMS:

- IT management framework
- Strategy
- Enterprise architecture
- Innovation
- Portfolio
- Budget and costs

- Human resources
- Relationships
- Service agreements
- Suppliers
- Quality
- Risk
- Security

Ensuring that cybersecurity policies and procedures are addressed within the QMS is important, because they play a role in determining the organization's overall risk. One way to address issues related to GxP-regulated systems and ISMS is to establish an information security officer (or other governance position) to support QMS security functions. The data steward from the *GAMP Records and Data Integrity Guide* would be an excellent choice for this job function.

As the ISMS is responsible for the cybersecurity posture of the infrastructure, it must also define the process for addressing risk from the infrastructure to GxP-regulated systems (and vice versa). Critically important areas are logging, monitoring, architecture, and access control, because each of these items directly affects production systems that require services from the infrastructure. Many can be done through documented procedures, others may require specific methods for defining requirements and testing during the CSV process.

In addition to infrastructure, another key component is how the ISMS manages threats and vulnerabilities. Those that affect data integrity for GxP-regulated systems should have a defined method for inclusion to CAPAs. Most ISMS operations actively monitor their local computer emergency response team for alerts and bulletins, and document findings from security devices like vulnerability-scanning software, which use traceability for tracking and remediation.

CYBERSECURITY CONTROLS AND TESTING

Beyond the issues of roles and responsibilities, there are other areas where guidance from ISPE could help improve cybersecurity. These are mostly technical, but a few procedural examples exist as well. When addressing cybersecurity risks, the most important part of the process is during the initial risk assessment. This is when the system security category (SC) should be established to determine technical controls and testing methods that will be used. The SC is based on a combination of items such as data classification, asset valuation, threat modeling, and system impact. Decisions about internal policies and procedures should also be made during the initial risk assessment because this determines the security controls that will be applied. NIST recommends using the highest level of the impact on any one area of CIA to determine an SC:

SC = {(confidentiality, impact), (integrity, impact), (availability, impact)}

where the acceptable values for potential impact are low, medium, or high.

This is different from traditional GxP testing based on GAMP categories 3, 4, and 5. When looking at cybersecurity risks, all systems are tested according to the computerized system security category defined during the initial risk assessment. Benchmarks like those from the Center for Internet Security incorporate this methodology, providing different levels of security controls.

Once the SC is established, it can be used to create templates to apply appropriate cybersecurity controls to data integrity issues. Guidance from ISPE and ISACA will be especially valuable in this area. Establishing how the quality unit should determine technical or procedural cybersecurity will take time and coordination with the ISMS, because many of these controls will be provided within the protection of the infrastructure. It's helpful to avoid duplication of work at this step, and to reference cybersecurity controls.

PII

Another consideration is the need to safeguard personally identifiable information (PII) in any system that processes it. Here, guidance from ISPE and ISACA based on typical situations could help reduce the amount of work required to create these methods for each organization.

Using encryption to protect data at rest (DAR) or in transit shows how portions will be provided by the infrastructure, depending on the situation. A portable system that contains PII and is GxP regulated, for example, must be protected by DAR encryption. This type of control, which is designed to protect data privacy and integrity, is usually provided by an infrastructure service—such as Microsoft's BitLocker, for example.

When considering data privacy for GxP-relevant systems, quality unit personnel can benefit greatly from cybersecurity professionals, as they are well versed in regulations like the European Union's (EU) General Data

GUIDANCE FROM ISPE COULD HELP IMPROVE CYBERSECURITY

Protection Regulation (GDPR), and have reporting mechanisms that allow companies to notify the EU of data breaches or compromised systems within 72 hours. This is important because the GDPR authorizes financial penalties of up to €20 million or 4% of annual worldwide turnover, whichever is greater.

In addition to controls identified within specifications documents, their associated qualifications could also benefit from ISPE cybersecurity testing guidance. At what stages, for example, and under what conditions should a penetration test or a simple vulnerability scan be performed? The PCI DSS standard provides explicit guidance on how and when penetration tests are to be accomplished, and could be instructive for application within a GxP environment. Any system that is publicly accessible via the internet, for example, should have a penetration test performed yearly. Other systems, depending on their functionality, makeup, and placement within a network may not require such costly and extensive evaluation. Creating test methods within qualifications will take the most work, as they are highly technical, but they will be the easiest problems to solve once the roles and responsibilities have been addressed.

Finally, a realistic view of risk assessment and risk acceptance can be summed up by the IT aphorism "garbage in, garbage out." If security gaps persist throughout a validation, it is natural to assume that neither GxP- nor non-GxP-relevant cybersecurity are included in the system risk assessment. This is not only incorrect, but it provides a false sense of security.

Much work must be done within the risk assessment to assign appropriate levels of risk to the cybersecurity requirements for other GxP controls, such as data integrity and risk acceptance or mitigation. How these controls affect CAPA and incident response should be explored as well. What time frame should be allowed to correct these types of problems? Who oversees the remediation? This will be true for all zero day[§] exploits that affect the confidentiality of any given process.

SUMMARY

As cybersecurity threats increase in frequency and intensity, it is important that organizations like ISPE continually improve their guidance to address such risks. Collaboration between ISACA and ISPE will be a big step forward in understanding many of the challenges that face the life sciences community. As security professionals, our goal is to enhance GAMP 5, clarify the ISMS role within the process, and address risks to GxP-relevant systems and data in a much more inclusive manner. ‹›

[§] Zero day: an unknown software vulnerability; code used to exploit this vulnerability

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