

PHARMACEUTICAL ENGINEERING®

The Official Magazine of ISPE

January-February 2018 | Volume 38, Number 1

François Sallans

**2017 MEMBER
OF THE YEAR**

Lilly CM Project Is 2017
Overall FOYA Winner

EU Biotech Conference

ISPE Process Capability
Model: How Robust Is
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SPECIAL REPORT — SERIALIZATION

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A NEW YEAR, A NEW DAWN



Anna Maria di Giorgio
Editor in chief

One year ago, I wrote about the industry's collective pathway to hope, lit by the desire to alleviate human suffering. One year on, extraordinary forms of hope became reality with the approval of CAR T-cell therapy, emergence of CRISPR technology, and advent of digital tracking devices that make life easier for patients. One year from now, I am certain even more along that pathway will have been revealed. And it will likely be tied to virtual or artificial intelligence.

In this issue we shine a light on people who bring hope, and the companies that deliver it. Our cover story features the recipient of ISPE's 2017 Max Seales Yonkers Award, François Sallans, Vice President and Chief Quality Officer for Johnson & Johnson. Among his many virtues, François works tirelessly to elucidate the drug shortages problem, champion the benefits of a quality culture, and enrich the library of ISPE tools on both topics.

Our feature story celebrates the 2017 Facility of the Year (FOYA) Overall Winner: Eli Lilly and Company. You'll recall that Lilly received Category Awards in Process Innovation and Facility of the Future for its continuous direct manufacturing kits 2 and 3 in Indiana and Puerto Rico. When accepting the award on Lilly's behalf, David Sternasty, Vice President, Director of Production Site, said "The most important thing a leader can do is find someone who's doing something well and say, 'Do more of that.' That's what the FOYA awards do: They advance pharmaceutical engineering and say, 'Do more of that.'"

This issue debuts two new ISPE columns. Sharing news and musings on the regulatory front is "Regulatory Update," by Carol Winfield, ISPE's Director of Regulatory Operations, Regulatory Affairs. From our knowledge networks is "Building Community," by Konyika Nealy, Senior Director of Guidance Documents and Knowledge Networks, Publications. We also welcome Caroline Rocks, the new International YP Chair, and her first column.

Our profiles take us to Europe to meet Belgian YP Lise Heyninx and the leaders of the UK Affiliate. And our "Back Page" infographic (a new feature) depicts Italy's role in the pharmaceutical industry.

We launched ISPE's biotechnology conferences in 2016 to bring together dreamers, thinkers, and strategists—those that can imagine and create therapies that have the widest reach, easiest access, and greatest impact on patients. We didn't know we'd attract so many of you! The 2017 edition, held in Dublin last fall and profiled in this issue, was a "standing room only" event. And mark your calendars for the 2018 event, which will be held next September in Lyon, France.

I hope you have registered for the European Annual Conference, to be held in Rome 19–21 March. It will be tough to beat the 2016 conference in Barcelona, but I think the Romans are up for it. ♦



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12

6 MESSAGE FROM THE CHAIR

Creating Member Value through Innovation

8 YP CHAIR EDITORIAL

New YP Chair Caroline Rocks Sets the Stage for Growth

12 COVER

François Sallans: 2017 Member of the Year



16

16 PEOPLE + EVENTS

Second Annual ISPE Europe Biotechnology Conference

Meet Young Professional Lise Heynink

UK Affiliate: Engaging Members, One at a Time

Regulatory Update: New RSC Provides Strategic Direction and Support

Building Community: Guidance Documents Published in 2017



24

23 CAREER Q&A

Ready, Set, Goals

24 FEATURES

FOYA 2017: Lilly Is Overall Winner

Being Patient-Centric in a Digitizing World

35 SPECIAL REPORT

Serialization: A Global Transformation



35

45 TECHNICAL

PRODUCTION SYSTEMS

ISPE Process Capability Maturity Model: How Robust Is Your Process Capability Program?

Phillippe Cini, PhD; Gretchen Allison; Gerald Leister; Eda Ross Montgomery, PhD; Julia O'Neill; Paul Stojanovski; Michael Thomas; and Arne Zilian, PhD

FACILITIES AND EQUIPMENT

Bowtie Analysis and Barrier-Based Risk Management
David Hatch

Effect of Low-Energy E-Beam Irradiation on Presterilized COC Packaging

Stefan Kleinmann, PhD; Werner Haag, Dipl. El. Ing. ETH; and Andreas Weidauer

INFORMATION SYSTEMS

Improving SSU and the Clinical Trial Continuum
Craig Morgan



45

71 INDEX + CLASSIFIEDS

72 INFOGRAPHIC

Italian Biopharma



PHARMACEUTICAL ENGINEERING

Pharmaceutical Engineering Reviewers

- Christopher Ames, Sanofi
- Joanne R. Barrick, Eli Lilly and Co.
- Brian Beck, Zoetis, Inc.
- Malik Belattar, Pharma Biot'Expert
- Theodore Bradley, Pfizer Inc.
- Rory Budihandojo
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- Jose A. Caraballo, Bayer Healthcare
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- James W. McGlade, BHDP Architecture
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- Donald Moore, Eli Lilly and Company
- Lars Olsen, NNE Pharmaplan
- Dr. Marianne P. Oth, Eli Lilly and Co.
- Andre J. Petric, Kraemer US LLC
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- James T. Robinson, Lachman Consultants
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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.

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CREATING MEMBER VALUE THROUGH INNOVATION

One of my key takeaways from the ISPE 2017 Annual Meeting & Expo is that as an industry, we need to focus on innovation. Keynote speakers from Pam Cheng and Roger Connor to Enno de Boer and Glenn Pierce reminded us that innovative thinking must come from outside our comfort zones, and stressed the importance of creating cultures that value innovation as much as caution.

STABLE AND STRONG

ISPE is the healthiest it has been in a long while, thanks in large part to the stewardship of our volunteer and staff leaders across the organization. We continue to see positive indicators and trends on all key metrics.

Success in our major lines of business—conferences, training, and guidance documents—contributes to that stability and strengthens our foundation. Our key indicators are strong, and the growth of our reserve fund has created financial stability. Since 2013, ISPE has seen a 74% growth in assets, a 31% rise in investment reserves, and a 7.4% increase in revenue. Our recent annual meeting in San Diego was a huge success, with over 1,850 total attendees.

And that's just what you can see. Behind the scenes there has been much work to improve your experience of ISPE. We continue to invest in new systems and technology to bolster our operational strength and improve our ability to serve members, communities of practice, affiliates, chapters, and operational committees.

This month, ISPE will add a new benefit that significantly increases the value of your membership: online access to our Good Practice Guides (GPGs). This library of 25 titles—a subset of the larger Guidance Document collection—encompasses a broad spectrum of highly applicable Guides, including Decommissioning, HVAC, and Operations Management. The GPGs were selected for this pilot effort because their content is critical to your daily work, providing the guidance you and your company need to succeed in our industry.

STAYING THE STRATEGIC COURSE

In last month's editorial, I said that in addition to maintaining the momentum created by Past Chair Mike Arnold, I would also continue to drive implementation of the 2016–2019 strategic plan. The Board and I are confident this plan is sound. As we conducted a midpoint review, however, we realized that cell and gene therapy were also integral to our strategic direction and an important response to market needs. While we had included these topics in select conferences over the past year, we have now formalized them as part of our plan.

Vice Chair Jim Breen also plans to integrate cell and gene therapy in the upcoming Facilities of the Future conference (20–22 February) as an



Tim Howard with Doug Oliver, Chair, South African Association of Pharmacists in Industry. Howard spoke at the annual SAAPi conference in October 2017.

individual medicines track. The annual Quality Manufacturing conference (4–6 June) will have content in this area as well. And that's just North America!

In addition, I have begun a conversation with Jim about what's important for the coming year. We want to find ways to enhance member value by feeding the Young Professionals pipeline, supporting the growth and promotion of Women in Pharma, and focusing on facilities of the future.

A BROADER FOOTPRINT

We also want to increase our geographic footprint. ISPE has a business model that has served its members well, largely in the United States, Europe, and Asia. But there are unmet needs in Africa and Middle East, as well as developing nations in Asia and South America. We have a tremendous body of knowledge that others would love to access—in fact, they need it. So I am happy to report that with the support of our CEO and Executive Council I will work with a small task team to explore and identify alternative business models that will allow us to serve those markets. Whether it's partnering with other societies or coming up with different delivery mechanisms, we will start with a blank sheet of paper and a problem statement and create a solution. This is an important initiative for me.

The next couple of months will be quite busy as we prepare for the Facilities of the Future conference in Bethesda, Maryland; the Aseptic Conference (6–7 March) in Reston, Virginia; and the Europe Annual Conference (19–21 March) in Rome, Italy. I will be attending each of these events and look forward to the conversations we will share. <>

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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New YP Chair **Caroline Rocks** Sets the Stage for Growth in 2018



Caroline Rocks, Senior Process Engineer, Mylan, and 2017–2018 International YP Chair

I am delighted to have begun my tenure as International Young Professionals (YP) Chair at the Annual Meeting in San Diego last October. I was a founding member and first Chair of the ISPE Ireland Affiliate YP Committee. At university I hold a degree in chemical engineering and a master's degree in biopharmaceutical engineering. I now work for Mylan as a Senior Process Engineer and while based in Dublin, Ireland, my role takes me to Mylan's facilities around the globe.

I joined ISPE early in my career when my manager, who was involved in the Ireland Affiliate, asked me to take part in a local event. Along with my new role as Chair, I remain a member of the Ireland Affiliate, the European YP Leadership Committee, and the Awards Committee.

YP Committee mission statement

To create a welcoming, comfortable environment at all levels of ISPE wherein Young Professionals have unrestricted opportunities to network with peers, mentors, and other professionals; gain fundamental and advanced knowledge about the industry and their areas of professional interest; and to grow their skills as needed to become industry professionals and the ISPE leaders of tomorrow.

MEET YOUR NEW CO-CHAIR

My Co-Chair LeAnna Pearson has been actively involved in ISPE since she was a student at North Carolina Central University. She is also Treasurer of the ISPE Carolina–South Atlantic Chapter Executive Board. She holds a bachelor of science degree in biology and a master of pharmaceutical sciences, and currently works as a project manager for Barry Wehmiller Design Group, based in North Carolina.

THANKS BRODY!

We are continuing from a successful year under the leadership of Brody Stara (Boston Area Chapter) and look forward to lots of activity and development for YPs globally through 2018. LeAnna and I, along with the ISPE committee, wish to acknowledge Brody's efforts and achievements during his tenure as International YP Chair. Among his major achievements was adding regional leaders to the committee, which allows more global collaboration; he also broke new ground as the first YP Chair to serve on ISPE's International Board of Directors.

YP GROWTH

ISPE's YP membership has grown since the first ISPE YP event was held at the Annual Meeting in 2007 and a YP group was established in the Boston Chapter.

"Young Professionals" became an officially recognized ISPE member type and community in 2010. From there, YP group formations accelerated across ISPE internationally and in 2015 the International YP Committee was formed to help with global collaboration among the ISPE YP groups.

The past year was a busy one for all local student chapters and YP groups globally. In Europe we held the "Pharma 4.0 YP Hackathon" at the Europe Annual Conference in Barcelona, Spain, the first YP event at a large ISPE European conference. Following its success, a second Hackathon is planned for the 2018 Europe Annual Conference in Rome, Italy. In September, the Ireland YPs hosted a European YP event at the Europe Biotechnology Conference in Dublin.

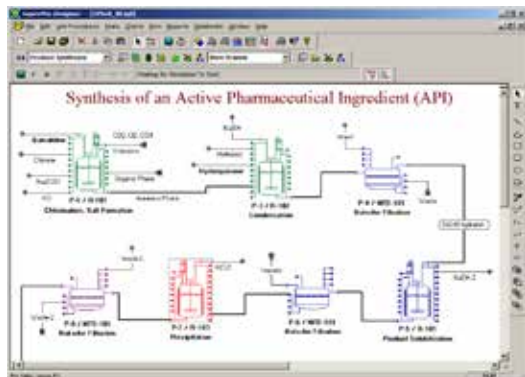
The North American YPs have expanded in multiple areas, with representatives on seven international committees and establishing four new student chapters. All North American Affiliate chapters have had a wide range of successful events, including mentoring, social, and educational events.

—continued on page 10

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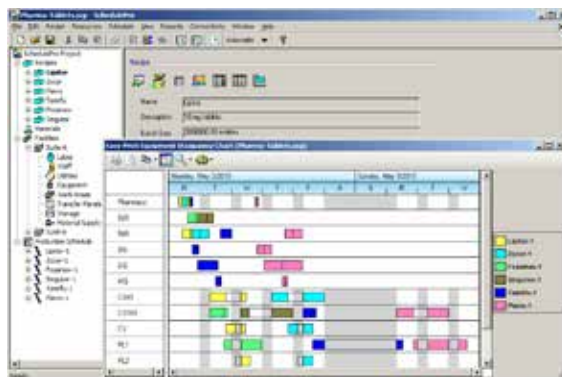
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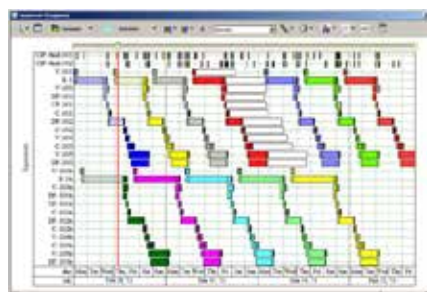
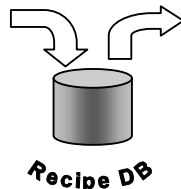


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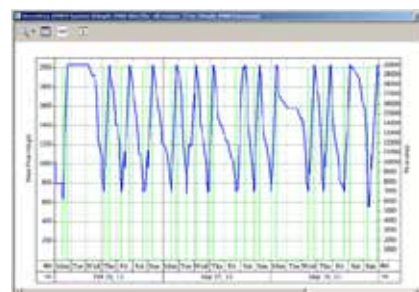
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Greater Los Angeles Area	Italy	
Midwest	Netherlands	
New Jersey	Nordic	
Rocky Mountain	Spain	
San Diego	Turkey	
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If you're in an active ISPE YP group that's not listed here, please let us know at ask@ispe.org.



LeAnna Pearson, Project Manager, Barry Wehmiller Design Group, Carolina-South Atlantic Chapter Treasurer.

In the Asia-Pacific region, a student poster competition was held at the India Annual Conference in April 2017, the Malaysia student chapter hosted education sessions and began a symposium series in collaboration with local universities, and the Singapore student chapter had three facility tours and an exciting networking event titled "YGEN 2017."

AN ANNUAL MEETING OF FIRSTS

I had the opportunity to attend my first ISPE Annual Meeting & Expo in San Diego, California. This had many YP education sessions with themes including "Career Strategies for Early Career Professionals" and "From College to the Real World: Biotech Facility Design." Also included over the week were the all-important networking events, such as the YP/student brunch and orientation, as well as a great networking night in downtown San Diego. Compared to previous gatherings, this year's Annual Meeting saw an amazing 480% increase in YP and student attendance.

I presented the 2018 IYP strategy to the Board of Directors and chaired my first IYP committee meeting with over 20 YP Chairs from North America, Europe, and Singapore in attendance. We shared our thoughts on what was going well and what we could do to improve and develop our YP communities. We also discussed the 2018 IYP strategy, which is shared on our community page. The IYP strategy mirrors key objectives of the overall ISPE 2016-2019 Strategic Plan. It also supports the global YP growth and collaboration, and

YP Committee strategy highlights

Formalize YP leadership succession planning

Establish additional leaders

Further integration of YPs at regional and international level ISPE events

Expand ways to make YPs more inclusive

Establish YP groups in more regions

Pilot program to improve membership metrics

Improve use of YP community page

provides a structure for future success.

We welcome more volunteers to grow our YP groups globally as there are still many regions to be established. In Europe, affiliates such as Poland and Czech Republic are looking for volunteers to establish YP groups. In India there are ISPE chapters in Bangalore, Hyderabad, and Ahmedabad that need YP volunteers, as do chapters in the Asia-Pacific region.

It's easy to join our YP community, just select it during your registration process or update your existing account on www.ISPE.org. This is the online community page where all the YP chapters and affiliates globally can share details and photos of their events so you can get new ideas and guidance for your own group. I will also blog on here on a regular basis to provide updates on the work of the IYP committee. <>

LeAnna and I are open to any feedback, ideas, or suggestions you may have. Email us at ask@ispe.org and put "IYP Chair" in the subject line.

About the author

Caroline Rocks, an ISPE member since 2014, is a Senior Process Engineer for Mylan's Strategic Manufacturing Biologics. She started her career with Jacobs in process and facility designs from concept to construction, and subsequently worked for Pfizer, Bristol-Myers Squibb, and Meda manufacturing facilities in Ireland in the areas of technology transfer, commissioning, qualification and validation of small- and large-molecule API, OSD, and fill-finish projects. She now works on developing and delivering capital projects and manufacturing strategies in Mylan's global biosimilars portfolio.

A Chartered Engineer, Rocks earned first-class honors in both her bachelor's degree in chemical engineering and her master's degree in biopharmaceutical engineering from University College Dublin, Ireland. She lectures at University College Dublin School of Chemical and Bioprocess Engineering and the National Institute for Bioprocessing Research and Training.



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FRANÇOIS SALLANS

2017 MEMBER OF THE YEAR



Maxine Seales Yonker was an active ISPE member, leader, and contributor to the industry. When she lost her battle with cancer in 2005, her memory was honored with an annual award that recognizes the same commitment to service.

As he announced this year's Member of the Year honoree during the 2017 Annual Meeting & Expo Membership Awards Breakfast, ISPE CEO and President John Bournas noted that "the memory of Maxine Yonker reminds us that we are all patients, and it reminds me of the vital work that each one of you do to advance the development, production, and delivery of a safe and reliable drug supply.

"It is fitting, therefore, that the 2017 Member of the Year be someone who exemplifies putting people and patients first. François Sallans, Vice President and Chief Quality Officer (CQO) for Johnson & Johnson, is a leader and visionary who is committed to sustaining a corporate culture that puts the patient first."

Shortly after he received the award, *Pharmaceutical Engineering* sat down with Sallans to talk about his career, dedication to preventing drug shortages, and thoughts on the ongoing hurricane-recovery efforts in Puerto Rico.

What does receiving this award mean to you?

It is a great honor and came as a surprise. I consider it an honor because this is a prestigious award, and it means so much more because of Maxine's legacy and unfortunate passing due to cancer. Being Chair of the Drug Shortages Initiative team, I am well aware that many shortages affect cancer drugs, so this award has a double meaning for me.

How did you come to specialize in operations, quality, and supply chain risk management?

I'm a pharmacist who is passionate about science and technology. When I graduated, I wanted to work in research and development, but instead, I began as a pharmacist in the pharmaceutical production unit of the French army. It gave me the opportunity to work with larger teams. This was during the early 1980s, at the start of good manufacturing practices. We had to learn how to train production workers who relied on procedures that they had written down in books, which they kept in their pockets!

I then joined the pharmaceutical industry in manufacturing, because it fit with my values of serving people and providing patients with innovative, safe, and effective medicines. And I learned a lot about the industry. I started discovering industry operations and working on the shop floor.

From operations, I moved on to learn about quality. I have always been interested in both quality and operations, and I never dissociate the two. When you're in operations you have to have a quality mindset; you have to know the consequences of decisions on quality. I really enjoy balancing the technical side of operations and risk management on the quality side. It's been a balance throughout my career.

I believe in the value of good science and my passion is to serve patients. I'm proud of the way our industry has brought in innovative new drugs and treatments over the course of my career. A good example is HIV. Thirty years ago, HIV was, simply, a death sentence. The average life expectancy with HIV was two years from time of diagnosis. Today, HIV patients are living normal life expectancy *minus* two years because of these innovative medicines.

You've been with Johnson & Johnson for 27 years. What is it about your role at the company that keeps you there?

I joined because of the values of the company and the quality of the people who work there. I had met some of them in my previous position at another company and they exhibited attitudes and values I admired. I could see that they put customers and patients at the center of things. They were making decisions that served their patients, decisions that served their employees and the communities in which they worked. It was all captured in the Johnson & Johnson Credo, which I learned when I was hired.

Twenty-seven years later, I still adhere to those values. Quality is embedded in the corporate culture; it's ingrained in everything we do. And our employees live it every day.

How did you become an ISPE member?

I started attending conferences in the mid-2000s. I was interested in acquiring knowledge and meeting colleagues, and ISPE had a great reputation. It was a passive, receptive type of membership. I had many of the books, guidances, and documents produced by ISPE, and this was a precious part of my education. When I came to the United States in 2012, I became an active member and got involved in the drug-shortages team. Then, during the ISPE Annual Conference, CEO Nancy Berg asked me to take the lead; I've been the Chair of the Drug Shortages committee ever since.

What does being an ISPE member mean to you?

Membership brings a variety of benefits. It allows me to network with engineers, pharmacists, scientists, and the community of industry experts in operations and quality around the world. It allows me to connect with regulators worldwide to assess new trends we need to pay attention to. And being a part of this community of practice means I learn at least as much as I share. ISPE also facilitates the development of future talent through conferences, webinars, and guidelines. These are excellent reference documents for young talent and a key contribution of ISPE.

How do you encourage your colleagues to become members?

I ask my quality leaders not only to participate and contribute to different topics, but to be strongly engaged, or take the lead, or both, on different ISPE initiatives. When I became CQO, I requested that my quality and compliance organization become more externally focused. We needed to learn more about what others were doing to ensure a culture of quality. This has brought great value to the Johnson & Johnson companies and also to our industry. I see a lot of Johnson & Johnson company employees

I'M A PHARMACIST WHO IS PASSIONATE ABOUT SCIENCE AND TECHNOLOGY. WHEN I GRADUATED, I WANTED TO WORK IN RESEARCH AND DEVELOPMENT, BUT INSTEAD, I BEGAN AS A PHARMACIST IN THE PHARMACEUTICAL PRODUCTION UNIT OF THE FRENCH ARMY.

engaged in many ISPE initiatives. In my quality team, part of our evaluation of their work is asking about their involvement in industry associations.

DRUG SHORTAGES

Are you content with the industry response to drug shortages?

We have accomplished a lot since 2012 in terms of addressing the challenge of drug shortages, but we have a long way to go. Recently, I was in Barcelona with colleagues and we were discussing the way forward. We agreed that we were satisfied with what we had done. Then, in September, Mother Nature taught us a lesson—in Texas, in Mexico, in Southeast Asia, in California, and in Puerto Rico—to a degree we never anticipated. Until then, resilience had been a vague and theoretical concept, but we learned its real meaning.

We have to keep in mind that this issue is ongoing for our industry. Shortages involving antibiotics are increasing, as are shortages of chemotherapeutics. It's a complex problem that involves quality, manufacturing complexity, and commercial, among other departments. But it also is affected by the withdrawal of applications that throw the market off balance. It's a problem that affects not the latest breakthrough products, but common, branded, and often generic medicines.

A recent example was sodium bicarbonate, used to treat metabolic acidosis. There were only two manufacturers, and in February one of them announced it was short of prefilled syringes, likely due to complexities in its supply chain. This wound up affecting a huge number of patients. And this is just one of the approximately 160 shortages that are projected to occur in 2017. It turns out that while we've made some progress, we have not improved enough the overall situation.



Education is key and that is largely the role of the ISPE's Drug Shortages Initiative. We created the Report on the ISPE Drug Shortages Survey (2013), ISPE Drug Shortages Prevention Plan (2014), ISPE Drug Shortages Assessment and Prevention Tool (2015), ISPE Drug Shortages Initiative Webinar (2016), and Drug Shortages, a collaborative report from ISPE and the Pew Charitable Trusts (2017). These all help members understand and mitigate drug shortages.

What did you learn from the 2017 ISPE-Pew survey of industry leaders?

The report focused on the sterile injectables market in the United States because this market accounts for almost three-quarters of the shortages that are listed by the U.S. Food and Drug Administration (FDA). By surveying 51 decision-makers at 10 companies, we discovered that quality problems were the main driver: they play a role in 45% of shortages.

The other big factor was limited flexibility to ramp up production to meet demand. This is a real problem for our industry. In today's world, supply chains are extremely complex. Active pharmaceutical ingredients (APIs) and bulk products are manufactured in different places and packaged in other places across the globe. Although supply chain risk management is applied across our industry and backup plans are defined for the most critical products, not all products have an active or at least an approved backup supply for every step in the network. If anything goes wrong anywhere along this complex network, including at a contract manufacturer, an alternate site might not be able to increase production within the requisite time frame and drug shortages may occur.

But quality and flexibility aren't the only factors. Market withdrawals, limited market insights into future demand, and a lack of clear expectations from regulators were also cited as a cause of shortages.

Limited market insights about future demand is an interesting factor. While it's a small percentage, it can have a longer-lasting effect on shortages. A company may have a good idea of what the current competition landscape

looks like, but it's difficult to have a clear view of the future.

The key is to establish appropriate and meaningful supply-chain risk management plans.

Don't companies already have robust supply-chain risk management plans in place?

We were surprised when we saw this data. All the companies that participated in our survey had business continuity plans in place to deal with supply-chain disruptions. If they have good risk management they shouldn't have drug shortages. So what happened here? We found that they had parts and pieces of a

good comprehensive supply-chain risk management plan. Others had safety stock of raw materials or finished goods—but not enough. Some had backup manufacturing, but it had not been tested; when they needed it, they didn't have the raw materials or the people to operate it.

You need to have a true, comprehensive understanding of your supply chain and its dynamics. This does not mean stopping at the most obvious first line of defense, which is safety inventory.

You espouse early collaboration with regulators, especially when shortages are anticipated. Why is that?

Yes, I encourage communication with the authorities as early as possible. Once a drug shortage occurs, it's too late to react. My experience is that the FDA is walking the talk on drug shortages: they are working with companies to fix problems and address risks to ensure supply continuity to patients. Take, for example, the sodium bicarbonate shortage. The FDA agreed to extend by six months the expiration date of some lots of this sterile injectable drug, once it was shown that the quality of the product wasn't compromised. The manufacturer worked directly with the FDA to make this happen.

What has been your most significant accomplishment as an ISPE member?

The most important contribution occurred near the beginning of my work with the Drug Shortages Initiative, which started in 2012 with a white paper. We presented it to the FDA during a meeting with Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research, and we proposed to run a survey of the 18,000 ISPE members to collect information and better understand drug shortages. Our idea was to prepare and run the survey during the next year and present the results at the end of 2013. Dr. Woodcock not only agreed with this idea but asked ISPE to deliver the report in record time, by May 2013 (something never done before), as shortages

had become such a critical issue in the US. And so we did. I remember the phenomenal engagement of the team, their engagement and relentless work, and seeing the smiles on my team members' faces when we were finished: they were so proud and energized by that accomplishment. And it continued over the next four years.

RECOVERY EFFORTS IN PUERTO RICO

What have your recovery efforts in Puerto Rico taught you about industry commitment to maintaining drug supply?

Our supply chains are fragile and vulnerable. I flew to Puerto Rico right after Hurricane Maria, along with leaders from Johnson & Johnson's supply chain. This is part of the company's culture of putting patients first. What we saw on the island was devastating. We were not prepared for the magnitude of the problem.

In our business continuity guides, we look at resilience and redundancy in a narrow way. Instead, we need to ask, "What is real resilience? What is real redundancy?" The technical points of resilience—facilities, equipment, quality, readiness of suppliers—were pretty much ready. But we had not anticipated the impact on the communities, the impact on people; without them, nothing can happen.

We have to be better prepared for these catastrophes, and learn how to deal with them. And that means we have to look at resilience in a nontechnical way. We also have to look at crisis management beyond supply-chain risk management. We have to have fuel reserves. And we have to make sure the satellite phones are working—they weren't in Puerto Rico. That can't happen again. We have to identify our risks ahead of a potential catastrophe and be prepared to manage and mitigate them.

And it is not only about the industry: the FDA immediately stepped up to support. The agency connected with us the day after the storm to find out what was going on and how it could help.

Our employees also rose to meet the challenge. I saw people coming back and restarting with the little they had at the time. They were willing and eager to fix the technical problems and restart production lines. All of this in a compliant way—I am insistent on this—which meant we were able to keep making safe and efficacious medicines. I am so proud of the preparedness, collaboration, and fighting spirit that enabled these teams to be where we are today. There have been no major shortages of our products. We restarted our facilities and we're supplying.

One of our technicians in quality lost everything, including her house. She returned to work a few days after the hurricane hit because she cared about the patients she had the privilege to serve. She's an example of hundreds of people standing up and doing their job, a living example of my company's credo: they are there to serve the patients, the customers, and the community. I know my ISPE colleagues have seen it in their people, too. This is the health-care industry at its best.

And this lesson that Mother Nature taught us says that we must be prepared and think about resilience for the future. What do we need to do as ISPE? As an industry? As regulators? Do I have answers? No, I just have questions. <

—Scott Fotheringham, PhD



ABOUT THE AWARD

The Max Seales Yonker Member of the Year Award honors the ISPE member who has made the most significant contribution to ISPE during the past year. The award is named after Maxine Yonker, who was an active ISPE member and leader, and a relentless contributor to ISPE and to our industry. When she died of cancer in 2005, ISPE chose to honor her by naming an award that recognizes the type of commitment she showed to the industry.

A significant global example of François Sallans's commitment is in his role as Chair of the ISPE Drug Shortages Initiative team, which began its work in 2012. Major deliverables of that initiative included an industry-wide survey in 2012 that provided a better understanding of the underlying issues and root causes of shortages, the release in 2014 of the ISPE Drug Shortages Prevention Plan, which provided a holistic view of the drug shortage problem from root cause to prevention, and, most recently, a survey of industry leaders about the causes of supply chain disruptions and recommendations for strong, end-to-end risk management planning.

This project has been tremendously successful and has served as a model ISPE project that provides innovative solutions to a current industry challenge. François Sallans has made exemplary contributions to ISPE and the industry, all in the spirit of dedication, sharing, and enthusiasm.



SECOND ANNUAL ISPE EUROPE BIOTECHNOLOGY CONFERENCE

Attendees Tackle Trends, Big Issues

On 26 and 27 September, 340 attendees came to the ISPE Europe Biotechnology Conference in Dublin, Ireland, to learn about and discuss current challenges and megatrends in biopharmaceutical production. Conference chairs were Liz Dooley, Director Operations (Biologics), Janssen, Ireland, and Alan MacNeice, Executive Director and Site Leader, Jazz Pharmaceuticals, Ireland and FOYA 2017 Category Winner.

Dominic Carolan, CEO of the National Institute for Bioprocessing Research and Training (NIBRT) in Dublin, presented the opening keynote, discussing the current biopharmaceuticals market. Global sales are \$202 billion, with a projected 9% annual growth rate. Monoclonal antibodies (mAbs) and vaccines combined represent two-thirds of all biologicals, and 40% of 2015 US Food and Drug Administration (FDA) approvals went to biological products.

Oncology is the current leading indicator; cancer therapies have changed with a better understanding of the immune system. Antidiabetic and dermatological drugs are rising, however,

and biosimilars, with their special challenge of analytics, have prompted the question, “How similar is similar?”

TRACKS 1 AND 2

In Track 1—“Technology, Innovation, and Factory of the Future”—participants heard about process science of fusion proteins from Stefan Schmidt, Rentschler; bioprocessing capabilities at Eli Lilly and Company from Diarmuid O’Connor; and cost calculation—single-use vs. stainless steel—from Fearghal Downey, Hyde Engineering and Consulting Limited. Christian Wölbelling, from Werum, explained ISPE’s model of holistic manufacturing control strategy, driven by Industry 4.0 and digitization. Richard Denk, from SKAN, reported about requirements for high-potency biologicals; René Labatut, from Sanofi Pasteur, discussed continuous manufacturing in bioproduction; Christoph Herwig, from the Technische Universität Wien (Technical University Vienna), talked about process characterization tools; David Estapé, from M&W Group, reported on the global environmental impact of

Also in this section

- 18 Meet Young Professional Lise Heyninck
- 19 UK Affiliate: Engaging Members, One at a Time
- 20 Regulatory Update: New RSC Provides Strategic Direction and Support
- 22 Building Community: Guidance Documents Published in 2017

a biopharmaceutical facility; and Gerben Zijlstra, from Sartorius Stedim Biotech, highlighted scalable technologies for process intensification in the factories of the future.

Track 2 was dedicated to process science, knowledge management, and regulatory affairs. Richard Shah, from Pfizer, started with a 2,000-L, single-use mAb process at the Pfizer Grange Castle, Ireland, site, followed by Regina Mulhall, Senior Quality Director at Janssen Biologics, who addressed the issue, “What Does Quality Look Like in the Future?” Michelangelo Canzoneri, from Sanofi, Chair of ISPE’s EU Biotech Special Interest Group, talked about knowledge management in the context of managing biologics innovation and technology at Sanofi.

TRENDS

In technology, trends like continuous manufacturing, new process analytical tools, single-use technology, alternative downstream processing techniques with dramatically improved yield, green chemistry, and better scalability (up and down) have emerged.

The leading trend in operations activities is still operational excellence, followed by continuous manufacturing and single-use technology.

Looking at innovation, continuous manufacturing is number one, followed by disposable technologies, testing methods, and downstream processing.

The starting point for biological production



today is still chicken eggs for vaccines and microbial cells for other therapies; in the future, cell lines from animals will feature more prominently.

The choice between single-use technology and stainless steel will be dictated by the batch size and the achievable titer in grams per unit. It is a typical optimization calculation with sensitivity analysis and break-even point between both technologies.

WORKFORCE OF THE FUTURE

What will the workforce look like? What skills will we need? And what should employers provide for their best skilled and educated employees? Carolan returned to provide insight on both employers' and employees' perspectives.

Gerald Kierans, Director of Technical Services, Pfizer, pointed out that the question of whether capacity constraints hinder patient access to biological medicines is rhetorical. The biggest challenge in operations is indeed to have the right capacity, at the right time, at the right cost. Cost drivers that affect manufacturing capacity are development (clinical supplies), launch, and optimization. All phases must be looked at very carefully. The result can be various manufacturing options, depending on the product life cycle.

Contract manufacturing organizations may play an important role at a certain period of life cycle management, but they have a number of pros and cons, therefore there is no golden rule for it.

After two decades of deployment, single-use technology has become a key enabler for the multiproduction paradigm, with some downside risks such as leaking and breaking, particle emission, limited-availability of gamma-irradiable sensor technologies, outsourced material control, low-volume production, and operating costs. This is also a typical optimization calculation, as the total cost of ownership shows a volume-dependent break-even point.

Paul Moody, Inspector at Ireland's Health Products Regulatory Agency (HPRA), addressed the most relevant European Union good manufacturing practice (GMP) guidelines for biologicals: EudraLex, Volume 4, Annex 1, "Manufacture of Sterile Medicinal Products," and Annex 2, "Manufacture of Biological Active Substances and Medicinal Products for Human Use."

Sterile dosage forms covered by the new Annex 1 include blow-fill-seal, form-fill-seal, sterilization process and controls, aseptic processing, and finishing. Technologies covered include filtration pre-use post-sterilization integrity test, sterilization, closed

systems, and single-use technology. Of course, quality risk-management-based environmental monitoring plays a major role.

Another important piece is the new draft GMP guidance for advanced therapeutic medical products (ATMPs). First issued by the European Commission in 2015, the guidance is now at the stakeholder consultation and comment phase. The summary of feedback is published on the EU commission website, along with details of the output from the consultation phase. Because manufacture of investigational and commercial ATMPs differs from other products in terms of variable starting materials, small batches, and short shelf life, there is derogation from existing GMP guidance, with some additional changes, particularly for early-stage development.

Andy Rayner, PM Group, Ireland, discussed BioPhorum's *Biomanufacturing Technology Roadmap* (free for download at www.biophorum.com/category/resources/technology-roadmapping-resources/introduction), which identifies current biopharmaceutical industry trends and biomanufacturer needs. Six teams from 31 companies, with help from innovation hubs and universities, contributed to the document, compiling key technologies and capabilities. Rayner also addressed future biologics facility design.

Mairead Looby, Bristol-Myers Squibb, presented a case study about her company's biologics manufacturing facility in Cruiserath. Noemi Dorival Garcia, from NIBRT, presented the "Characterization of Extractables and Leachables in Bioprocessing Consumables." Mat Landowski, DPS Engineering, addressed process design innovation and the migration to a modeling-based workflow. Data science workflows were outlined by Patrick Sagmeister, from EXPUTEK. Benefits and recent advances of a platform technology approach for the generation of production cell lines were shown by Christoph Zehe, Head of Technology Development at Cellca (Sartorius Stedim BioOutsource, Ltd). The day was closed by Roche Diagnostics' Annette Peceny, who offered insights on using diagnostic tools for process control in production.

Participants were very satisfied with the 2017 content and the opportunities to meet real experts in the biotech sector, with many promising to attend next September's ISPE Europe Biotechnology Conference in Lyon, France. <>

—Thomas Zimmer, Vice President, ISPE Europe

COMPLEMENTARY POINTS OF VIEW?

	EMPLOYERS	EMPLOYEES
Professional effectiveness	Leadership, communications, teamwork, problem solving, business acumen	Rewarding work Recognition of contributions Get along with the boss
Technical breadth	Connecting the dots, knowledge of complementary disciplines	Company makes a difference Investment in their development
Technical depth	Expertise in a biopharma discipline and manufacturing process	Clear career opportunities

MEET YOUNG PROFESSIONAL LISE HEYNINCK



Lise Heyninck, Validation Project Lead, Novartis

They say that ongoing growth is the key to a fulfilling career. If that holds true, young professional Lise Heyninck of Belgium has the mindset and drive to build a long and successful career in the pharmaceutical industry.

Born and raised in Sint Niklaas, a city of 75,000 located between Antwerp and Ghent, Heyninck is a Validation Project Lead for Novartis, a leading pharma company. She began her undergraduate studies in bioscience engineering at Ghent University in 2008, followed by a master of science in bioscience engineering, chemistry and bioprocess technology.

During her first year of graduate studies in 2011, she participated in an exchange program at Kansas State University in the United States. "That was quite an experience for me," says Heyninck. "I learned a lot and I was also there by myself, which was hard because I started without knowing anybody. It was good to see that I was quite independent and could do that on my own. I was so proud."

FIRST INDUSTRY EXPERIENCE

She returned to Belgium in December 2011; the difference in exam periods between the two countries, had given her some free time before the next semester. She took an internship at Genencor International Belgium, a biotech company.

"It was my first experience in the industry, and I got to experience what it is like to work at a company," she says. "I was a process engineer and I really liked that I could think about the processes, perform the tests myself, and then work through problems that were triggered."

After completing her master's degree in the spring 2013, Heyninck almost immediately found her first real industry job as a process validation engineer at Novartis. There, she explains, process validation engineers not only devise the testing schemes to ensure products meet their requirements, but perform the tests and write the subsequent reports as well. "That is an asset because you go everywhere in the factory," she says. "There is a lot of interaction with all departments, so I really learned a lot."

She held that position until May 2016, when she was appointed as an interim project and validation team leader. In November 2016 she was appointed

to her current position as Validation Project Lead, where she manages a variety of projects within the validation department.

ISPE INVOLVEMENT

In 2014 Heyninck was introduced to ISPE by a manager at Alcon who was also a former board member at ISPE's Belgium Affiliate. "He heard that the Affiliate was looking for Young Professionals to start up the ISPE YP initiative in Belgium, and he asked me and another colleague to join," she explains. "I was very enthusiastic about it because I think ISPE is a great opportunity to learn about the industry and to meet new people, so I said yes and got involved."

Her involvement has been active. She was appointed Chair of the YP Committee in July 2015. "So far, it has been difficult, because we really had to start from nothing," she says. "We were just a group of YPs coming together and it was hard to find a common interest and to know which direction we would go. One of the first things I did was to bring some structure into the group by creating different working groups and set the dates of our committee meetings for the next year."

Today, the YP Committee has grown to 16 people out of the 20–25 YP members of the Belgian Affiliate. The committee organized its first event in June 2016, with attendance exceeding 80 people. "We didn't limit it to ISPE members; we kept it open to all young professionals in the industry. We hope that by organizing more events like this, they will see the added value of becoming an ISPE member."

LOOKING AHEAD

Heyninck acknowledges that the Affiliate has not yet reached out to the student community, but sees that as a future goal. "We are still starting up with the young professionals, so we first want to reach the ones who are already in the industry and then we can target universities students."

For her own career, Heyninck's ambitions are predicated on her quest for ongoing growth. "For me, it is important to keep learning," she says. "When I am in a position where I don't learn anything new, that is not good. I have the ambition to go higher, to become a team leader or a manager. But before I can do that, I still have a lot to learn about the different divisions and departments." <>

—Mike McGrath

ENGAGING MEMBERS, ONE AT A TIME

UK Affiliate

These are interesting times for the pharmaceutical industry in the United Kingdom. According to a recent report, the industry employs more than 73,000 people and contributes £30.4 billion (\$40 billion) to the British economy, including £4.2 billion (\$5.5 billion) in R&D expenditures. As the country prepares to leave the European Union, however, Brexit's unknown effects on regulations, taxation and other facets of the pharmaceutical industry leave many questions unanswered.

Founded in 1988, ISPE's United Kingdom Affiliate is focused on growth and continued membership engagement. It serves more than

QUICK FACTS

Founded	1988
Membership	850+
Chair	Jonathan Youles, Ytron-Quadro (UK) Ltd.
Treasurer	Philip Hill, Fulkers
Secretary	Bruce Williams, Williams Process Ltd
Past Chair	Dr. Peter Dodd, formerly of Fujifilm Diosynth Biotechnologies UK Ltd
Membership Secretary	Dr. Phillip Richardson, AstraZeneca
Education Advisor	Roger Shillitoe, AstraZeneca
CoP Liaison	Lynn Bryan, Ballygan
Young Professional and Student Liaison	Craig Milner, Sanofi
Communications Chair	Philippa King-Smith, Ardmac Ltd.
Professional Organisation Liaison	Adam Hawthorne, PM Group
North West Region Chair	Rob Walker, Rob Walker GMP Consultancy
North East Region Chair	Dr. Peter Dodd
Central Region Chair	Shaun Baker, Newman Labelling Systems Ltd.
Southern Region Chair	Shawn Whitfield, BTG International PLC

850 members in four regions: Southern, Central, North East, and North West.

"Half of our membership comes from the South," says UK Affiliate Past Chair Dr. Peter Dodd. "There are two concentrated spots: the London area out to Oxford and Cambridge, and another concentration around Manchester and Liverpool, which is partly on the border of the Central and North West regions."

On average, the affiliate holds monthly events in addition to factory visits and an annual conference. "Because we are split into four regions, we target three education and networking events, per region, per year," says Affiliate Chair Jonathan Youles. "The UK is not that big geographically, so people can attend pretty much any event that we organize. Last year we introduced a Summer Conference, a one-day event that allows us to focus on a topic in more detail." This year's Summer Conference was held in June and covered containment and decontamination.

The highlight event of the year is the Annual Conference, held each November. Between 50 and 80 people usually attend the one-day event. The conference is followed by a formal dinner and awards ceremony, an event typically attended by up to 500 members and invitees. The 2017 Annual Conference was held on 30 November in beautiful Stratford-upon-Avon—the birthplace of William Shakespeare—and focused on "New Dimensions in Pharmaceuticals."

Membership is a focus for many chapters and affiliates, and the UK Affiliate is no different. Responding to an initiative from ISPE Headquarters, the affiliate established a Membership Development Committee.

"We recognized that there was a gap in getting relatively new members in the profession together at a substantial event that was good value," says Youles. "That was the purpose of the Summer Conference."

"We are also focusing on young professionals (YPs) and linking to universities," says Lynn Bryan, Past Chair and current Community of Practice (CoP) Liaison.

"We feel that ISPE offers an ability to learn; to figure out what you want in your professional career,"



says Youles. "If we can engage people at an early point in their careers, then hopefully we can help them learn more about what they want to do. We will be learning from other affiliates' success; the Ireland Affiliate is more advanced with the YPs and we will try to learn from their knowledge in this area."

"The good news is that we have a young professional on our board who is super enthusiastic to take the initiative forward, and I think that is half the battle," says Bryan, referring to Craig Milner, the UK Affiliate's Young Professionals Chair and Student Liaison.

Bryan, Dodd, and Youles agree that ISPE provides a unique wealth of opportunities for meeting people within the industry. "ISPE is the broadest group of pharma engineering professionals in the UK," says Dodd. "It includes regulators, entrepreneurs, people working in research, and everyone in between. It really is a very broad spread of people."

As they look ahead, the leaders discuss the uncertainty surrounding the upcoming Brexit.

"Whether you wanted Brexit or not, this is where the challenge is going to be in the next 18 months or two years," says Bryan.

"We still don't know how negotiations will shake out in terms of investment or retention of manufacturing and R&D within the UK, whether it is likely to encourage people to move, or maintain the status quo," concluded Youles.

One thing is certain, however: The UK Affiliate will continue to engage its membership throughout the country. <

—Mike McGrath

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REGULATORY UPDATE

New RSC provides strategic direction and support

ISPE's regulatory groups play a key role in bringing industry and regulators together to advance pharmaceutical quality for the benefit of patients. This new column, penned by Carol Winfield, ISPE's Director of Regulatory Operations, is being introduced to keep ISPE members informed of the important work being done by these members.

ISPE's regulatory-focused groups are tasked with ensuring that all members have access to the latest regulatory developments. These groups include the Regulatory Quality Harmonization Committee (RQHC) global and regional groups, the Product Quality Lifecycle Implementation (PQLI®) Committee and its technical subteams, and ISPE initiatives such as Quality Metrics and Drug Shortages.

The volunteers in these groups establish relationships with key global regulators and agencies, and serve as technical resources to align ISPE's activities and products with evolving regulatory expectations.

In 2017, volunteers from these groups:

- Developed and produced three successful ISPE conferences: Cultural Excellence, Process Validation, and Statistics in Process Validation
- Chaired and developed regulatory tracks in the ISPE European Annual Conference and the ISPE/FDA/PQRI Quality Manufacturing Conference
- Led development of the Regulatory/Quality track, the Regulatory Town Hall, and five

sessions at the 2017 ISPE Annual Meeting

- Harnessed members' expertise to provide technical feedback on five regulatory draft documents in Europe and the United States.
- Published "Drug Shortages," a joint effort with the Pew Charitable Trusts; the ISPE Quality Excellence report; two technical papers on process validation; and an online training course on quality metrics
- Enhanced written feedback on proposed quality metrics guidance with industry/regulator face-to-face conversations and workshops aimed at advancing pharmaceutical quality.

In late 2017, the Regulatory Steering Committee (RSC) was created to establish ISPE's international regulatory strategy and intelligence interface, and to ensure ISPE's regulatory activities are integrated throughout the society, consistent with our members' needs and business imperatives. The RSC is charged with assessing new regulatory-focused opportunities and advising on ISPE's engagement in new and ongoing activities. The RSC will also provide strategic direction and support to ISPE's regulatory volunteer groups and, where appropriate, recommend collaborations with regulatory agencies or other organizations to the ISPE International Board of Directors.

The RSC brings together the expertise of ISPE's key regulatory volunteer leaders and staff:

Roger Nosal, Vice President and Head of Global Chemistry, Manufacturing and Controls, Pfizer Worldwide Research and Development, will chair the committee in its inaugural year. Committee members will comprise the Global RQHC and PQLI Committee Chairs, leaders of ISPE's major regulatory initiatives, plus representatives from the ISPE Board of Directors. Staff members include the ISPE President and CEO and Director of Regulatory Operations. The RSC will seek additional input from ISPE's Regulatory Advisor/Consultants, communities of practice, affiliates and chapters, the Global Pharmaceutical Manufacturers Leadership Forum (GPMLF), and other industry leaders.

This new structure supports enhanced collaboration and communication among the volunteer groups with functional links to other key areas within ISPE. In the coming weeks and months, the RSC will be reaching out to ISPE committees and communities of practice to initiate information flow and communication as they support ISPE's regulatory and quality mission, as outlined in the current ISPE Strategic Plan:

Regulatory resources: Leadership in regulation and quality affairs associated with ISPE core concerns and priorities.

ISPE strives to facilitate industry wide clarity of new applicable regulations on regulatory matters relevant to ISPE's attention and expertise, advising on impacts and resolving towards solutions, seeking harmonization of regulatory expectations where desired and possible.

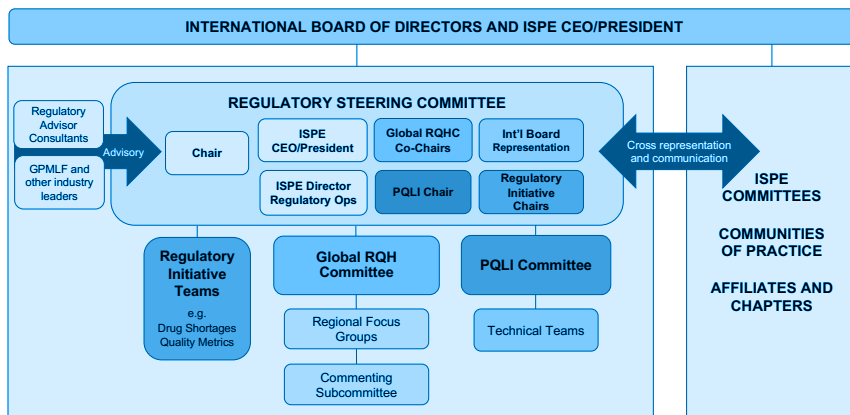
ISPE COMMENTS ON REGULATORY DRAFT DOCUMENTS

Following are brief summaries of ISPE's official response to US FDA on three recent draft guidances. Comments are developed by subject matter experts within the ISPE membership and reviewed by ISPE's regulatory volunteer leaders. All quotations are from the comment documents.

Docket No. FDA-2017-D-1105. "Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11—Questions and Answers." 21 August 2017. <https://www.regulations.gov/document?D=FDA-2017-D-1105-0027>

The ISPE response highlighted two general concerns for consideration:

THE RSC IS CHARGED WITH ASSESSING NEW REGULATORY-FOCUSED OPPORTUNITIES AND ADVISING ON ISPE'S ENGAGEMENT IN NEW AND ONGOING ACTIVITIES.



RSC ROLE

- Build effective partnerships with regulators and agencies globally and assist in the translation of regulatory expectations into practical solutions for ISPE members
- Ensure ISPE provides transparent, progressive, coherent and consistent regulatory perspective in alignment with the ISPE Strategic Plan
- Communicate ISPE regulatory vision, strategy, and priorities to global membership
- Ensure a consistent “one ISPE” voice to global regulators

First, the document describes “the sponsor’s EDC system [as] a sort of platform where all clinical data are finally generated and/or transferred. This is a simplified logical construct of many collaborative processes, which eliminate the sponsor’s sole control on the clinical data and shifts the responsibilities to the clinical investigators.” ISPE believes this does not represent the current industry environment and changing it to match the FDA’s concept of the sponsor’s EDC system “would require a significant re-engineering of most existing computerized systems.”

Second, the guidance does not address the possibility of “having a technology service provider database as part of the data flow,”* which could lead to conflicting interpretation of full control by the sponsor:

The guidance should provide directions on how to meet the fundamental expectations that 1) the sponsor does not have exclusive control until the data is in their EDC, and 2) the clinical investigator must appropriately control the data prior to that transfer since they typically have continuous access to the data. The current language seems to allow the direct transfer of mobile data to the sponsor’s EDC system without mentioning how clinical investigators should be ensuring proper controls over that data.

Other detailed comments covered topics such as clarifying the difference between data audit trails and other system logs, and retaining the distinction between actual signature events and other events such as logging on to a system,

* See US FDA. Guidance for Industry: “Electronic Source Data in Clinical Investigations,” September 2013. <https://www.fda.gov/downloads/drugs/guidances/ucm328691.pdf>

in order to remain consistent with the current FDA Guidance on Part 11 Scope and Application.

Docket No. FDA-2017-D-2232. “Product Identifier Requirements Under the Drug Supply Chain Security Act—Compliance Policy; Draft Guidance for Industry; Availability.” 1 September 2017. <https://www.regulations.gov/document?D=FDA-2017-D-2232-0012>

ISPE made five key recommendations:

- ISPE supports the proposed the delay of enforcement from the current proposed date of November 27, 2017, to November 27, 2018, for manufacturers to affix or imprint a product identifier on product placed into commerce.
- ISPE suggests the agency consider a delay of two years beyond November 27, 2018, for repackagers to engage only in transactions involving products that bear a product identifier (i.e., a compliance enforcement date of November 27, 2020, for repackagers) to allow for a greater attrition of unserialized product in commerce.
- ISPE suggests a commensurate delay in the parallel requirements for wholesale distributors compliance (i.e., a compliance enforcement date of November 27, 2020), and the proposed incremental compliance enforcement time for dispensers (i.e., a compliance enforcement date of November 21, 2021).
- ISPE suggests that a waiver/exception reporting system be implemented for those products introduced into commerce before November 27, 2018, which have not been serialized, which have not been consumed, and have a shelf life in excess of November 27, 2020.
- ISPE recommends that the agency address

gaps in its own serialization implementation plan. Specifically, the FDA should deliver the needed guidance for proper design, implementation and on-going management of product identifier data. Technical guidance should be issued regarding how product identifier data is requested, communicated and controlled and the Agency should address who will have access to ePedigrees, and to what level will that access be granted.

Docket No. FDA-2017-N-2697. “Submission of Proposed Recommendations for Industry on Developing Continuous Manufacturing of Solid Dosage Drug Products in Pharmaceutical Manufacturing.” 21 September 2017. <https://www.regulations.gov/document?D=FDA-2017-N-2697-0014>

The comments provide ISPE’s view of the desired content of a future FDA or international guidance on continuous manufacturing for solid oral dosage forms. They contain detailed recommendations for general definitions and principles; control strategy definition and design; clinical supplies/IND phase; commercial implementation, validation and verification; and life cycle maintenance and change management. <>

—Carol Winfield, Director of Regulatory Operations, ISPE

BUILDING COMMUNITY

ISPE was a publishing powerhouse in 2017, producing 10 documents that reflect new titles and refreshed content. Each was made possible by a group of talented professionals, both staff and members, who harnessed laser-focused determination to put current, practical information into your hands.

SUCCESSSES

The Risk-MaPP guide was well received by both industry and regulators for its focus on shared facilities and health-based exposure limits. It also included a special acknowledgement to the EMA's Health-Based Exposure Limit Guide EU Implementation Team for their valued review and contributions. Another highlight was the *GAMP® Guide: Records and Data Integrity*, published at the end of March, which sold over 1,000 copies in just over six months.

What does that tell us? ISPE provided what the industry needed, when it needed it—and the industry noticed.

CHALLENGES

ISPE's Publications Department lost some familiar faces in 2017, and some momentum along with them. But we rallied and were soon back on track. New folks like me and our technical editor Nina Wang found ourselves in a flurry of activity. Coming from industry ourselves, we were energized by the conversations in our Communities of Practice around changing regulations, reducing risk, and leveraging scarce resources. The question was how to share that dynamic thinking and problem-solving ability more broadly with our members. And thus, the work of planning for 2018 began.

WHAT'S NEXT?

The new year will build on the successes of 2017. We'll continue to streamline processes and incorporate new technology to drive ISPE forward. Long-awaited revisions to the Baseline® Guides for commissioning and qualification and sterile product manufacturing facilities are coming in 2018. Several new Good Practice Guides (GPGs) covering process validation, single-use technologies, HVAC and process equipment filters, asset management, and equipment reliability will also debut.

Because our membership survey revealed that Guidance Documents are ISPE's most valued asset, we've made access to all ISPE GPGs (25 titles) free to members. Members now have unlimited access via our new online publishing portal. Online communities will also be refreshed with new features and content.

GUIDANCE DOCUMENTS PUBLISHED IN 2017

GAMP® Guide: Records and Data Integrity

GAMP Good Practice Guide: Validation and Compliance of Computerized GCP Systems

GAMP Good Practice Guide: Global Information Systems (GIS) Control and Compliance (Second Edition)

GAMP Good Practice Guide: IT Infrastructure Control and Compliance (Second Edition)

Baseline® Guide: Risk-Based Manufacture of Pharmaceutical Products (Second Edition)

ISPE Good Practice Guide: Decommissioning of Pharmaceutical Equipment and Facilities

BECAUSE OUR MEMBERSHIP SURVEY REVEALED THAT GUIDANCE DOCUMENTS ARE ISPE'S MOST VALUED ASSET, WE'VE MADE ACCESS TO ALL ISPE GPGS (25 TITLES) FREE TO MEMBERS

YOUR ROLE

What can you do to help? First, join one or more of our CoPs if you have not already done so (ispe.org/communities-practice). You'll have access to information, tools, and best of all, a connection to your peers to exchange ideas and find solutions to everyday problems. Next, join a writing team. We have several technical guides and papers in development and your expertise is always welcome. Finally, if you see that there's question that is not being addressed in our library, submit a proposal and let's work together to find some answers.

With a new year comes new challenges and goals. There's a lot to do to outpace last year. I would like to thank each of you for your continuous support, enthusiasm, and dedication—we couldn't do this without you. <

—Konyika Nealy, Senior Director, ISPE Knowledge Networks and Guidance Documents



READY, SET, GOALS

I'm setting a New Year's resolution to find a new position in 2018. Any advice on how to get started?

The New Year often inspires new goals, and as with any resolution it's important to create a plan. Let's explore five goals that can lead you to that new position.

GOAL 1: KNOW WHAT YOU WANT

Define the job you want. Title, scope, and function are obvious focus areas, but others may be equally important, such as commute, relocation, travel, and flexible work arrangements. Salary or title may not be as important as health insurance, continuing education reimbursement, or vacation days. Make a list and set some priorities. What are you best at? What do you really dislike doing? The company you target can be as important as the role itself, so do your homework: Review websites, news articles, and social media to learn about the company culture, pipeline, priorities, and values.

GOAL 2: DUST OFF THE RÉSUMÉ

Once you've set your priorities, make sure that your résumé matches them. Review the requirements for the position you're seeking, then compare it to your résumé. Which of your skills and experiences are most relevant? Use a reverse chronological format, and divide the content into education, work history, publications, and any relevant awards or volunteer activities.

Try to define a value for your past work. Descriptions that highlight time savings, reduced errors, or other benefits help you stand out from other candidates. Avoid including nonrelevant skills and experiences, which may lead the reader to think you are better suited for another job.

Simplicity is the golden rule. Don't use a font that's decorative or smaller than 10 points, and avoid graphics. Few résumés need more than two pages. If yours is longer than that, it probably includes

unnecessary information or is needlessly wordy.

Ask others you trust to review your résumé. Is it easy to navigate? Targeted and well written? How's the overall presentation? Be sure to share a job description to provide the context necessary for accurate feedback.

GOAL 3: GET ACTIVE ON SOCIAL MEDIA

Most employers use social media to look for candidates, so an online presence is crucial; invisibility can be a severe liability. LinkedIn is the most common resource, but Facebook and Twitter are also important. If you're already on these sites, make sure your profile matches your résumé. Update your picture with one that makes you look professional, friendly, and energetic, and use the same photo for all sites. Your profile descriptions should include the most common keywords for your field to help recruiters find you. Look at other profiles in your field to learn best practices for showcasing your skills and interests. You can also read my November–December 2017 column for more social media guidance and best practices.

GOAL 4: NETWORK, NETWORK, NETWORK

Hiring managers tend to hire people they know and trust or who have been referred by others they know and trust. Sending out several applications may feel like an accomplishment, but you are likely not as competitive as if you were recommended by others—or at least had more knowledge about how the group operates. Here's how to start networking:

- Get involved with your local ISPE chapter and volunteer to help with an event, join a committee, or serve as a speaker. You will find yourself surrounded by volunteers who may well be hiring managers or other influencers.
- Reconnect with former classmates and col-

leagues who are working for your targeted companies. This group should be the easiest to meet with and most likely to recommend you.

- Contact your university alumni and career center to see if they work with or can connect you to your targeted companies.
- Use social media to find lost or potential contacts.
- Don't overlook contacts outside the industry, such as neighbors and friends.

Try to network daily, whether meeting with a former colleague, conducting an informational interview, asking for an introduction to a decision-maker, or attending an event to grow your network. For more tips, read my July–August 2017 column on landing an informational interview.

GOAL FIVE: DEVELOP A SUPPORT SYSTEM

A support system can help you remain focused on your goals, pick you up during the low spots, and celebrate victories. Choose someone you trust, and ask that they encourage you to remain accountable. Job-search support groups also provide training and presentations by industry professionals and are great places to exchange information such as openings and contacts. People that attend these groups tell me consistently that they have been key to finding new leads as well as staying positive and focused.

I'm sure that these goals will keep you on track and lead to great success in 2018. <>

If you have a question about career development, send it to me at david.g.smith@biogen.com, and I will try to answer it in a future column.

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



Global health care leader Eli Lilly and Company is the 2017 Overall Winner of ISPE's Facility of the Year Award (FOYA) for its Continuous Direct Compression Manufacturing Kits 2 & 3 projects in Indianapolis, Indiana, and Carolina, Puerto Rico. The facilities had garnered 2017 category wins for Facility of the Future and Process Innovation earlier in the year—the first time ISPE honored a single project with two FOYAs. Lilly's designation as Overall Winner was announced on 31 October at the 2017 ISPE Annual Meeting & Expo Membership and Awards Breakfast in San Diego, California.

"Considering the quality of the projects and facilities that were submitted, we were both pleased and humbled by being selected as this year's Overall Facility of the Year Award winner," says David Sternasty, Vice President, Corporate Engineering and Global Health, Safety, and Environment at Lilly. "This award is the result of many talented and committed individuals at all levels within Lilly who spent the last half decade designing, piloting, modeling, building, and operating these facilities across functions such as development, corporate engineering, quality, manufacturing and even external regulatory authorities."

Lilly's forward-thinking approach has enabled the implementation of continuous direct compression (CDC) processes along with other process innovations in its oral solid dosage (OSD) facilities across its manufacturing network. In the CDC process, materials, excipients, and active ingredients are blended and compressed directly; there is no preprocessing to granulate or change the materials in any way before they enter the tablet press.

The company built sequential OSD installations at three separate locales. Each installation was implemented more quickly than the one before, and

showed operational and budgetary improvements as well. Future formulations or products could also be run on any of these three platforms. Today, Lilly is the only company with multiple, replicated, and operational CDC facilities.

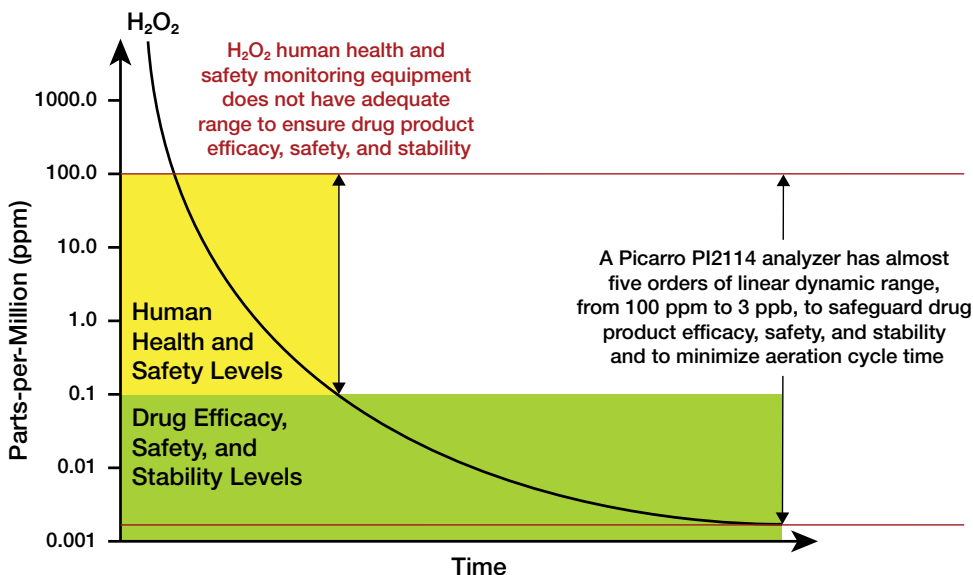
PROTOTYPE

The company's quest to build a network of state-of-the-art good manufacturing practice (GMP) OSD facilities for delivery of new advanced therapies began about five years ago, when Lilly's development group considered implementing continuous manufacturing (CM)—one of the pharmaceutical industry's newest and most advanced production methods—for its OSD products. They began to work with the technology to ensure that they fully understood CM and its potential benefits, integrating process analytical technology (PAT) into the initiative. Their initial platform, known as CM1, was completed at the company's development facilities in Indianapolis, Indiana, in the United States.

The Lilly team immediately recognized the positive effect CM could have on the new product development cycle. "From a development standpoint, this was the reason that we originally started moving to CM," says Sternasty. "Under an older production model, a development scientist might make 16 or 32 discrete batches of product in a designed experiment that then had to be lab tested to determine how process parameters impact production. In a continuous processing unit, parameters are established by adjusting controls, and consequently you can do multiple experiments very quickly. This is a huge advantage for development scientists, because it allows them to gain product understanding quickly."

Integration was a central principle that influenced all aspects of the project. At the system level, feeding, mixing, and tablet-compression unit operations are integrated seamlessly with online process analytical technology (PAT) and

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LILLY WINS FOYA 2017 OVERALL WINNER

PROJECT: Continuous Direct Compression Manufacturing Kits 2 and 3

LOCATION: Indianapolis, Indiana (CM2) and Carolina, Puerto Rico (CM3)

PROJECT MISSION: Design and implement a network of state-of-the-art continuous manufacturing process facilities for commercialization and production of tablets.

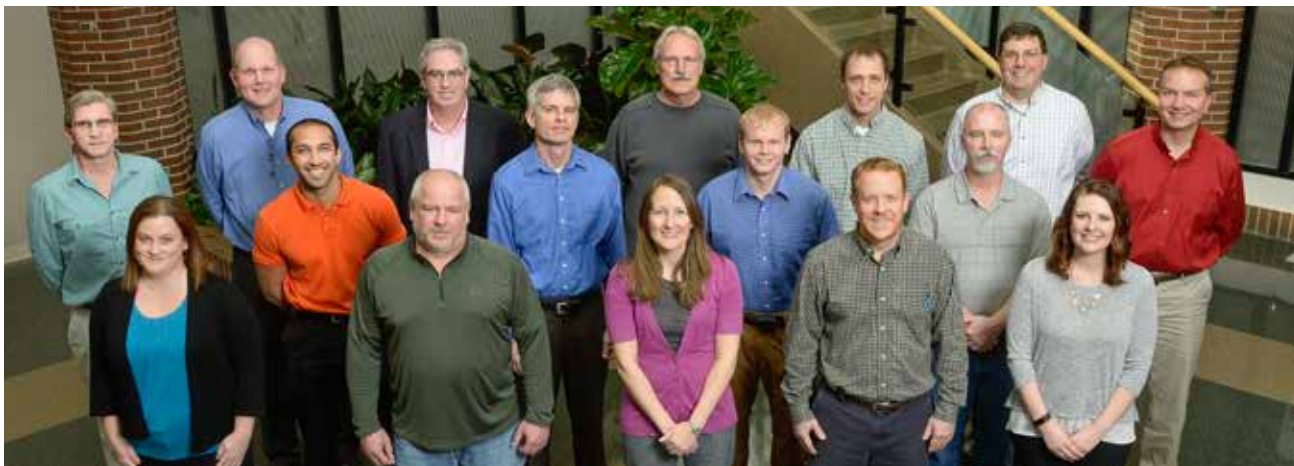
Total facility floor area (associated with project in existing facility): **CM2:** 4,975 sq. ft. **CM3:** 4,720 sq. ft.

KEY PROJECT PARTICIPANTS

CM2: INDIANAPOLIS

CM3: PUERTO RICO

Manufacturer/Owner	Eli Lilly and Company Lilly Corporate Center Indianapolis, Indiana 46285	Lilly del Caribe, Inc. 400 Calle Fabril Carolina, Puerto Rico 00987
Engineer/Architect	Mussett Nicholas & Associates 502 S. West St. Indianapolis, Indiana 46225	
Engineer/Architect	TLF Engineering 3901 W. 86th St., Ste. 200 Indianapolis, Indiana 46268	Babilonia Engineering Group 1223 Cll Juan Ponce De Leon San Juan, Puerto Rico 00926
Construction Manager	Davis & Associates, Inc. 2852 N. Webster Ave. Indianapolis, Indiana 46219	Fluor Daniel Caribbean, Inc. Parkside Plaza, Ste. 500 St. 2 No. 14 Metro Office Park Guaynabo, Puerto Rico 00969
Main/General Contractor Piping Subcontractor HVAC Subcontractor	Davis & Associates, Inc. 2852 N. Webster Ave. Indianapolis, Indiana 46219 Prozess Technologie 6124 Delmar Blvd. St. Louis, Missouri 63112	Alproem Engineering Contractors Carr. 168 #63 Hato Tejas Bayamon, Puerto Rico 00959-5259
Automation and Control Supplier	Cornerstone Controls Inc. 8525 Northwest Blvd. Indianapolis, Indiana 46278	Emerson Process Management Los Frailes Industrial Park 475 Calle C, Ste. 501 Guaynabo, Puerto Rico 00969
Major Equipment Supplier	Korsch America Inc. 18 Bristol Dr. South Easton, Massachusetts 02375 Bruker AXS Inc. 5465 East Cheryl Pkwy. Madison, Wisconsin 53711	CDM (Creative Design & Machine Inc.) 197 Stone Castle Rd. Rock Tavern, New York 12575
Major Equipment Supplier	Coperion K-Tron 590 Woodbury Glassboro Rd. Sewell, New Jersey 08080 Gericke USA, Inc. 14 World's Fair Dr., Suite C Somerset, New Jersey 08873-1364	



Indianapolis development team



Indianapolis development team



Lilly technology center, Indianapolis

first-principles modeling to provide a comprehensive unified control strategy. The Lilly CM platform also relies on integration at the individual unit operational level, as shown by its novel approach for the dispensing and feeding unit.

Feeders are controlled as an integrated system rather than a series of independent set points using a cascade control loop, also known as ratio control. By designating a master feeder (typically the drug substance feeder) and modulating other feeders in response to variation in the master feeder output, the concentration of formulation components is maintained more consistently. The powder-feeder feedback control loops automatically adjust for raw-material changes such as density and powder flow.

As they completed tests with the CM1 development unit, the team learned how to deal with other variables such as environmental disturbances, vibration, and room pressure changes. “These feeders are incredibly sensitive, and they are on very sensitive scales,” explains Timothy Pletcher, an Associate Senior Consultant Engineer at Lilly. “We learned that we needed to be mindful and design a system that could provide as much stability as possible. We worked closely with our architecture and engineering firm to design structurally independent platforms, such as on the mid- and upper-level feeders, which were mass-dampened to give us as much stability as we could achieve.”

EFFICIENT REPLICATION

With bugs and inefficiencies worked out of the process, Lilly determined that it had a platform mature enough for replication in a commercial manufacturing environment. In September 2014 the company launched its CM2 project to integrate the platform into its existing OSD facility in Indianapolis. Building on lessons learned in the development phase, the CM2 line progressed quickly through construction, commissioning, and qualification; the unit was ready for production of three developmental molecules, in line with GMP, in November 2015. A mere 15 months had elapsed between the company’s funding approval and its ability to produce commercial products destined for patients.

As CM2 was being completed, installation of a second GMP unit (CM3) at Lilly’s existing OSD manufacturing facility in Carolina, Puerto Rico, began in November 2015. The unit was qualified and placed into service in only 11 months. “Because of the efficiencies and the fact, we were replicating an installation we had just completed,” says Pletcher, “we were able to reuse



Puerto Rico team



Puerto Rico site



Second floor feeders, Puerto Rico

and leverage commissioning and qualification protocols as well as much of the design work. This approach has proved to be a very efficient and effective way to replicate units from one facility to another.”

With the completion of CM3, Lilly demonstrated that it could quickly augment its production capacity at low capital investment, should the need arise. Within a time frame of 12 to 15 months, a replicated CM unit can be integrated into an existing facility with limited free floor space (due to the CM unit’s small footprint).

Both the Indiana (CM2) and Puerto Rico (CM3) units are functional replicates with identical equipment, layout, PAT instrumentation, and automation and control schemes. According to Sternasty, the design of both GMP equipment sets benefited from years of optimization and evolution work on the prototype CM1 installation.

“One of the benefits of the CM process is that there is no scale-up,” he says. “Because we are using continuously running equipment that is very small in scope, the equipment deployed in development is the same as that used in manufacturing. So there is no cost and time associated with scale-up and technology transfer. From a manufacturing standpoint, the capital investment is significantly lower, the equipment offers a more compact footprint, and the process uses less energy than what you would see in a traditional wet-granulation fluid-bed drying process. While we started on the course because of the gains we would see in development, we have gained continued benefits all the way through to commercial manufacturing.”

Pletcher credits the teams’ close working relationship for the project’s success. “We had an unprecedented level of collaboration,” he says. “Finding ways to replicate that team effectiveness and cross-functional teamwork on other projects would be beneficial on any other endeavors that we undertake. The success of these projects was very much built on how effectively these groups worked together—from development to manufacturing.”

“Lilly is focused on innovation,” concludes Sternasty. “We believe that continuous manufacturing is an innovative way to provide a reliable, safe supply of high-quality medicines, and to be able to bring our product through the pipeline, from development to manufacturing, as quickly as we can. So, we are really very pleased with the results of what we have installed here.” ◀

—Mike McGrath



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Main processing suite, Puerto Rico



API feeders on vibration isolation pad, Indianapolis



Feeders, Indianapolis

CM-PRODUCED CANCER TREATMENT RECEIVES FDA APPROVAL

Eli Lilly and Company’s continuous manufacturing (CM) kits have proven to be an important manufacturing platform for the company’s oral solid dosage products (OSD). “CM is very important to Lilly as one of our proven manufacturing platforms for commercial dry products,” says David Sternasty. “We’ve seen a number of benefits and advantages, and our development pipeline is directed towards this technology where applicable.”

The company’s most recent success with CM technology was acknowledged on 28 September 2017, when the US Food and Drug Administration (FDA) approved Lilly’s Verzenio (abemaciclib) for the treatment of advanced breast cancer. Verzenio is Lilly’s first approved oral dosage medicine made using the CM process, and only the third CM-made medicine approved by the FDA. Verzenio’s approval represents a significant milestone in Lilly’s efforts to advance CM science and engineering. The company credits strategic partnerships among its development, manufacturing, quality, and regulatory teams as key to the successful implementation of CM and approval of Verzenio.

Lilly noted during project development that CM had the potential to shorten the drug development cycle. “Verzenio is our first medicine to be manufactured using CM and the other products are still in the pipeline, so it is still early to draw conclusions,” says Sternasty. “However, by doing our development at the same scale as manufacturing, and by

replacing large-scale tumble blending with in-line mixing, many lengthy late-phase batch development activities are eliminated, which can make overall development timelines shorter.”

Verzenio, which works by blocking molecules (cyclin-dependent kinases 4 and 6) involved in the growth of cancer cells, was approved in combination with fulvestrant for the treatment of women with hormone-receptor-positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer with disease progression following endocrine therapy. It is also approved as monotherapy for the treatment of adult patients with HR+, HER2- advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

Breast cancer is the most common form of cancer for women, according to the American Cancer Society, comprising as many as 25% of all new cancer diagnoses in women worldwide. In the United States, the National Cancer Institute at the National Institutes of Health estimates that nearly 253,000 women will be diagnosed with breast cancer this year, and 40,610 will die of the disease. Approximately 72% of patients with breast cancer have tumors that are HR+ and HER2-.

As with any of its manufacturing platforms, Lilly’s plans for further replication or expansion of CM will be driven by business needs and other aspects considered part of its strategic planning process.

TO ME, PATIENT-CENTRICITY MEANS BEING DEEPLY ENTRENCHED IN PATIENT'S NEEDS, NOT JUST THINKING ABOUT HOW TO DEVELOP NEW PRODUCTS AND NEW FEATURES. IT MEANS REACHING OUT TO PATIENTS AND CONSIDERING TREATMENTS THAT WILL HELP THEM IN WHATEVER SITUATION THEY FIND THEMSELVES IN.

Gitte Aabo: That is a huge challenge and clearly not something that happens overnight. We've done a number of things. Every employee who joins LEO Pharma, for example, meets a patient as part of the induction. And the incentive schemes for all senior managers are now split into three categories: patients, people, and performance—with patients being the one that has the heaviest weighting.

Other elements still need to change. Take our clinical trials. What does a successful clinical trial look like in a patient-centric culture? It requires a focus on convenience—ease of use—and on reported patient outcomes as much as on safety and efficacy, and it requires openly sharing the results. As an example, we have taken steps toward the latter with our commitment to transparency. We were the second company, globally, to commit itself to increased disclosure of clinical-trial information. We are proud of that commitment but want to do even more.

The Quarterly: Can you tell us about the LEO Innovation Lab? Why did you create a separate unit, and what is its relationship with the rest of the company?

Gitte Aabo: The idea behind the LEO Innovation Lab has been to build and test digital technologies and platforms that will address areas the pharmaceutical industry typically overlooks. We wanted, above all, to create an environment that resembles a start-up company because we realized that

the competencies we need are very different from what we find in many employees with scientific backgrounds. A company with a more than 100-year history probably doesn't have that start-up environment. Hence the decision to opt for a separate unit, with a different way of working that would attract people wanting to innovate in the digital space.

The Quarterly: How did you decide where to locate the LEO Innovation Lab?

Gitte Aabo: We felt it was important to locate the lab in the center of Copenhagen, where younger, digitally savvy people are more likely to want to work, rather than in the suburbs, where LEO Pharma is headquartered. And it was important to be in Copenhagen—not, say, Silicon Valley—so that we could more easily transfer all the insights we have in the company about the physical, social, and psychological impact of living with a skin disease.

To guide the LEO Innovation Lab, we have put in place an advisory board that combines people from the business in LEO Pharma with people well known within the start-up and digital space. The latter bring knowledge, experience, and networks to the table, but, most important, they set the tone for a start-up environment in culture and values.

Besides Copenhagen, we have satellite labs in the UK, France, and Canada—all markets where we have a very strong presence and close relationships with dermatologists, payors, and pharmacists. To reach out to patients, we need a deep understanding of the ecosystems surrounding them.

The Quarterly: What results are you expecting from the LEO Innovation Lab, and how will you measure them?

Gitte Aabo: In the first instance, we aim to develop specialized apps to give people living with skin diseases resources like dietary advice, beauty tips for psoriasis sufferers, and general ideas on how patients can benefit from their interactions with healthcare professionals. We will have KPIs to track how many people with skin diseases use our solutions and continue to use them. We believe that the better patients are informed and understand a disease, the better they will be able to take control of it and adhere to treatment.

The Quarterly: How flexible is the operating model of LEO Innovation Lab?

Gitte Aabo: It's flexible in the sense that it's scalable. The lab operates a lot through external partnerships and hiring people with specialized competences on shorter assignments to work on a particular digital solution.

We've allocated around €60 million for the next three years and are already considering how to continue the initiative, and in what form, when that period is up. We want to strike a balance, ensuring that there is enough funding to have an impact, while not providing so much money that it discourages the sort of risk taking, pragmatism, and agility that distinguish the best start-ups.

I hope that some of the thinking applied in LEO Innovation Lab will rub off on how we run projects or processes inside the traditional, nondigital part of LEO Pharma. In LEO Innovation Lab, we have an innovation process that runs within 100 days—100 days from the point we have an idea to the moment we have a solution on the market. Although I would love to see that kind of speed in my innovation process in more traditional research and

development, that's not possible for many reasons. Still, there are elements that we can learn from and apply elsewhere in the business.

The Quarterly: With LEO Innovation Lab, you've been active in seeking innovation partnerships. What technologies are you most interested in, and what characteristics do you look for in potential partners?

Gitte Aabo: We are particularly interested, at the moment, in the combination of imaging and artificial intelligence. Currently, general practitioners, or family doctors, have a limited ability to diagnose a skin disease. Studies show that only about 50 percent of eczema cases, for instance, are correctly diagnosed by these GPs. By combining imaging technology with pictures taken on a mobile phone, you can build up knowledge, over time, about what eczema looks like or what a melanoma looks like. We've recently invested in a company whose app to detect melanoma can provide as accurate a diagnosis, with images taken by an individual patient, as the best specialists.

The Quarterly: How does the legal and regulatory framework affect LEO Pharma's strategy?

Gitte Aabo: The legal and regulatory frameworks reflect the credibility of our industry in the eyes of society. Credibility is crucial to the industry because a lot of people don't trust pharma companies. That's something we need to address and change in the coming years, and there's only one way to do it—by being transparent about our clinical trials and our other activities.

GITTE AABO BIOGRAPHY

Education

Earned an MBA at Copenhagen Business School

Career Highlights

LEO Pharma (1992–present)

President and CEO (2008–present)

Deputy group managing director (2007)

Vice president and senior vice president,
finances and IT (1999–2006)

Fast Facts

Member of the board of directors of the
Danish National Bank

WE BELIEVE THAT THE BETTER PATIENTS ARE INFORMED AND UNDERSTAND A DISEASE, THE BETTER THEY WILL BE ABLE TO TAKE CONTROL OF IT AND ADHERE TO TREATMENT

The Quarterly: As you look ahead, what worries you and what excites you?

Gitte Aabo: One of the things that excites me is the level of access to information that patients now have, which will further increase. I believe this is going to change the whole dynamic of the healthcare system. We've only scratched the surface at the moment, but more information will have a profound impact on the physician's role, the patient's role, and our role as a company. Patients will have more decision power, at least when it comes to chronic diseases, and as a citizen I think that's a healthy development. It's also challenging because it requires a completely new business model, in which the patient gradually moves to the foreground.

The Quarterly: Is it important for LEO Pharma to prioritize long-term success over short-term gain?

Gitte Aabo: I think it's important for the entire pharma industry if we want to be perceived as credible and to run a sustainable business. In the years to come, people will increasingly select not just a pharmaceutical product but the company behind that product—and that's where trust is vital. That mind-set is embedded in how we run the business and how we make investments. The fact that LEO Pharma is owned 100 percent by a foundation strengthens our ability to think and act for the long term and is closely related to our credibility.

*For more interviews on how the pharmaceutical industry is evolving and how leaders can adapt, see *Biopharma Frontiers* (<https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/biopharma-frontiers>).*

About the author(s)

Gitte Aabo is the president and CEO of LEO Pharma. This interview was conducted by Martin Møller, a senior partner in McKinsey's Copenhagen office.

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DEADLINES ARE LOOMING



Mark Davison (left), and Eric Tjoa

Whether serialization deadlines have arrived or are imminently approaching, smaller companies along pharmaceutical supply chains are scrambling to prepare—and for many, it’s a problem. TraceLink, a track-and-trace network for pharmaceuticals, estimates that half of contract manufacturing organizations won’t be compliant in time to meet serialization regulations in the United States and Europe.¹

“The nuclear scenario is that regulators will say, ‘No compliance, no business,’” said Mark Davison, Senior Operations Director, Europe, at rfxcel, a track-and-trace software provider. “The FDA (US Food and Drug Administration) is not prepared to push that button yet. Its deadline for compliance has been kept, but enforcement has been pushed back until November 2018. That’s a holiday for those who are not yet ready, but I expect the FDA to come down hard after that. We are not seeing any slowdown in customer activity.”

Serialization regulations are meant to reduce the threat of falsified and/or stolen drugs, enhance supply chain integrity, and ensure patient safety. The European deadline for serialization implementation is February 2019.

“Generally, the industry has been slow to adopt serialization,” said Eric Tjoa, CEO of Tjoapack, a pharmaceutical packaging company. “There is a widespread misconception that introducing serialization to packaging lines is a simple process, and because of this, many companies involved in the manufacturing, packaging, and distribution of drug products are underprepared. Companies just starting to consider serialization will struggle to fully implement a compliant solution in time.”

¹ These are saleable units only in the United States.

² A nonprofit organization that develops and maintains global standards for barcodes and other unique identifiers.

³ Originally devised for Bitcoin, blockchains are “blocks” of digitized, decentralized, linked, and secured information that reside on millions of computers. For more information see: <https://hbr.org/2017/01/the-truth-about-blockchain>

SERIALIZATION AND TRACEABILITY

Regulations require that pharmaceutical products at the saleable unit* (e.g., bottle, vial, blister pack), secondary packaging (carton), and shipping (pallet, container) levels be labeled with a unique product identifier, usually as both human-readable numbers and as a scannable barcode or 2D data matrix code (DMC). These regulations differ from country to country.² In the United States, saleable units must be labeled with a DMC that carries the product’s serial number, global trade item number (GTIN), batch number, and expiration date. In the European Union, packaging labels must also bear a national reimbursement code, if applicable. These labels allow products to be tracked from point of manufacture to dispensation.

“Luckily, within the diversity of detail, there is a common theme that mostly follows the GSI³ data structure,” said Davison. “This means that a company that can meet the regulations of one country typically has the systems needed to meet all of them, with some additional configuration.”

MAKING THE BUSINESS CASE

By streamlining operations and logistics, serialization and traceability offer business advantages beyond compliance.

“End-to-end visibility will lead to better supply chain management,” said Tjoa. “Companies will be able to analyze serialization data to gain strategic insight into their operations.” Increased visibility of stock levels will allow for more accurate order forecasting, which will reduce stock levels across the supply chain and potentially save the industry billions of dollars. “It will continue to drive consolidation across distribution networks, simplifying supply chains and lowering costs.”

Davison sees serialization as a step toward personalized medicine. “We think that if we can link the patient to individual medicines then we can start to personalize their experience and drive up adherence. We can link medication to reimbursement and link reimbursement of medical professionals to the health outcomes that they generate and to the medicines they prescribe. It will allow society to justify choices as opposed to merely paying for products.”

SECURING DATA, MANAGING COSTS

“The amount of data to be stored and shared is significant,” said Davison. “Companies will generate billions of code numbers every year as well as monitor business transactions as products move through the supply chain.”

Auditing and security issues are both central and disseminated, involving internal databases and information that needs to be shared with business partners and regulators. While blockchain³ is being discussed as a means of securely sharing data among companies, partners, and regulators, Davison is currently unconvinced. “I haven’t seen a mature industrialized offering yet, though it’s being trialed in a number of areas and will have a place in the future. An issue to be investigated is whether it will be appropriate for the high volume of data points that serialization will produce.”



A concern for smaller packaging companies is the up-front investment required to equip their lines to ensure supply to multiple markets. “In most cases, contract packaging organizations (CPOs) can recover the costs once their customers have finished the onboarding process,” said Tjoa. “However, with many pharmaceutical companies failing to recognize the urgency to implement a solution, a number of CPOs will have to make the decision to withdraw from certain markets that have more complex requirements.”

Serialization and traceability programs require new software, hardware, and processes to identify, track, and share information—and this can be expensive.

“One important equipment issue is that the format of the data matrix can only be read by camera or an image-based scanner, not a red-laser scanner,” said Davison. “Upgrading an individual reader is inexpensive, but multiplying for a large install base makes it significant, especially for pharmacies.

“On the manufacturer side, a small company could go out of business because the economics to upgrade their systems to be compliant are not feasible or they could botch it by not being ready on time,” said Davison. “I think we’ll see examples of both.” <>

—Scott Fotheringham, PhD

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MAKING A SERIALIZATION PROGRAM OPERATIONAL

The Johnson & Johnson Supply Chain Experience

Thomas J. Pizzuto

Regulations around the world are driving pharmaceutical companies and their supply chain partners to develop serialization and track-and-trace programs. In the United States, the Drug Supply Chain Security Act (DSCSA) came into effect in November 2017, though the US Food and Drug Administration agreed to forestall enforcement until November 2018 to help companies catch up. In the European Union, the Falsified Medicines Directive (FMD) regulations will come into effect in February 2019.

The DSCSA and the FMD require saleable units to be labeled with unique identifying information that will allow the product to be traced through the supply chain from manufacture to point of dispense. The data will be embedded on labels and consist of at least a global trade item number (GTIN), unique serial number, batch number, and expiry date contained in a data matrix code.

THE J&J EXPERIENCE

Serialization affects the entire pharmaceutical industry, and almost every department at Johnson & Johnson has felt its enormous impact. We manage more than 265 operating companies in 65 countries, and sell products in more than 175 countries.

Johnson & Johnson's Supply Chain division (JJSC) initiated its serialization and traceability program in 2012 in anticipation of the regulations described above. We had to ensure that we would be globally compliant across each of our three sectors—pharmaceutical, device, and consumer—in a cost-effective way. We recognized early on that our program required an enterprise approach that would be centrally coordinated and locally executed. Fortunately, we had early alignment about the benefits of supply chain visibility both internally and with our partners.

Our experience over the past six years has provided key takeaways:

- While the ultimate goal is enhanced patient safety, regulations are the primary driver of serialization and traceability.
- Interoperability relies on global standards.
- A multidisciplinary approach is essential for designing an end-to-end program; it involves IT, packaging, manufacturing, labeling, master data, distribution sites, contract manufacturing organizations (CMOs), and third-party logistic partners.

- Serialization and traceability create significant change for the workforce; this underscores the importance of effective training, documentation, and communications.
- Continued collaboration with our customers is critical to maintaining patient access to our medicines while we deploy these new capabilities and explore innovative uses of this new platform.
- Supply chain digitization will improve data and product integrity and drive innovation.

The Importance of operationalizing

All of J&J's operations are founded on our commitment to patients. That is why operationalizing our serialization program started with a focus on regulatory compliance, which helps to ensure patient safety and continued access to medicines.

Many companies seem to be approaching serialization solely as an exercise in regulatory compliance. For those that embrace the opportunity, however, there are enterprise-wide benefits beyond patient care that include innovation and improved product and data integrity. Inventory management, for example, is often cited as one area where improved supply chain visibility can provide benefit: serialization and traceability can help manage and validate product returns and process the correct refund.

Unprecedented confluence of regulations

At least 46 countries now require a unique identifier at the saleable unit. Argentina was an early adopter: Because it saw patient safety benefits, the country expanded its regulations to require serialization on Class III implantable medical devices. Serialization and traceability are expected to become ubiquitous across health-care supply chains over the next 10 years.

In terms of labels, or product identification license plates, most regulations align around GS1 standards but vary from country to country. These slight but important differences in label data reflect the needs of each country. The one constant is the 2D data matrix code, which can be read by bar code scanners from Dubai to New York City.

IMPACT OF GLOBAL COMPLEXITY

Johnson & Johnson—like other large pharmaceutical manufacturers—must be able to trade serialization information across internal and external supply chains. GS1 standards play an important role in that exchange. We use the EPCIS (electronic product code information services) data standard to share serialized product information with our trading partners.

Hundreds of standard operating procedures (SOPs) have been updated to inform operators of what is required when working with serialized products. People are used to working with the physical product, but we've now added a digital twin that must be tracked with the same care. When we physically remove a serialized case from a pallet, for instance, we must also logically decommission or dissociate that serialized case from that pallet.

A company our size has thousands of stock-keeping units (SKUs), creating an enormous volume of artwork changes at the saleable unit and case level. This is in addition to the routine label changes that are part of our base business. Detailed work planning is key to making sure that as label changes are demanded, they occur in the most efficient way possible.

MANY COMPANIES SEEM TO BE APPROACHING SERIALIZATION SOLELY AS AN EXERCISE IN REGULATORY COMPLIANCE

Interoperability and standards

The development and adoption of standards, both global and internal, allow us to identify, capture, and share data according to GS1 standards and achieve end-to-end product traceability. As a result, we can:

- Identify a product's GTIN, global location number, and serial shipping container code
- Capture bar codes (and sometimes radio-frequency identification tags), which are scanned for product information such as the universal product code (in the US), European article number (in the EU), and electronic product code
- Share information via formats such as the electronic data interchange (EDI), the global data synchronization network, and EPCIS, which improve supply chain efficiency

Ideally, license plates should be interoperable across the globe. GS1 has long provided venues for industry discussion of these standards; JJSC worked with GS1 to shape these standards as a starting point. We were able to suggest improvements that came from our experience, including an extension to the GS1 EPCIS specification that allowed it to handle serialized products in Brazil. The unique differences between regulatory regimes make this type of collaboration a global phenomenon.

Industry forums provide opportunities for discussion and alignment on the implementation of standards to ensure as smooth a transition as possible. Some of these forums included the Healthcare Distribution Alliance, a wholesalers' trade association; the Pharmaceutical Distribution Security Alliance; and the European Federation of Pharmaceutical Industries and Associations, which hosts meetings focused on compliance with the FMD.

Following our understanding of the law and GS1 general specifications, we operationalized those standards within J&J to design and deploy our serialization program.

Multifunctional approach

Implementing serialization and traceability is a business transformation. If it is to be successful, collaboration and communication are critical.

The JJSC serialization program is coordinated by a Program Management Office (PMO), which works closely with decentralized site teams. The PMO,



comprised of experts from each functional area, is an essential part of realizing the program's goals. The functional leaders guide and support the site teams, while the PMO provides monthly updates to a steering committee. Our success depends on the inclusion and coordination of work across multiple functions: IT and technical operations, change management and training, labeling and master data, regulatory affairs and quality assurance, legal and finance, distribution and customer service, and commercial. Of these, IT, packaging, and change management are the most influential.

The IT solution we implemented spans manufacturing to distribution across all three J&J sectors. It begins at the enterprise level and goes all the way down to packaging lines at any one of our plants (or one of our partner CMOs) around the world. Technical operations established requirements and standardized solutions for manufacturing sites that facilitated the implementation and qualification of new line-level, serialization print-and-check systems, and serialized product-aggregation systems. The focus on change management allowed us to assess the effect on our workforce, implement changes to SOPs, and develop training to ingrain product serialization and traceability as a new core competency.

Implementing product serialization and traceability across J&J sites required a structured approach. Site core teams were established to ensure that local activities, funding, and priorities aligned with enforcement dates and program standards. Site core teams met weekly to review how the operationalized standards were performing, which allowed us to follow an improvement cycle to ensure compliance and cost-effectiveness. The site core team lead represented the site at the central program level and reported to the site's local steering committee.

Regular, frequent communication between the central program office and site teams were imperative given the many sites in different parts of the world, all working to meet the unique regulations of numerous countries. Communication occurred through weekly calls, workshops, an annual meeting, and via the steering committee. It was truly end-to-end, involving people from manufacturing, distribution, customer service, and IT, all talking to each other

about how to solve an issue. This gave us all a respect for the complexity that exists in other functional domains, how that complexity is amplified through the supply chain, and how to meet J&J's serialization and traceability needs.

Communications and business simulation training were critical to facilitate the transition to good serialized product management practices. The JJSC has a robust communications team that works on change management, organization design, and training, all of which are critical areas needed to engage the workforce. It wasn't enough to put new printers, cameras, or IT systems on our packaging lines without having a workforce that knew why it was being done, what serialization and traceability are, and how to operate and maintain the equipment effectively.

Our multidisciplinary program made effective use of the agile methodology. It has helped us ensure on-time, on-budget deployment of new capability. Brazil was our first deployment where we used agile methodology. Scrums—regular morning meetings—became routine as teams reviewed the day's to-do list and burn-down charts. Teams were pleased to see software releases sooner, which allowed them early access to see how the code was performing, rather than waiting six months to first review.

CHANGE MANAGEMENT

Managing global teams

To manage these global teams we had to clearly define things such as what the PMO was expecting from sites, what had to be reported to the steering committee, and how best to track and record risks and progress. We had to ensure that standards were being used for master data, to exchange serialized information with our customers, and for labeling. Cultural and language differences can be challenging—we work with partners in regions as distinct as Korea, Brazil, the United States, and Africa—but we found that the famed Johnson & Johnson Credo bound us as colleagues and mitigated any differences. Frequent interactions helped, including our annual meeting, which grew over the six years of the program from 35 people to more than 100.

Organizational impact

Serialization and track and trace is now a core competency at J&J. From the start of the program we quantified organizational change readiness by surveying our workforce about their understanding of serialization and traceability and the impact it has had on them and the company. Over the program's six years, we have measured continual progress up the change continuum, from awareness through adoption to internalization. Sustaining and optimizing the processes lie ahead of us with serialization and traceability 2.0.

LESSONS LEARNED

- Agile methodology: We applied this first in Brazil and then elsewhere, and found it valuable to deliver numerous complex pieces of software on time and efficiently.
- Lead times: Internally, we are not the only program competing for scarce resources (e.g., from our labeling group or master data), so we had to allocate sufficient lead times. Externally, only a handful of technology partners have the products and services equipped to deal with serialization and traceability, so we had to ensure adequate lead times to reflect their burgeoning workload.
- Robust communication: To be successful, trading partners up and down the supply chain must collaborate and communicate. Collaboration helps us to align on objectives and resolve issues.
- Utilization of partners: Our partners serve a number of clients in addition to J&J. There is a symbiosis in terms of learning from this explosion of regulations, all driving toward the 2018, 2019, and 2023 deadlines.
- Strategy and execution: Some companies seem to approach this solely as a compliance requirement and devote minimal investment to it. At J&J we started from patient safety and worked down, analyzing what else this dense, item-level information might provide to enhance the customer experience or internal efficiency. Serialization and traceability 2.0 is now incorporated into the essence of the J&J supply chain.

Digitization of the supply chain

With our digitized supply chain, we currently exchange EDI messages as well as shipment and transport status. Serialization along with product master data will enhance that data flow with dense, item-level information about the saleable unit and its associated metadata. This

includes a time-date stamp of each business event that's logged as the saleable unit moves through the supply chain. This means that in addition to moving physical product, we are now managing its digital twin. We exchange this digital twin data with our trading partners.

Supply chain digitization has great potential for managing the movement of saleable units, giving us much deeper insight into our inventory disposition. With appropriate access rights, we're now able to see the status of a product throughout the supply chain. This allows us to work with our customers and trading partners to provide an enhanced

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customer experience. Serialization can help facilitate the returns process, and traceability can facilitate investigation of suspect product. Having that level of data and inventory visibility will be tremendously valuable.

Product identification at J&J has improved as we scrutinized our labels and worked with customers and regulators to make sure master data is current and accurate. Improvements in supply chain integrity also advance patient safety and efficiency.

COMBATING COUNTERFEIT DRUGS

By enhancing visibility, serialization and traceability should make it more difficult to introduce counterfeit products into the legitimate supply chain. While not a silver bullet, they deliver additional levels of protection, control, and visibility that enhance patient safety. And when counterfeits are discovered, serialization and traceability may help us determine where the falsified product was first introduced into the legitimate supply chain.

All of this improves patient safety and the five Rs: the right medication, dose, patient, time, and route of administration.

BLOCKCHAIN—THE NEXT BIG THING

We are investigating how compliance with DSCSA and other regulations around the world might benefit from blockchain, the foundational technology best known for its use with Bitcoin. Blockchain uses distributed databases, or ledgers, with no central authority holding the data. Each “block,” or record, contains a time stamp and a link to the previous block. The beauty of a blockchain is that the data is inherently resistant to modification; it can be updated but not changed retroactively. Blockchain can record transactions between two parties efficiently and in a verifiable and permanent way; it can be managed autonomously and authenticated by mass collaboration.

Blockchain is in its infancy and will need a lot of collaboration and consensus-building across the industry if it is to be adopted successfully. We can envision a time when everyone in the supply chain—manufacturer, regulator, or trucking company—would have a ledger and receive the same data, but nobody could see all of the data. Data could be masked and unmasked as it moves from the manufacturer through the distributor

to the point of dispense, with intellectual property remaining protected.

Several industry consortiums are exploring the details of using blockchain to store and share serialization and track and trace data. Johnson & Johnson actively supports work led by the Center for Supply Chain Studies to explore blockchain for DSCSA. We also support efforts by GS1 to work with IBM and others to establish blockchain standards.

Industry as a whole is working to ensure we have a global serialization and track-and-trace system that meets regulatory requirements and does so in the most efficient and least disruptive way. Johnson & Johnson’s Supply Chain division has effectively operationalized its serialization program and looks forward to continual improvement of its internal processes on behalf of the patients it serves. <>

This article is based on “Effectively Operationalizing Your Serialization Program,” presented at the 2017 ISPE Pharmaceutical Serialization Workshops, 8–9 May 2017, Philadelphia, Pennsylvania.

About the author

Thomas J. Pizzuto, Global Process Owner, Product Serialization & Traceability, Johnson & Johnson Supply Chain, has over 20 years of experience in the pharmaceutical industry. He holds a bachelor of arts degree from Williams College, a master of business administration degree from Fordham University, and a master of science degree from Temple University School of Pharmacy. In his current position he teams with colleagues to institutionalize product serialization and traceability as an enterprise competency to improve patient safety and supply chain security. Pizzuto currently represents J&J as a member of the Pharmaceutical Distribution Security Alliance, a multistakeholder and interdisciplinary initiative that spans the US pharmaceutical distribution system.

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SERIALIZATION AFTER THE LINE IS READY

The Lilly Experience

Bryan Orton and Stephen Prifogle



Much of the attention on serialization is focused on technical solutions for packaging lines. Marking and vision systems are key ingredients in efforts to meet global serialization requirements, but many other areas also need attention as companies start (or continue) to produce serialized products.

At Eli Lilly and Company, our global serialization program has been in place for nearly a decade. What began as a small technical team focused on the application of 2D codes and movement of data developed into a cross-functional, centralized organization responsible for the implementation of serialization across the company.

Implementing and leveraging serialization is a priority in securing Lilly's supply chain. Because it's also an important part of the company's global anti-counterfeiting strategy, we were quickly able to gain the support of senior management. Having this support from the outset was key in gaining program funding and sponsorship.

Our focus is first on meeting compliance requirements. This includes collaborating with our downstream customers to ensure we are working together to be prepared to pass product and data as required. In addition, we maximized our corporate affairs participation in industry groups and other organizations to help understand and influence emerging legislation related to serialization.

With one global serialization solution, including aggregation on every line, it was important to have a strong central understanding of the process. Internally, we had to prepare our systems to operate in a serialized state by thinking about the life cycle of a serial number from creation to decommissioning. We also had to prepare to support serialization and future changes, not just by establishing a "project" team but by adopting a program approach.

UNDERSTANDING THE SERIALIZATION SPACE

Serialization brings a new vocabulary to the pharma industry. Terms like aggregation, data broker, and 2D bar code are familiar now, but there are people in our companies who may not know the difference between a QR and Data Matrix code.

Understanding that our team would need education in multiple areas, we adopted the method for managing the intellectual assets we gained through a knowledge management process. Making sure the right person has the right knowledge at the right time is important to enabling personnel capability. Utilizing tools to identify, capture, transfer, and evaluate critical knowledge is as important for the operator running the packaging line as it is for the

affiliate regulatory team or the person taking a call from a concerned patient.

While training and historical assets are important, it is also important to have a way to manage change. We divided our change management into two areas: technical and business. A team of technical SMEs managed technical changes, including software and hardware updates and revisions. Almost all other activities—from quality changes to data management—were covered by a business change-management process. On occasion, there was a need for both aspects of the change management process to assess a significant event, like the recent changes in China's serialization requirement. The change-management process also allows our sites to propose changes so that they can be assessed against the central solution.

UNDERSTANDING THE SUPPLY CHAIN

Mapping the life cycle of a serial number and where it intersects with different company functions was an eye-opening exercise. It confirmed the need to have a well-defined approach for building and sustaining serialization globally. We began with a focus on understanding both product and data flow from purchase order to delivery in a warehouse. Establishing this map early on helped steer our efforts in the right areas.

Maintaining alignment with our affiliates around the world is important in understanding and complying with serialization requirements. Through key contacts within these markets, we have been able to navigate sometimes murky requirements. Developing processes for technical assessments against a country's requirements, and utilizing a fully serialized "test line" at one of our Indianapolis facilities, we were able to challenge our single solution and verify capability before activating a product in a market.

Once we understood the technical requirements, we began to use standardized processes for artwork updates and data-transfer needs. Starting the process to activate a product for serialization is a coordinated dance between the central serialization team, the affiliate regulatory, printed material development, and the supplying manufacturing site. Having standardized specifications for global trade item-number creation, master data setup, artwork updates, and data transmission keeps everyone in rhythm.

DATA MANAGEMENT

Who is responsible for the serialized master data and generated data? While you may have answered this question for the initial operation of the line,

the life cycle of a serial number is measured in years. Using various system components, companies must examine the security model and control points within each system that ensure data integrity, from provisioning to decommissioning. It's critical that you develop a sound data management strategy that aligns your IT and business processes under one approach. Once developed, any changes in data use will be much easier to assess and provide a quicker approach to implementation.

QUALITY CONSIDERATIONS

Maintaining a quality standard for serialization is the bedrock of a strong serialization program. Even if you are operating different solutions at your sites, a strong quality standard will help guide decisions across geographies and functions. The partnership between the serialization program and our quality unit has been solid since the early days. Together, we have established several standards, standard operating procedures (SOPs), and practices to ensure consistent quality in the serialized product we produce.

Existing quality standards and SOPs must be evaluated to maintain good manufacturing practice operations while serializing. Challenges exist, as some activities are new and have never been used before (aggregations, virtual/physical serial numbers, cameras inside a bundler). Conducting an exhaustive failure mode effects analysis across your operation—from serial number generation in your top level/enterprise resource planning system through the packaging process and into distribution—and is an important activity. Even with careful analysis, you will face new challenges running in a serialized mode. Whether you lead a central team or not, this information must be shared between sites or it *will* happen again.

Most serialization solutions include excellent vision system tools with high-quality cameras. These cameras are so good that they can accept poorly printed 2D codes that would be unreadable by a hand-held unit downstream. How is your company dealing with bar-code grading requirements? Whether as an in-line solution, in-process checks, or betting on your qualification to cover this, you will run into a situation when your product can't be scanned. Establishing a defect classification/standard for grading may be new for secondary packaging, so spending time getting alignment within your company *before* the first complaint is important.

PRODUCTION METRICS

Anyone working in serialization invariably asks about its effect on production. Establishing a baseline metric prior to serialization will help you understand how your packaging line is running afterward. Adding new unit operations on a packaging line will have some type of effect on overall efficiency. Serialization brings new equipment, processes, and expectations, like bundle scanning, aggregation, and bar-code grading.

At Lilly, we focused on key metrics that can be measured simply and consistently across our sites globally. Measuring line efficiency is good for an overall measure, but it can hide other contributing factors. Taking account of downtime associated with serialization issues and the eject rate at each serialization/aggregation station can provide deeper insight on the health of the line.

AFTER THE PRODUCT LEAVES

Once the marked packs leave your site, you must be prepared for issues that will occur. Depending on the market, you may be required to maintain a



process to respond to suspect product inquiries or handle requests to confirm a serial number for complaints. Does your system allow quick verification of numbers by the right people? This will be key to realizing the power of a serial number in your company. Another area to consider is the return of product and the power of using a serial number to confirm its identity.

SERIALIZATION BEYOND COMPLIANCE

Now that capability and implementation are underway, we are also finding ways to maximize serialization beyond the regulatory requirements—such as using 2D code and associated data transactions—a popular topic at conferences and among consulting/technology companies. Your serialization team will need to partner with your business units and other functions to discover new and exciting ways to use the process to your advantage. Internally, we published a white paper with some of these ideas to seed other areas. We've already implemented some solutions that utilize serial numbers, and more are on the horizon.

Your serialization team may centralize or spread across multiple functions or geographies. Regardless of how it is structured, the same needs exist to determine how to operate in a serialized mode. If you do not have a technical solution in place yet, you had better get moving quickly. If you haven't thought about how to manage serialization beyond marking and vision systems, now is the time to start. Thinking about the life cycle of a serial number as both physical and digital will set you on a path to determine how serialization will affect your organization. <>

This article is based on information presented by the authors at the 2017 ISPE Pharmaceutical Serialization Workshops, 8–9 May 2017, Philadelphia, Pennsylvania.

About the authors

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ISPE PROCESS CAPABILITY MATURITY MODEL: HOW ROBUST IS YOUR PROCESS CAPABILITY PROGRAM?

Philippe Cini, PhD; Gretchen Allison; Gerald Leister; Eda Ross Montgomery, PhD; Julia O'Neill; Paul Stojanovski; Michael Thomas; and Arne Zilian, PhD

ISPE’s Process Capability team has developed an industry-specific maturity model that can help companies design a robust process-capability program and compare it to those of their peers. The model has been substantiated by surveying 15 companies.

Process capability is an index that compares quantitative process variability to its specification limits over a predefined period. Typically, the higher the index, the tighter that process property has remained within its specifications.

There are different types of process-capability indices (Table A). Some predict future capability while others describe past performance. Some are based on long-term variability, others on short-term variability. While all serve the same high-level purpose, different indices are better suited to certain situations.*

Process capability indices can help identify opportunities to improve manufacturing process robustness, which ultimately improves product quality and product supply reliability; this was discussed in the November 2016 FDA “Submission of Quality Metrics Data: Guidance for Industry.” For optimal use of process capability concept and tools, it is important to develop a program

* To learn more about the mathematical and technical considerations of process indices, refer to references 1–3 and Table A.

around them. We have identified nine areas that should be considered and for which a certain level of proficiency or understanding is recommended:

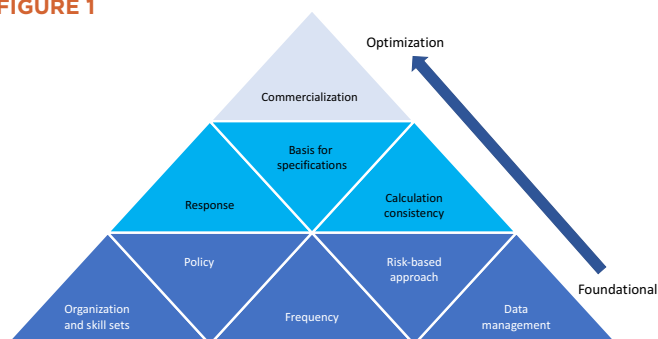
- Policy: A framework that provides direction and sets process-capability expectations in an organization
- Data management: A system for collecting, managing, and assessing data
- Frequency: How often process-capability indices are calculated
- Basis for specification: How specifications are developed and linked to clinical studies
- Calculation consistency: Process capability calculation methodology.
- Response: Thresholds that specify required action(s) and shift attention to low-capability products
- Organization skill set and execution: Process capability knowledge across the organization
- Risk-based approach: How process capability supports an overall risk-management program
- Commercialization: The stage at which product life cycle monitoring and variability sources are optimized

These focus areas have been assembled into the ISPE Process Capability Model (Figure 1). Foundational areas constitute the base of the pyramid, while more advanced areas geared toward manufacturing optimization constitute the second and third tiers. This identifies organizational strengths and weaknesses and helps prioritize efforts.

TABLE A

Capability Indices	Formula	Estimation of $\hat{\sigma}$
Process Capability: The 6 σ range of a process’s inherent variation (short term)		
C_p	Tolerance width divided by the short-term process variability, irrespective of process centering. $C_p = \frac{USL - LSL}{6\sigma}$	$\hat{\sigma} = \bar{R}/d_2$
C_{pk}	Capability index which accounts for process centering $C_{pk} = \min \left[\frac{USL - \mu}{3\sigma}, \frac{\mu - LSL}{3\sigma} \right]$	
Process Performance: The 6 σ range of a process’s total variation (long term)		
P_p	Tolerance width divided by the long-term process variability, irrespective of process centering $P_p = \frac{USL - LSL}{6\sigma}$	$\hat{\sigma} = \sqrt{\frac{\sum_{i=1}^n (x_i - \bar{x})^2}{n - 1}}$
P_{pk}	Performance index which accounts for process centering $P_{pk} = \min \left[\frac{USL - \mu}{3\sigma}, \frac{\mu - LSL}{3\sigma} \right]$	

FIGURE 1



Each focus area has a five-stage maturity continuum: initial, repeatable, defined, managed, and optimizing. These are summarized in the sidebars on pages 48 and 49.

We do not recommend using process capability as a reportable compliance metric, due mainly to associated statistical issues and complexities. There is no industry consensus, for example, on how specifications should be set. Process capability values could therefore differ between two pharmaceutical companies that use the same manufacturing process to produce the same product; specifications established and negotiated with regulatory agencies could be different.

We conducted a survey asking companies to rate their organizations on a scale of 1 (basic) to 5 (advanced) in each area, both as they are today (current state) and as they intend to be in 2–3 years (future state). This survey may help the biotech and pharmaceutical industries to:

- Increase familiarity with process capability, enable a process improvement mind-set, and socialize the process-capability model
- Assess the efficiency and effectiveness of process-capability program
- Develop a consistent approach for calculating process-capability indices, and conduct a systematic assessment to measure and compare process-capability maturity within and across organizations
- Determine which level of maturity is appropriate for an organization based on its business needs and desired risk profile

The results of that study are shown in Figure 2. Colors indicate the gap between the current state (delta) and the desired future state (2–3 years away); green represents the smallest difference and red the greatest. Users can focus on foundational areas first, then shift to optimization areas.

DEMOGRAPHICS

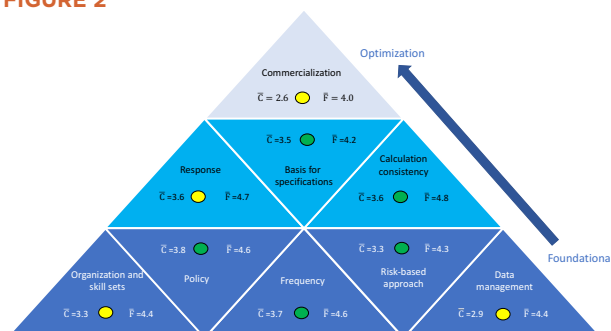
There were 15 respondents from 11 “big pharma” companies (annual sales > \$1 billion) whose level of understanding using process-capability indices, level of involvement, and statistical understanding were rated as good to excellent. Of these respondents, 53% used Cpk for calculating process capability, 27% used Ppk, and 20% used both. The demographics of the 15 respondents are further described in Figure 3 and Figure 4.

Participants measured process capability for between 3 and 15 years; all reported a minimum of 2 years to see benefits.

POLICY

The goal of a global procedure is to define process-capability standards regarding the application scope, capability calculation, and response to

FIGURE 2



\bar{C} = Average current value
 \bar{F} = Average future value
 Averages based on 15 respondents from 11 companies.
 Delta = Future value – Current value

low-performing processes.

On a scale of 1 to 5, survey participants rated their current state on average at 4.2, indicating that process capability SOPs exist globally or at a business unit level, capability analysis is done for the product portfolio, and a response is defined for low-performing products.

Some respondents stated that their process-capability program began several years ago and according to a respondent, now include “... all drug substances and products, global, includes third parties, fairly matured, structured process for years.” For those in an earlier phase of the journey, as one respondent indicated, “policy expectations are defined, [but] contract manufacturers may not be up to speed yet.”

Because of the small body of data available, companies typically struggle to include products from development. Some respondents in commercial manufacturing recommended starting with control charts for all products, and expanding later to evaluate process capability.

Participants clearly recognized the benefits: “Because of the procedures we have in place to address low-capability products, we have seen our capabilities rise over the years, greatly reducing our number of out of specifications (OOSs).”

When asked where they would like their program to be in 2–3 years, the average response was 4.9. To achieve this level of improvement, process capability should be evaluated not only at internal manufacturing sites, but also at contract manufacturers, testing laboratories, and in development.

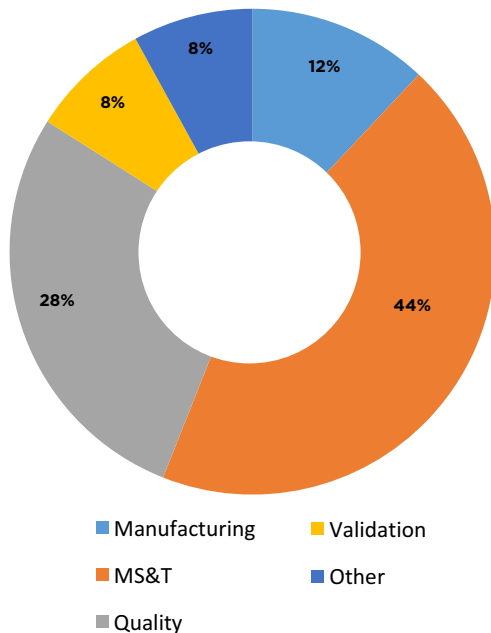
On their journey to achieve this higher level of maturity, some survey respondents expressed the intent to extend their capability analysis to low-volume products, as well as older and local market products. Once a low-performing product is identified, process issues must be differentiated from testing issues. Cpk and Ppk indices (probabilistic measures) should also be compared to the actual OOS rate.

Several opportunities for further development were also mentioned. One discussed the scope of variables, saying “Go beyond quality control data and find additional leading indicators of potential batch rejections.” Another comment said that process capability may be just one of several indices for monitoring: “[Craft] a comprehensive quality scorecard for the product with more than Ppk.”

DATA MANAGEMENT

Data management is a foundational element of the process-capability pyramid, and it must be addressed in a satisfactory manner to reap its benefits. This

FIGURE 3: TYPE OF ORGANIZATION INTERVIEWED



seemed to be well understood by survey respondents, as this area showed the largest gap between the current and desired future states.

The goal of data management is to:

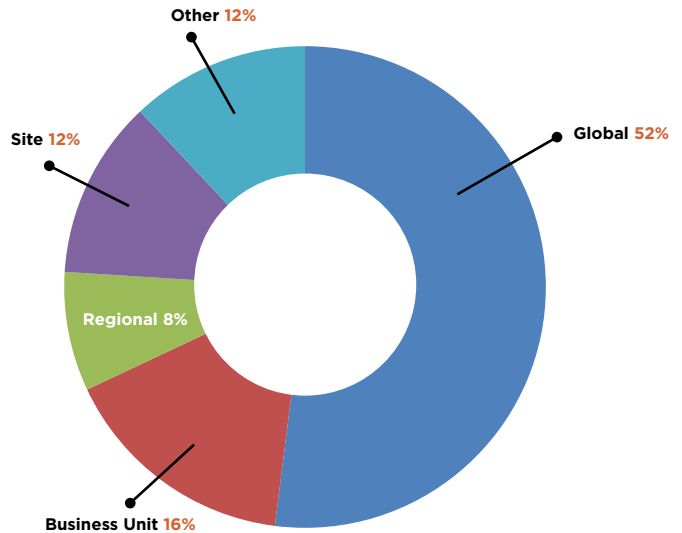
- Capture, organize, control, and distribute product and process data across organizational boundaries
- Support collaboration and decision-making among strategic partners, suppliers, and customers
- Make on-spec product in a reliable and efficient manner

Data gathering and management can be arduous if the data are recorded on paper-based systems (e.g., batch records, certificates of analysis, printouts) and then transcribed into a secure electronic database. This process is prone to errors and requires that the data integrity be checked.

On a rating scale of 1 to 5, survey participants rated themselves an average of 3.1 for this area. At this level, databases are structured consistently across products and across sites; data compilation is in part manual and in part automated. Participant comments included: “Some databases are structured; some are manually entered/updated. Network roll-up not available (in some cases 100% manual). Product-specific databases may or may not be automated.”

When asked where they would like their data management programs to be in 2-3 years, the average response was 4.5. To accomplish this, manual processes that require data verification must evolve to automated processes that include data integrity authentication. Unfortunately, pharmaceutical data management has not kept pace with industry changes and expansions over the past three decades. Local systems are still being used, even though a global system would allow data aggregation and comparison within and between product groups. It is difficult to make real-time decisions or obtain information on demand using slow off-line systems.

FIGURE 4: SCOPE OF INVOLVEMENT



As pharmaceutical and biologics companies become virtual, using contract manufacturing organizations and contract laboratories, linking external sources will become more critical.

FREQUENCY

As an organization begins to develop a process-capability program, it must determine how often process capability should be calculated, and who should be involved in the review and discussion of those indices. Capability index calculation requires a minimum number of data points; statisticians often recommend 20 or more if the results are to be meaningful. Hence, process-capability indices that measure lot-to-lot variability cannot be calculated too early in the development process or the start of commercial manufacturing.

The minimum frequency is annual, given the regulatory requirement of assembling annual product reviews (APRs), which typically report process-capability indices, assuming that the number of available data points is sufficient. Process capability calculations also support continued process verification (CPV) programs, so the frequency of the calculation may also be set by a company’s CPV program.

At the other end of the spectrum, capability indices could theoretically be recalculated with every new batch, although this is unlikely to yield significant additional information unless a dramatic change occurred with the last batch. Other tools, such as process control charts, may be more

—continued on page 50

CURRENT FREQUENCY IS ANNUAL. IMPLEMENTING QUARTERLY PROGRAM BASED ON RISK. IF PPK IS > 1.3 WILL EVALUATE ANNUALLY.

—SURVEY PARTICIPANT

PROCESS CAPABILITY MATURITY MODELS

This information was first presented at the ISPE Annual Meeting & Expo, 8–11 November 2015, and was updated in 2016 and 2017.

POLICY

Initial	Process capability is not defined in SOPs or policies; response is left to individual judgment
Repeatable	Site process capability SOPs may exist; there is no global policy, however
Defined	<ul style="list-style-type: none"> □ Site process capability SOPs exist; global policy may exist □ Process capability SOPs apply to all routinely tested product release COAs from internal manufacturing □ Definitions of statistical procedures are basic, with few details □ Response is defined for individual products
Managed	<ul style="list-style-type: none"> □ Process capability SOPs exist at the business unit level or globally □ Global policy exists; definitions are more detailed and specific. □ Calculation methodologies may be included □ Response is defined for an entire product portfolio and is more programmatic in nature
Optimizing	<ul style="list-style-type: none"> □ A global procedure on process capability exists and covers: <ul style="list-style-type: none"> – Internal manufacturing – Contract manufacturing – Development – Testing laboratories

DATA MANAGEMENT

Initial	<ul style="list-style-type: none"> □ Data collection is manual; individuals primarily use their own spreadsheets, desktops, or notebooks; data collection occurs for each calculation/need □ No “living” data set □ Collecting and compiling data constitutes a major portion of the overall time commitment for process capability use
Repeatable	<ul style="list-style-type: none"> □ Some data collection is automated and/or uses a “living” dataset that is stored in a central location for a given product/site □ Significant part of the overall time commitment for process capability use is spent cleaning data and structuring databases consistently □ Data integrity requirements are defined for selected business processes
Defined	<ul style="list-style-type: none"> □ Databases are structured consistently across products and across sites □ Data compilation is in part manual and in part automated □ Data integrity requirements are clearly defined across the organization □ A defined data collection strategy roadmap describes how data sources will be connected, accessed, or (manually) input
Managed	<ul style="list-style-type: none"> □ Product attribute data is aggregated across sites in a consistent and well-defined manner □ Data system validation requirements are clearly defined across the organization □ Data collection strategy roadmap has been executed for a site
Optimizing	<ul style="list-style-type: none"> □ On-demand pull of process capability data from real-time or near real-time databases by an authorized, cross-functional audience □ Data collection strategy roadmap has been executed across sites □ Organization proactively addresses the data collection challenges associated with divestitures and acquisitions

BASIS FOR SPECIFICATIONS

Initial	<ul style="list-style-type: none"> □ Specifications are not directly linked to product-specific requirements; they may be compendial (e.g., 95%–105%) or based on process variability estimated during development □ Release limits do not account for shelf life and stability
Repeatable	<ul style="list-style-type: none"> □ Manufacturing and development scientists collaborate to establish product specifications based on process development data and similar manufacturing platform variability □ Collaboration is based on scientist experience and takes place near process transfer
Defined	<ul style="list-style-type: none"> □ Specifications are based on knowledge of product attribute ranges necessary to achieve safety and efficacy goals □ Variability over shelf life is accounted for in release specifications
Managed	<ul style="list-style-type: none"> □ Specifications are linked to target product profile and are clinically relevant □ Control strategy is fully integrated □ Process is designed and optimized early in development to have high capability with relevant specifications for all attributes
Optimizing	<ul style="list-style-type: none"> □ Specifications are linked to target product profile and are clinically relevant □ Control strategy is fully integrated □ Process is designed and optimized early in development to have high capability with relevant specifications for all attributes □ Clinical experience covers the range for each attribute specification

CALCULATION CONSISTENCY

Initial	<ul style="list-style-type: none"> □ Inconsistent use of CpK/PpK <ul style="list-style-type: none"> – No process to define which to use – No limits defined □ Ad hoc only, or inconsistent use of calculations across a given site and between sites □ No recommendations established for data set size, confidence limits, which batches to include, impact of normality □ No recommendations on when to use quantitative vs qualitative results
Repeatable	<ul style="list-style-type: none"> □ Site SOPs or recommendations may exist □ No global policies or SOPs
Defined	<ul style="list-style-type: none"> □ Consistent use of process capability approach, calculations, and metrics across a site □ Site SOPs or recommendations exist for data set size, confidence limits, batches to include, impact of normality, when to use qualitative vs quantitative results □ May have global policies
Managed	<ul style="list-style-type: none"> □ Consistent use of process capability approach, calculations, and metrics across all sites □ Site SOPs exist □ Global policies exist for data-set size, confidence limits, batches to include, impact of normality, when to use qualitative vs. quantitative results
Optimizing	<ul style="list-style-type: none"> □ In addition to “managed” achievements, results used to set longer-term strategies, integrated into culture and management reviews □ Calculation approach continuously improved

RESPONSE

Initial	<ul style="list-style-type: none"> □ No response to low or high Cpk or Ppk; response is to actual failures (OOS) □ May calculate process capability following OOS □ Effectiveness verification is not done or is done ad hoc
Repeatable	Cpk or Ppk may be calculated, but no response has been predefined; responses vary
Defined	<ul style="list-style-type: none"> □ Procedures may be in place to define a response for individual sites, possibly only for select parameters □ Predicted rate of failure from Cpk or Ppk is compared against actual failure rate (OOS)
Managed	<ul style="list-style-type: none"> □ Global thresholds require action □ Both low and high capability values have predetermined responses
Optimizing	<ul style="list-style-type: none"> □ Part of a suite of statistical tools; response is not based on a single result, but taken in context with all these tools □ Effectiveness of monitoring leading indicators is verified against predicted rate of rejected batches

ORGANIZATION SKILL SET AND EXECUTION

Initial	<ul style="list-style-type: none"> □ Roles and responsibilities have not been defined □ Organization does not proactively support the organization's process capability needs □ No formal training is in place □ The organization lacks subject matter experts and statisticians □ Process capability considerations are not on the agenda of senior management
Repeatable	<ul style="list-style-type: none"> □ Some level of subject matter expertise is available in the organization □ Training is available and provided to involved associates
Defined	<ul style="list-style-type: none"> □ Organizational structure is suitably designed and staffed to: <ul style="list-style-type: none"> — Collect, compile, analyze process capability information and signals — Make recommendations — Take timely action □ Roles and responsibilities are clear □ All associates involved are experienced in determining process capability □ Expert statistical support is readily available
Managed	Progressive penetration of process capability knowledge across the organization, including management has occurred.
Optimizing	<ul style="list-style-type: none"> □ Process capability activities are well defined for key business processes (tech transfer, CPV, etc.) □ Process capability knowledge is pervasive and an integral part of business □ Management fully embraces the use of process capability to drive process robustness improvements and create value

FREQUENCY

Initial	Process capability is calculated without a set frequency, to support deviation or nonconformance investigations
Repeatable	<ul style="list-style-type: none"> □ Process capability is periodically calculated by technical support team □ Results may be used to initiate continuous improvement but are unlikely to be summarized to measure overall process performance
Defined	<ul style="list-style-type: none"> □ Process capability is periodically calculated, summarized, and shared with site leadership □ Frequency may vary between sites or networks □ Current period process capability is compared to previous period to drive continuous improvement
Managed	<ul style="list-style-type: none"> □ Process capability is periodically calculated, summarized and shared with site leadership □ Frequency and process capability targets are standardized for the corporation
Optimizing	Process capability is used continuously, in conjunction with a suite of statistical analysis tools, by all levels of the organization to track and communicate process performance and drive continuous improvement

RISK-BASED CONTEXT

Initial	Risk is not considered in the application of process capability tools to product quality attributes such as the selection of products, the selection of quality attributes, the prioritization of product or process improvement or remediation actions
Repeatable	<ul style="list-style-type: none"> □ Risk is considered in the application of process capability inconsistently across products, functions, or sites □ Risk tools may be used, but they may not be fully or consistently defined
Defined	<ul style="list-style-type: none"> □ Process capability approaches, policies and SOPs are risk-based, and include the use of well-defined risk management tools □ Those risk-based approaches, policies, and SOPs are in place and mostly in use across the organization □ Those approaches strengthen the organization's compliance record
Managed	<ul style="list-style-type: none"> □ Risk-based approaches, SOPs, and policies for process capability are consistently applied in a standardized fashion across the entire organization □ Proficiency in the application of risk-based approaches increases □ Business value is created as monitoring including process capabilities are aligned with the risk of out-of-specification
Optimizing	<ul style="list-style-type: none"> □ The risk-based approach to process capability is part of an overall corporate risk management framework □ Those approaches are widely recognized as a way to apply resources intelligently where they are needed most, enhancing compliance and driving business value

COMMERCIALIZATION

Initial	<ul style="list-style-type: none"> □ Commercialization site must identify and reduce sources of variability at launch to improve capability for several attributes □ The manufacture of medicine requires significant oversight due to low process capability
Repeatable	<ul style="list-style-type: none"> □ Experienced commercialization sites understand and know which attributes may have marginal capability at launch □ Mitigation and improvement plans exist at commercialization site □ Manufacturing is robust, but high safety stock may be required
Defined	<ul style="list-style-type: none"> □ Any commercialization site will understand and know which attributes may have marginal capability at launch □ Mitigation and improvement plans exist at commercialization site □ Manufacturing is robust however high safety stock may be required
Managed	<ul style="list-style-type: none"> □ Commercial site has high capability at launch for all attributes □ Manufacturing is robust, with low inventory required □ Process design adjustments made during mid- to late-development phase may increase commercialization site risk
Optimizing	<ul style="list-style-type: none"> □ Commercial site has high capability at launch for all attributes □ Supply is robust with low inventory required due to high process capability □ Process capability is designed into process from beginning □ Commercialization site risk is low

useful for detecting minor within- or between-batch changes. Some survey responses below indicated that the more robust an organization's product and processes are, the less frequently they conduct capability calculations.

Some respondents calculate process capability for all batches manufactured as part of a campaign, which allows them to compare product and process performance across campaigns. One respondent indicated that “[I]f a process change has been made, it may be wise to increase the frequency with which process capability is calculated to ensure that the change is not resulting in unintended situations. Once that concern has been alleviated, the frequency of calculation of process capability can be reduced.” Another said that “[F]or products for which very few batches are manufactured, they will calculate process capability less frequently due simply to the scarcity of the data.”

Because process-capability indices are simple performance measures that allow organizations to monitor how the robustness of a product or a process evolves over time (from one campaign, year, or month to the next), they are excellent tools that can inform both technical and nontechnical managers in their resource-allocation decisions for continuous-improvement projects. Clearly, there is no single way to set the frequency with which capability indices should be calculated. At the same time, it is apparent that criteria or rules for that purpose should be defined and used consistently across an organization.

For this area, respondents rated themselves 3.7 on average, indicating that process capabilities are periodically calculated, summarized, and shared with site leadership (although the frequency of calculation may vary from site to site), and the results are used to drive continuous improvement efforts.

Respondents also indicated that in 2–3 years they expect to reach an average maturity level of 4.5. At that level, the frequency with which process capability is calculated has been standardized across the organization manufacturing network. Process capabilities, in conjunction with a suite of other statistical analysis tools, are used continuously by all levels of the organization to track and communicate process performance and drive continuous improvement.

BASIS FOR SPECIFICATION

A consistent basis for specification is essential for comparing process capabilities across sites, manufacturers, etc. The concept of process capability rests on the comparison of actual manufacturing results to a meaningful specification range. In their purest form, drug-product specifications should represent the needs of the patients receiving them.

To set specifications for pharmaceutical products based on patient needs, however, clinical experience would have to cover relatively broad ranges for each product attribute. This kind of clinical data is rarely available, unfortunately. In its absence, manufacturers rely on an assortment of other approaches, including assessments of achievable variation based on process development experience and analytical method performance, USP compendia specifications where available, specifications established for similar products manufactured with the same technology platform, bioequivalence studies, and previous manufacturing history.

The latter is the most challenging situation for process capability. Since most process-capability indices are based on a ratio of the process-variation range to the specification range, when specifications are based on process variation (commonly referred to as “process-capability specifications”), the calculation becomes circular. Process capability will inevitably fall close to 1.0, since both the numerator and denominator are based on process variation. To avoid this, the regulatory agency (often driven by risk consideration) may

SOME PRODUCTS WHERE SPECS ARE TIGHT, THEREFORE LOWER CAPABILITY BUT CAPABLE.

—SURVEY PARTICIPANT

ANALYTICAL METHOD SPECS ARE TYPICALLY BASED ON USP. PRODUCT SPECIFICATIONS SUCH AS CONTROL RELEASE DISSOLUTION ARE BASED ON BIOEQUIVALENCE STUDY AND MAY REQUIRE SOME DISCUSSION/NEGOTIATION WITH THE FDA.

—SURVEY PARTICIPANT

request tighter limits based on the available test data during the approval process. These would automatically result in process capabilities lower than 1.0.

Survey participants rated their current state of specification bases at an average of 3.5. This indicates that, where possible, specifications are based on knowledge of the product attribute ranges necessary to achieve safety and efficacy. Participants cited examples of the current mix of bases for specification setting (below). This shows that when specifications are based on previous manufacturing history, it will inevitably fall close to 1.0.

When asked where they would like their program to be in 2–3 years, the average response was 4.2. Some participants provided examples of mature specification-setting approaches already in place, including: “Specs linked to quality target product profile.”

The quest for more clinically relevant specifications is the subject of a newly formed ISPE team called the Clinically Relevant Specification Work Group. When consistently set, specifications that truly represent patient needs open the possibility for meaningful process-capability comparisons as envisioned in the FDA's quality metrics draft guidance. Without universal specifications for a given product, comparisons of process performance across sites or manufacturers remains a challenge.

CALCULATION CONSISTENCY

On average participants rated themselves 3.6 for their current state; this reflects consistent use of a process-capability approach, calculations, and metrics across an organization. At this level, methodologies to outline data set size, confidence limits, number of batches, effect of normality, and indication for using qualitative vs. quantitative results are documented in guidelines or SOPs across at least part of the organization (local, regional, and/or global).

Organizations chose to use short-term (Cpk) or long-term capability indices (Ppk) and control charts to monitor their processes. Of the 15 survey participants, eight used Cpk, four used Ppk and, three used both Cpk and Ppk, depending on the situation. The key is to be consistent in the calculation and use of such metrics.

When respondents were asked how much further they would like to take their programs in 2–3 years, the average rating was 4.8. At that stage, capability results are used to set long-term product and process robustness improvement strategies, which are integrated into the organization’s culture and management review processes. According to one respondent, “We are working on site harmonization around using consistent metrics, implementation of remediation plans, and identification of future process-capability opportunities.”

RESPONSE

The response section maturity model is intended to identify events that trigger a response, the consistency of the response when those events occur, how well events and responses are aligned across products and sites, and the extent to which leading indicators and/or combinations of events are used to evaluate whether an event has occurred. An “event” is defined as an abnormal shift, trend, or low Cpk.

Maturity of the response portion can mean responding to failures, responding to both favorable and unfavorable changes in process capability, or responding to indications of a potential event based on leading indicators (e.g., comparing the predicted failure rate to actual failures). Maturity is also affected by the degree to which the effectiveness of the action is verified (e.g., ad hoc or no effectiveness check for a single event for a single critical quality attribute (CQA), or measuring effectiveness checks for all sites and all relevant products based on a specific event).

A robust response results in action based on established process or product thresholds, with resources and improvement activities for products with poor process capability. This consistent, focused response results in continuously improving process capability.

Survey responses for current-state maturity averaged 3.5 (defined-managed). Respondents reported that Cpk or Ppk are routinely calculated for CQAs and some other parameters such as process parameters or raw material attributes; this practice is not in place at all sites, however. At this level, the parameters, attributes, and/or CQAs where process capability is measured can also vary. Sites with response systems at this maturity level show a measurable influence on process capability. According to one survey respondent, “If Cpk < 1.33, it is discussed. Cross-functional team to understand ‘why’ are formed and plans are developed. Heads of quality or technical services will weigh in on Cpk < 1.0 ... 95%–98% of Cpk are > 1.3.”

Average future-state response maturity was 4.7 (managed-optimizing), indicating that companies believed that significant benefits would result from efforts to set consistent standards, respond to process-capability signals, report progress, and measure effectiveness across products and sites. More extensive and effective use of leading indicators with comparison to actual results was also desired. “Being able to predict problems before they occur results in significant business benefit,” explained one respondent.

ORGANIZATION SKILL SET AND EXECUTION

Survey participants rated themselves an average of 3.3 at current state, indicating that respondents found that their respective organizational structures suitably designed and staffed to collect, compile, and analyze process-capability information and signals; make recommendations; and take timely action. Roles and responsibilities are clear, associates experienced in determining process capability, and expert statistical support are readily available. Process capability programs have been in place for 3–15 years on average, an indication of the time

typically required to achieve this level of organizational proficiency.

When asked to describe their future state organization and skills, the average response was 4.4. To achieve this level of maturity, process-capability activities must be well-defined for key business processes (e.g., technology transfer, CPV). Process capability knowledge must be pervasive and integral. Importantly, management fully embraces process capability to drive process robustness improvements and create value for the organization.

Comments indicated that as SOPs and organizations are created and training is provided, a culture change begins in which process capability becomes a standard approach to conducting business. Comments also emphasized the need for management support.

RISK-BASED APPROACH

A risk-based (e.g., ICH Q9) approach to process capability prioritizes and applies resources where they are needed most to enhance patient safety, guarantee compliance, ensure efficient use of resources, and drive business value.

Participants rated themselves an average of 3.3 at current state. This means process-capability approaches, policies and SOPs are risk-based, in place, and mostly in use across the organization. Risk-management tools are also in use and are well defined. These approaches strengthen the organization’s compliance record and align with the FDA’s “Pharmaceutical cGMPs for the 21st Century, A Risk-Based Approach.”

When asked where they would like their program to be in 2–3 years the average response was 4.2. To achieve this level, use of risk-based context must be applied consistently across the entire organization; increased proficiency in the use of risk-based approaches should also be demonstrated. Process capability monitoring must be aligned with the risk of processes performance. Business value is derived from the use of process capabilities at this maturity level.

Comments from respondents indicate that the use of process capabilities often start with a set frequency. As process-capability programs mature, the higher the risk, the more frequent the monitoring. Comments also indicate that risk analysis is used to prioritize processes to be improved upon, and can include more than just capability data.

COMMERCIALIZATION

Prior to process validation, scientific evidence must establish that the process is capable of consistently delivering quality product. The commercial process control strategy is defined in Stage 1, process design, and based on knowledge gained during development activities. Development data collection and evaluation is focused on process understanding, often including data from operating the process at extreme ranges to determine the relationship between operating parameters and quality attributes. Calculating process-capability indices at this stage may provide limited benefit because of the forced variation. In addition, at this stage of development, few runs at normal operating conditions have typically been completed (< 10). This can lead to considerable uncertainty in the process-capability estimate.

Evaluation of the process control strategy occurs during Stage 2, process qualification/validation. As appropriate and with proper scientific oversight, Stage 1 and 2 data may be combined to assess process capability. In Stage 3, continued process verification, a product- and process-performance program—including process-capability indices—can provide assurance that the process remains

in a state of control and identify opportunities for continuous improvement.

Survey participants rated their current state an average of 2.6. This indicates that while the control strategy is sufficiently robust for validation purposes, the commercialization site may need to allocate resources to mitigate the risk of variability not apparent during development. Participants rated their future state at 4.0, on average. This indicates a desire to further optimize the control strategy during development and possibly find ways to enhance the use of process-capability indices at that stage of the product life cycle. Both averages (current and future) are the lowest observed in the survey. This is not unexpected as the commercialization area is the highest level on the process-capability pyramid (Figure 1).

CONCLUSION

This paper introduced a process-capability maturity model with nine focus areas specific to the pharmaceutical and biotech industry. It also establishes a hierarchy of needs among those nine areas. Pharmaceutical and biotech executives that wish to assess whether and how process-capability indices may be used in their organizations may find this framework useful.

We conducted a survey in which participant companies were asked to rate their organizations on a scale of 1 to 5 in each of the nine areas: as they are today (current state) and as they intend them to be in 2–3 years (future state). On average, respondents indicated that their current state is close to the desired future state in five of the nine areas (policy, frequency, risk based approach, basis for specification and calculation consistency). There are four areas where on average respondents wish to continue to improve their capabilities (organization and skillsets, data management, response and commercialization). Among those four, two are foundational areas that should be addressed first (organization and skillsets, data management).

In general, respondents believe that such programs will help their companies comply with key regulatory requirements (process validation, process control) and improve the business bottom line by tracking and communicating process performance effectively; this, in turn, will drive continuous improvement.

Survey responses also indicated that process-capability index may not be a stand-alone program, but rather be integrated with key elements of a quality-management system such as APRs and various process-monitoring efforts in the context of a CPV program.

Last, but not least, respondents also emphasized the need for engagement of key functional areas such as technical services, quality and compliance, R&D, and product development for a successful process-capability program that promotes a culture of continuous improvement. <>

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BOWTIE ANALYSIS AND BARRIER-BASED RISK MANAGEMENT

David Hatch

Every business has legal, economical, and ethical objectives that range from mandatory safety to commercial goals to corporate citizenship. Businesses undertake a certain amount of risk to achieve these objectives. The balance between risk and reward is an ongoing challenge regardless of the activities involved. The bowtie technique can be used to visualize, assess, and manage risk.

CH Q9 defines risk as “[t]he combination of the probability of occurrence of harm and the severity of that harm,” and defines harm as “[d]amage to health, including the damage that can occur from loss of product quality or availability.”¹ ISO 31000 offers a broader definition of risk as the “effect of uncertainty on objectives.”²

Hazards (assets or activities with the potential to cause adverse effects) exist and must be contained or controlled to avoid undesirable outcomes, particularly those that are unexpected. In the pharmaceutical industry, examples of hazards include flammable solvents or dust, and quality failures that lead to material reprocessing or rejection.

Safety, environmental concerns, quality, and asset management are not new topics, and proven standards exist to guide duty holders through their obligations. These can very be difficult to interpret, however, and problematic to implement. It’s also often a challenge to involve all stakeholders.

Bowtie analysis offers a simple but effective method to visualize risk and show that hazards are under control.

BOWTIE ANALYSIS

How and when the bowtie analysis originated is not completely clear, but the first bowtie diagrams appeared during a lecture on hazard analysis given at the University of Queensland, Australia, in 1979. In the early 1990s, the Royal Dutch Shell Group adopted the bowtie method as the company standard for analyzing and managing risk. Shell conducted extensive research in the application of the bowtie method and developed strict rules for the definition of all parts, based on their best practices. Shell’s primary motivation was the necessity of ensuring that appropriate risk barriers were in place throughout all worldwide operations.

Following Shell, the bowtie method rapidly gained support in the oil and gas industry, as the diagrams helped visualize oversight of risk-management practices. In the last decade, the bowtie method spread to the aviation, mining, maritime, chemical, and health care industries, to name a few.

Bowtie was created by merging two existing risk-analysis tools: fault trees, which illustrated the potential for multiple faults to lead to a single failure, and event trees, which illustrated the different effects that could be predicted from a single event. Together, these form a connected diagram that

make relationships more obvious and provide a clear “line of sight” between causes (faults or failures) and effects.

At a high level, the bowtie for a hazard could look like Figure 1.

APPLICATION

Although the number and nature of materials processed in the pharmaceutical and life sciences industries differ significantly from those in the oil and gas field, both use hazardous, flammable, and toxic fluids. The 2012 incident at Neptune Wellness Solutions (formerly Neptune Technologies and Bioresources Inc) showed that on-site fatalities are possible.^{3,8-9}

The uncontrolled release of intermediate/final products, cleaning materials, and utilities is another hazard that can significantly damage the local or wider environment. Failure to operate and maintain a plant properly can also result in costly downtime and equipment repair or replacement. Finally, patient safety is a key driver for quality and reputation—particularly in the age of social media, where bad news travels fast.

The bowtie enhances understanding of industry-specific scenarios and provides clear indication that the safeguards (risk-control measures) are in place and performing. It summarizes and communicates the health (effectiveness) and importance (criticality) of these safeguards to encourage more informed and objective decision-making.

Consider the simple representation shown in Figure 1. When a cause (“threat”) occurs, a fire or explosion is not guaranteed to happen immediately. Controls should be in place to prevent the liquid release—loss of control or containment (“event” or “top event”)—or to mitigate the effects of any release. The route from cause to effect (“consequence”) is therefore not direct, because the path is blocked. This is illustrated in Figure 2 by the Swiss cheese model developed by James Reason.⁴

The cheese slices represent risk controls, which could be physical (equipment) or procedural (process or behavior). Weaknesses (holes) are either built-in or appear under failure. If the holes align coincident with the threat, an unimpeded path allows the consequences to occur.

A holistic overview of the scenario appears when this linear (one-dimensional) model is translated into a two-dimensional format, with barriers positioned appropriately between threats and the top event (where/when the loss of control or containment occurs) and between the top event and the consequences (where the effects are realized). Representing a risk assessment visually rather than textually helps to focus attention on vulnerable areas—either threats or barriers—that require scrutiny or improvement.

SIMPLE ILLUSTRATION

Consider a familiar application within the pharmaceutical community: a filter dryer and some of the possible risks associated with it (Figure 3).

While a variety of barriers may be in place, they may not be as effective or independent as they appear. The majority could be controlled by the same computer system, for example, or access to susceptible equipment may not be as limited as assumed. Increased inspection combined with enhanced or alternative barriers could ensure that all barriers are underpinned by competent personnel, current procedures, and contemporary maintenance.

The bowtie technique allows even those less familiar with the circumstances to make an intuitive judgement on:

- The number and type of threats that could lead to a flammable liquid release
- The number and type of consequences that could occur following the release
- The number and type of barriers that could prevent a release
- The number and type of barriers that could mitigate negative effects or help recovery from a release

In its current form, the representation provides information to support intelligent risk management for health and safety—the default focus of conscientious corporations. The following risk receptors, however, are also significant:

- **Environment:** On- or off-site natural impact
- **Production:** Reduced or ceased output
- **Equipment:** Repair or replacement
- **Quality:** Recall or reprocess
- **Regulatory:** Approval or compliance
- **Reputation:** Public and investor confidence

Robust asset and operations management are at the heart of strong and successful safety, environmental, financial, and quality management. If equipment doesn't leak or break down, for example, or if people don't make mistakes, then control or containment is not lost and adverse effects are avoided (or at least reduced).

GENERIC EXAMPLE

Not all barriers are created equal, however, and appropriate attention should be given to those that pose a higher risk. Categorizing the bowtie components and then color-coding them helps prioritize risk by providing immediate impact, as shown in Figure 4.

This displays a variety of parameters, each with a key message to help inform decision-making. In simple terms, the robustness of risk (or failure) management can be broken down as:

- **Quantity:** Presence (how many and where they are located)
- **Quality:** Performance (how effective they are)
- **Diversity:** Independence between associated threats and other barriers

Barriers are often classified as:

- **People:** Personnel who design, operate, maintain, monitor, and manage
- **Process:** Organizational measures (procedures)
- **Plant:** Technical measures (equipment or structures)

These can be considered in several additional ways:

- Too few barriers may suggest inadequate protection, but too many may be excessive and costly
- Barriers that rely heavily on human interaction (operation) or intervention (maintenance) are typically weaker than more passive barriers and often have a lower lifetime cost

FIGURE 1: BASIC BOWTIE FOR FLAMMABLE LEAK

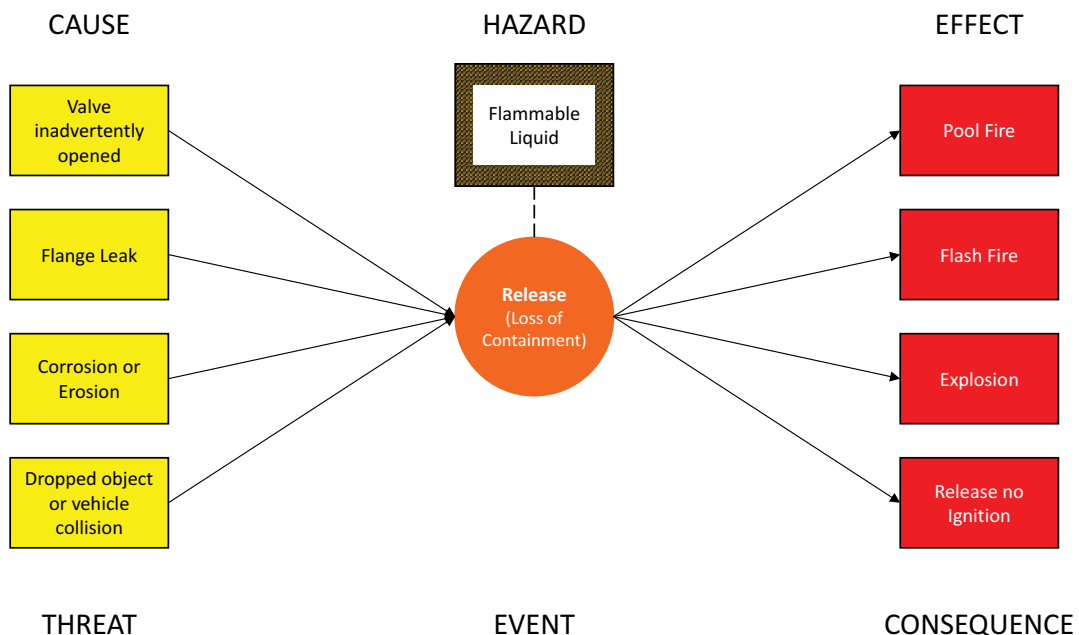
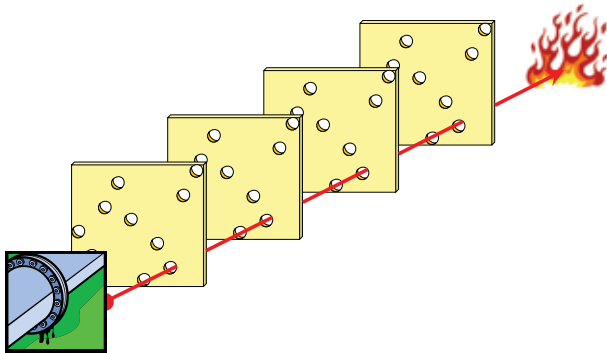


FIGURE 2: SWISS CHEESE DIAGRAM



- All eggs in one basket: If one party (role) is responsible for multiple barriers, or if technology (e.g., electrical) is applied within several barriers, the absence or reduced performance of that single element can have widespread effects
- Barrier criticality (requirement) and effectiveness (achievement) are of major concern when a high criticality is combined with low effectiveness.

In Figure 4, the barrier types are categorized as:

Red	Safety instrumented functions/systems
Pink	Human action or response
Cyan	Basic process control system
Yellow	Control of ignition sources (electrical and mechanical)
Black	Building layout
Grey	Other measures

Colors also categorize barrier effectiveness:

Green	High
Yellow	Medium
Red	Low

Threats can be classified as:

- **Type:** Equipment failure, control malfunction, human error, or external/environmental influences
- **Contribution:** Anticipated scale of possible effects
- **Frequency:** How often the threat is likely or is known to occur

Two colors categorize threat types:

Pink	Human acts or omissions
Cyan	Basic process control system

Since prevention is better than cure, attention should focus on threats with high contribution and high frequency. A quick scan of threat types related to human factors or errors, for example, can reveal where more training is required. Other approaches could be adopted for predominately computer-related threats, as is the case in Figure 4.

At the end of the scenario, consequences might be classified by:

- **Category:** The predominant risk receptor or scale of concern related to the consequence
- **Type:** The urgency of response required if/when the consequence occurs
- **Risk:** A combination of the severity and likelihood of the inherent (unmitigated, no barriers) and residual (mitigated, with the barriers) risk

Consequences are categorized using the following colors:

Red	Health and safety
Magenta	Quality
Green	Environment
Grey	Commercial (asset or production)

More attention should be paid to consequences of major concern and/or those with the highest (mitigated or unmitigated) risk, since the barriers associated with these scenarios are neither actually or potentially effective in the overall risk-reduction strategy.

ADVANTAGES

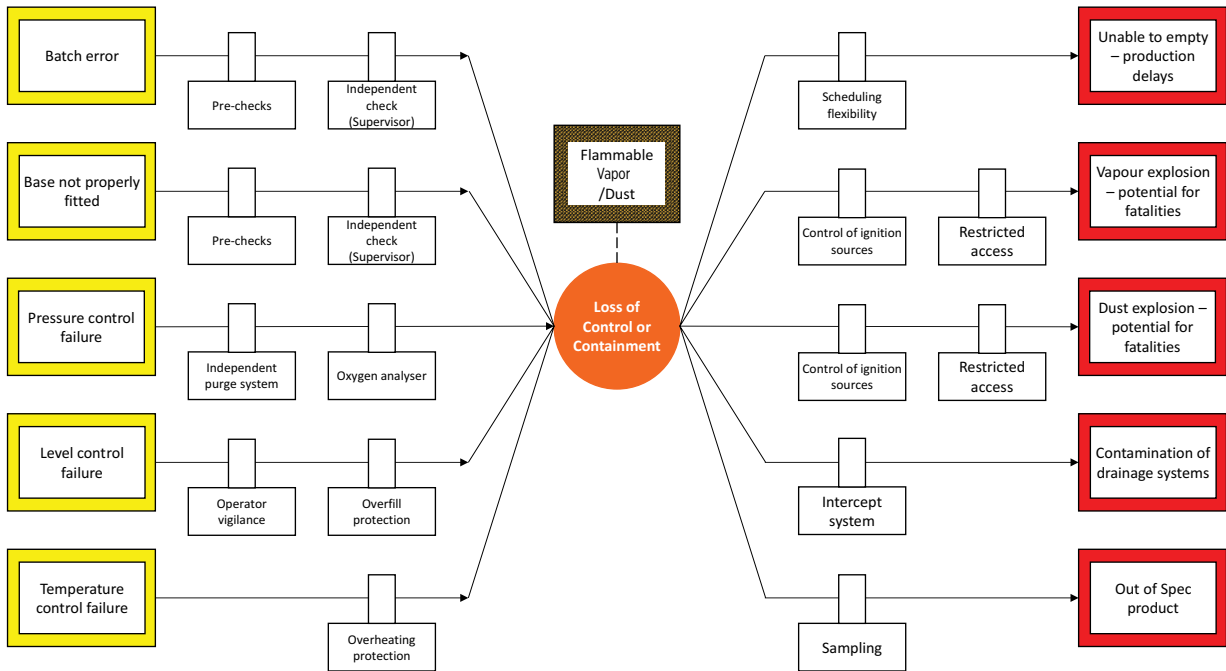
Bowties offer the following advantages:

- Visualization and communication: Knowing, showing and sharing the basis of integrity
- Risk-based decision-making: Are there enough barriers to mitigate the risk appropriately?
- Barrier dependency visualization: What if the resource responsible for multiple barriers is compromised, e.g., the engineering manager is ill or power is lost?
- Display risk assurance: How are the barriers performing?
- Informed decision-making (change management): What happens if a barrier is removed or degraded?
- Risk-based management: Identification, analysis, evaluation, and treatment

An alternative view on risk management could simply be “failure management.” Failures often begin as threats that start a chain of undesirable events; they must be stopped or slowed by measures that themselves have the potential to fail.

New projects may be able to implement additional barriers. Established facilities may only be able to improve existing barriers. When resources are

FIGURE 3: SIMPLE BOWTIE FOR A TYPICAL FILTER DRYER



limited, management must be confident that they are investing in improvements (training, maintenance, inspection, etc.) that can deliver results.

EXISTING METHODS

The pharmaceutical industry is not unfamiliar with hazard and risk analysis tools and techniques. The most common, from ICH-Q9, are listed below.¹

- Failure mode effects analysis
- Failure mode, effects and criticality analysis
- Fault tree analysis
- Hazard analysis and critical control points
- Hazard operability analysis (HAZOP)
- Preliminary hazard analysis (PHA)

A more extensive list is available from the Center for Chemical Process Safety.⁵

All these methods have strengths and weaknesses, which are documented in a UK Health and Safety Laboratory research report.⁶ HAZOP, for example, is a widely used hazard-identification methodology; it is not effective in identifying where multiple cause can lead to the same consequence, however.

Bowtie analysis is not intended to replace existing tools and techniques, but to enhance them by helping those involved in the original identification or analysis studies to confirm their discussion, and those not involved in the studies (but still responsible for managing risk) to understand and address relevant issues.

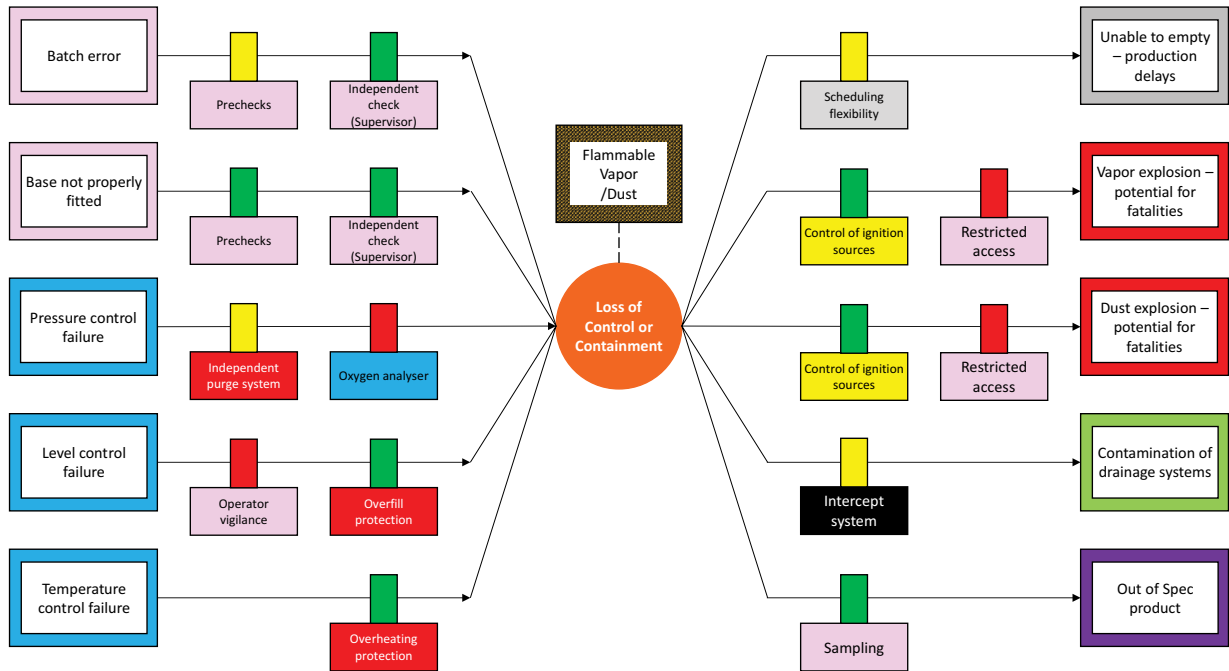
One major limitation of most common techniques is that they are typically performed by specialists and documented in a technical language and format that does not easily support communication and ongoing collaboration. The

UK Health and Safety Executive recognizes that a barrier (bowtie) approach is a useful tool in communicating major hazards information to the workforce.⁷

The clarity that bowties provide can also be used to validate existing studies more efficiently, e.g., to identify errors or omissions in the causes, effects, and control measures associated with particular scenarios. This is a key issue in high-hazard facilities that are mandated to revisit their PHA or HAZOP every five years under regulations such as the US Occupational Safety and Health Administration or the Seveso Directive.

BOWTIE ANALYSIS OFFERS A SIMPLE BUT EFFECTIVE METHOD TO VISUALIZE RISK AND SHOW THAT HAZARDS ARE UNDER CONTROL

FIGURE 4: ENHANCED BOWTIE FOR A TYPICAL FILTER DRYER



BARRIER QUALIFICATION

The simple diagrammatic representation of a process or plant provides an effective, transferrable platform for knowledge that passes from the designers to those who build, operate, maintain, and monitor these facilities. This knowledge is challenged by a series of qualification activities at key stages.

- **Design qualification (DQ):** Does the proposed design of the barrier meet the intended purpose?
- **Installation qualification (IQ):** Has the barrier been installed correctly?
- **Operational qualification (OQ):** Is the barrier capable of operating within established limits?
- **Performance qualification (PQ):** Does the barrier perform effectively and reproducibly?

These physical, functional, and procedural barriers can also be applied to change management in which people adapt, processes or plants are modified, and the effects of change must be evaluated and addressed.

Ongoing assurance that the barriers are still present (IQ) and performing (OQ/PQ) can be confirmed by regular inspection and auditing, with the results shown (or suitably summarized) to highlight vulnerabilities. In fact, since many facilities or processes utilize familiar equipment (often from the same manufacturer) it is prudent to develop a bowtie template for that equipment or unit operation with the actual or ideal barriers in place. This can become a stencil for other instances of the same (or similar) equipment/operation, and can be surveyed to determine if the

barriers meet—or exceed, which may suggest overengineering—the protection model.

Such an approach can be deployed across an organization to highlight inconsistencies and provide justification for improvement (and subsequent investment).

INCIDENT ANALYSIS

Most organizations find it a challenge to learn from incidents, often because the post-event analysis does not produce high-quality but realistic recommendations that could change the organization for the better. To uncover the lessons that should be learned on both organizational and operational levels, it's crucial to untangle the event. A sensible starting point is to establish how it happened, then consider which barriers should have prevented it.

Once the barriers have been mapped onto the incident timeline, their states can be determined as:

- **Effective:** Functioned as planned and stopped the next event in the incident scenario
- **Unreliable:** Stopped the next event in the incident sequence, but the organisation is uncertain if it will do so in the future
- **Inadequate:** Functioned as intended by its design (envelope), but was unable to stop the sequence of events
- **Failed:** Implemented, but did not function according to its intended design
- **Missing:** Described in the organization's management system or was considered an industry standard, but it was not successfully implemented

From this, a corrective and preventive action strategy can be developed with due attention to barriers to prevent the incident (and similar events) from occurring. The bowtie analysis should then be updated with a range of prioritized solutions:

- **Short term** (barrier level): Improve barrier quality before resuming operations
- **Medium term** (barrier level): Add barrier at earliest opportunity
- **Long term** (organizational level): Correct management system / underlying cause

SUMMARY

Bowties are a proven method in a wide variety of high-hazard/-risk industries that are used to visualize the integrity of the business from equipment all the way up to the enterprise. Bowties complement and supplement existing hazard identification and risk-analysis tools to create a framework for ongoing risk management. They offer user-friendly engagement and empowerment from the board room to the control room and can provide a live source of knowledge and understanding that underpins all critical decisions. Bowties assist with audits, inspections, and assessment to confirm actual vs. assumed barrier presence and performance, threat frequency, and consequence severity. Finally, they support incident investigations by indicating what the barriers should have done and what they actually did (or did not) do. <>

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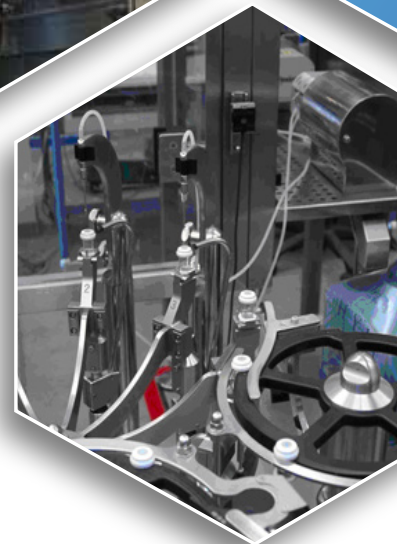
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EFFECT OF LOW-ENERGY E-BEAM IRRADIATION ON PRESTERILIZED COC PACKAGING

Stefan Kleinmann, PhD; Werner Haag, Dipl. El. Ing. ETH; and Andreas Weidauer

Does electron-beam surface decontamination radiation damage COC syringes? Experimental investigations confirm that no measurable dose is delivered if irradiation parameters are selected correctly. Even a dose of a few kGy (equivalent to a few 0.1 Mrad) would not cause significant change.

Aseptic filling of sterile drugs is a critical process in biopharmaceutical manufacturing. Ready-to-use presterilized syringes must be transferred into the isolator for filling. Electron-beam (e-beam tunnel) radiation that decontaminates the outer surfaces of the tubs containing presterilized syringes (and other containers) is generally seen as a best practice solution for high-speed filling lines. Figure 1 shows a typical combination of an e-beam tunnel and a filling line.

The typical e-beam tunnel contains three electron accelerators, called e-beam emitters, arranged in a triangular configuration for optimal decontamination of all surfaces (Figure 2). The tubs move on a conveyer belt through the electron cloud generated by the e-beam emitters. Electrons in the 100- to 150-kiloelectron-volt (keV) energy range have very limited penetration power. Using a minimum surface dose of 15 kilogray (kGy)* on all external surfaces leads to a greater than 6-log reduction of colony-forming units.¹ Before the decontamination process can start, however, the entire e-beam tunnel (and possibly the isolator as well) must be decontaminated with hydrogen peroxide gas (H₂O₂).

* Gy (100 rad) is defined as the absorption of one joule of radiation energy per kilogram of matter (1 J/kg).

FIGURE 1: EXAMPLE OF A FILLING LINE WITH AN E-BEAM TUNNEL

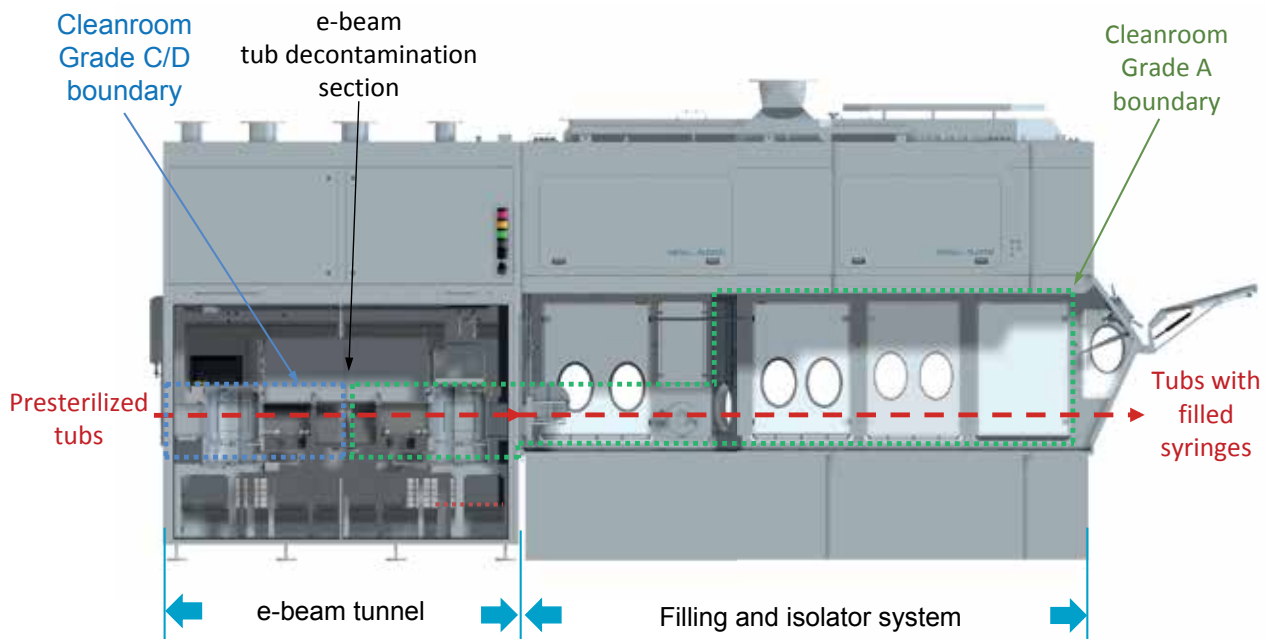
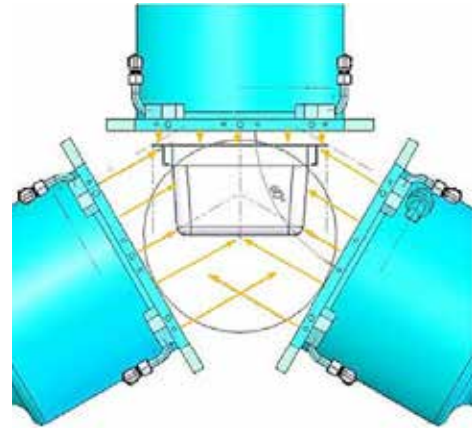


FIGURE 2: E-BEAM EMITTER (LEFT), AND TRIANGULAR ARRANGEMENT (RIGHT)



Source: Metall + Plastic GmbH

E-beam tunnel irradiation ensures that the aseptic zone in the filling area remains uncompromised. Its main benefits over alternative techniques such as rapid transfer port, high-intensity ultraviolet light surface sanitization, and double debagging are high microbial kill efficacy, throughput of up to six tubs per minute, well-defined dose and validation requirements, and few control parameters (voltage and current of e-beam emitters and speed of the tubs moving through the e-beam zone).²

E-beam tunnels are well established for aseptic filling, with more than 30 units in operation worldwide. In the past, they were used to decontaminate tubs containing glass syringes. Because it is possible that some radiation might penetrate the tub and damage the syringe material, objectives included avoiding glass discoloration and preventing ozone accumulation inside the syringes.³

Recently, however, pharmaceutical companies have begun to use polymer syringes made of cyclic olefin copolymer (COC). But the behavior of this material when irradiated is not as well understood as that of glass. It was important, therefore, to investigate the decontamination of tubs containing COC syringes.

EVALUATION

As already mentioned, the purpose of the e-beam tunnel is to decontaminate the outer surfaces of the tub. Because radiation can penetrate the tub and the syringes, however, we must determine the dose (if any) delivered to the syringes and assess the damage (if any) to the COC material. For this purpose, it is important to understand the physical design of the tub.

As depicted in Figure 3, the syringes are contained in a nest, and covered with a Tyvek liner. The nest sits in a polystyrene tub that has a Tyvek lid glued to its edges.

In addition to e-beam radiation, an e-beam emitter produces an extremely small dose of x-ray radiation as the electrons are stopped in the titanium foil or the copper support of the electron window. Our measurements showed these values to be below 0.2 Grays per second (Gy/s), equivalent to 20 rads per second (rad/s) inside the tub. Given an exposure time in the e-beam

radiation zone of approximately 10 seconds, the deposited dose amounts to only a few Gy (100 rad) at most, or approximately 0.1% of the dose needed to decontaminate the outer surfaces. Therefore, no significant effect can be expected, but the x-ray dose must be added to the electron dose when evaluating the whole effect of the radiation.

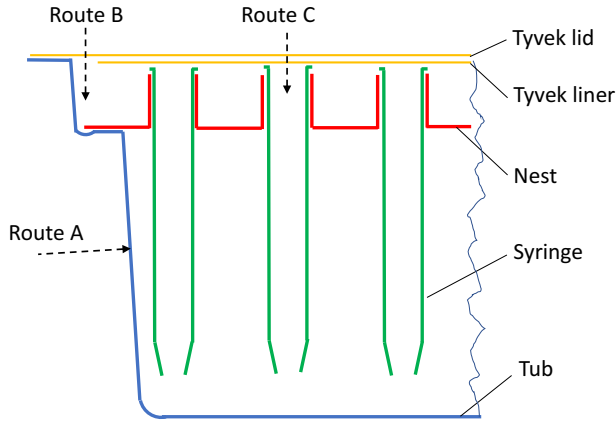
We must also determine the penetration capabilities of low-energy electrons and examine the different routes by which they might enter the tub. Given the physical design of the tub, one can find three entry routes (Figure 4).

We measured the depth dose using the RisøScan dosimetry tool⁴ and the D_μ concept of low-energy electron dosimetry.⁵ As Figure 5 shows, penetration

FIGURE 3: SYRINGES, NEST, LINER, TUB, AND LID



FIGURE 4: SIMPLIFIED CROSS-SECTION SHOWING POSSIBLE ROUTES OF E-BEAM RADIATION



in a material with a density of 1 gram per cubic centimeter at a voltage of 150 kilovolts (kV) is 0.25 millimeters (mm). At 120 kV it is 0.16 mm, when the distance between emitter and material is 20 mm.

Route A is through the side walls or the bottom of the tub. Given a wall thickness of 0.8 to 1.5 mm—which is greater than the 0.25 mm penetration

even at a maximum voltage of 150 kV—no electrons will penetrate the walls of the tub, and no radiation will be deposited on the syringes.

Route B is through the lid and into the gap between tub liner and wall (Figure 6); following this route, the electrons will hit the nest, and thus will not deposit any dose on the syringes.

Route C is through the outer Tyvek lid and the inner Tyvek liner. The medical and pharmaceutical packaging foils typically used (1073B, 1059B, and 2FS) have basis weights of 59.5 grams per square meter (g/m^2) to 74.6 g/m^2 .⁶ Using one Tyvek foil as lid and a double Tyvek foil as liner, the total basis weight is between 178.5 g/m^2 and 223.8 g/m^2 . With a voltage of 120 kV (typical voltage ranges between 100 and 115 kV) on the e-beam emitter facing the top of the tub, the penetration in terms of basis weight in the Tyvek foil will be 160 g/m^2 (Figure 7). For this configuration, no electrons will enter the tub.

We must also consider the nonhomogeneous thickness of the Tyvek foil. To assess whether this might transmit some radiation to the syringes, we conducted an investigation using a tub configuration and voltage used by pharmaceutical companies.

We selected a tub with a lid of basis weight 87.3 g/m^2 and a single liner of 76.1 g/m^2 , and irradiated it with a voltage of 115 kV, measuring the doses above the lid as well as above and below the liner. Figure 7 shows that below the liner, which touches the top of the syringes, there is no measurable dose (i.e., it is below the 0.2 kGy measurement sensitivity threshold of the

FIGURE 5: DEPTH DOSE CURVES SHOWING PENETRATION OF LOW-ENERGY ELECTRONS

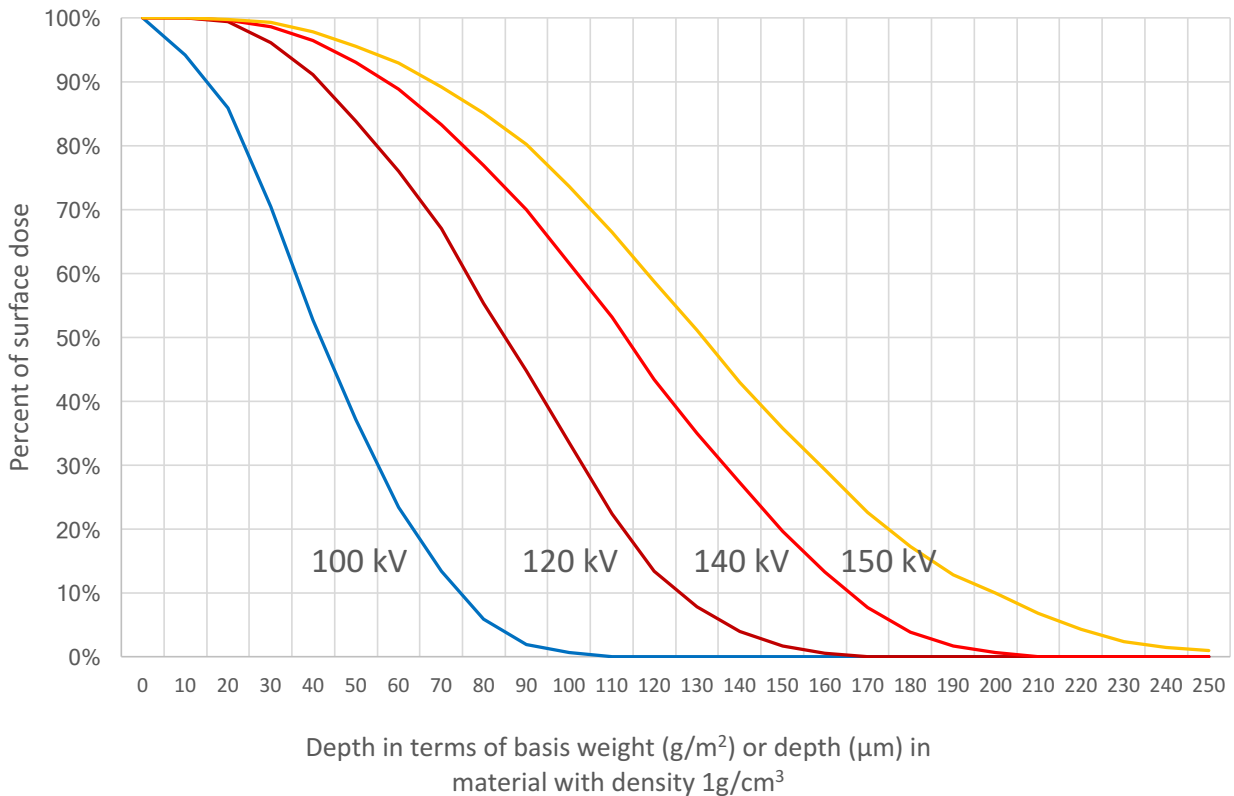


FIGURE 6: GAP BETWEEN LINER AND WALL

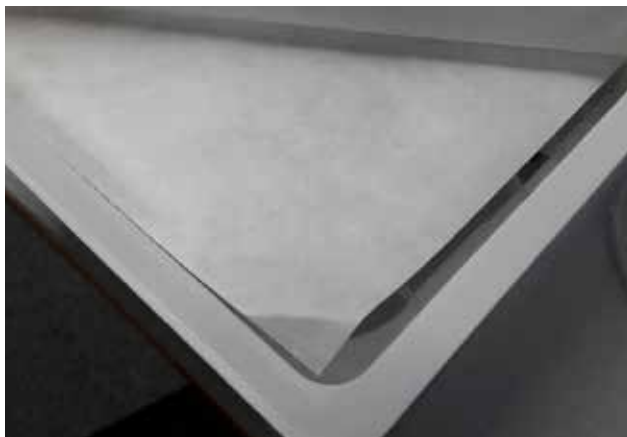
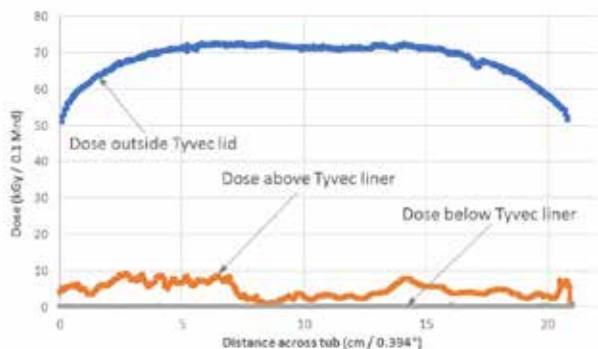


FIGURE 7: EFFECT OF NONHOMOGENEOUS TYVEK FOIL THICKNESSES AT 115 KV



dosimetry tool). In other words, if the parameters (voltage and foil thickness) are selected correctly, then the dose on the syringes will be close to zero.

But what if unsuitable parameters are chosen, such as a very thin liner or a voltage that significantly exceeds 120 kV? To estimate the radiation dose that might be delivered under these conditions, we assumed the same foil thicknesses as in the initial investigation, but increased the voltage to 140 kV. We then used a simple graphical method based on the depth dose curves, which is commonly used with homogeneously thick material by users of e-beam equipment (Figure 8).

We overlaid the depth dose curves with rectangles that represent the different objects in front of the electron window. In the initial investigation they include the additional air gap of 35 mm (total air gap 55 mm, air gap of 20 mm already considered in the depth dose curves) converted to a basis weight of 41.1 g/m², the lid with a basis weight of 87.3 g/m², and the liner with a basis weight of 76.1 g/m².



E-BEAM TUNNELS ARE WELL ESTABLISHED FOR ASEPTIC FILLING, WITH MORE THAN 30 UNITS IN OPERATION WORLDWIDE.

E-BEAM TUNNEL IRRADIATION ENSURES THAT THE ASEPTIC ZONE IN THE FILLING AREA REMAINS UNCOMPROMISED.



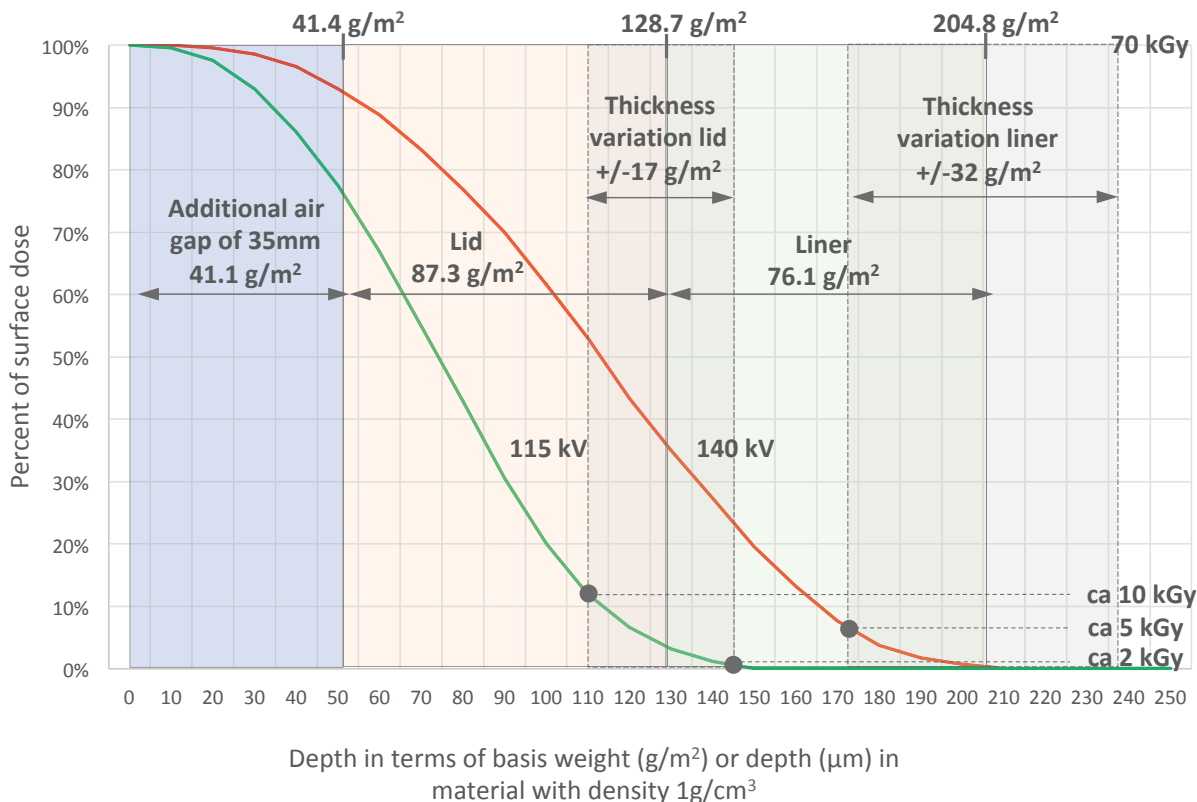
The initial investigation had shown a below-lid dose variation of approximately 2–10 kGy, which implies a thickness variation of the lid of approximately ± 17 g/m². This allows us to assume a correspondingly higher thickness variation for the combination of lid and liner of ± 32 g/m². Figure 8 shows that the area of lowest thickness of the combination of lid and liner received a dose of approximately 5 kGy (0.5 Mrad). Based on this maximum dose below the liner (and therefore on the syringes) we can evaluate the changes to the characteristics of the syringes, drawing on research by other groups.

COC material damage might occur in two ways: 1) directly, from low-energy electrons or 2) indirectly, from irradiation of the air in the tub, which leads to the formation of ozone (O₃), nitric acid (HNO₃), and nitrogen oxides (NO_x), all of which oxidizing gaseous agents.¹

The direct effect of electron-beam irradiation leads to chain scission, cross-linking, oxidation, and grafting. These in turn may change the mechanical or surface properties of the polymer, leach low-molar mass molecules from the polymer into the drug solution, allow the polymer to absorb the drug, or affect the compatibility of the packaging and its content.⁷⁻⁸

But does a moderate dose of no more than 5 kGy (0.5 Mrad) lead to significant damage on COC packaging? Because research is usually conducted at high doses, typically between 25 and 200 kGy, we must interpolate between the points of no irradiation and irradiation at 25 kGy. Two papers by Barakat report measurements on modifications of the characteristics of COC with respect to polymer degradation, effect on the antioxidant degradation, effect on the generation of low-molecular-weight compounds, chemical modifications, and interaction with drug solutions. All measurements showed only a small difference between the points of no dose and a dose of a few kGy.⁷⁻⁸ This means that no significant changes to the COC polymer characteristics would be expected.

FIGURE 8: ESTIMATED MAXIMUM DOSE ASSUMING 140 KV ON E-BEAM EMITTER



CONCLUSION

We have investigated the effects of x-ray and e-beam radiation on syringes made of COC material located inside a tub.

Very low doses of x-ray radiation (a few Gy or 100 rad) are negligible in comparison with estimated e-beam dose of 5 kGy (0.5 Mrad) in case of unsuitable parameters.

Experimental measurements showed that for well-chosen parameters the e-beam radiation delivered to syringes inside the tub will be close to zero. Even in case of unsuitable parameters, a dose of 5 kGy (0.5 Mrad) would still not produce significant changes to the COC polymer characteristics, as it has been shown by other groups.⁷⁻⁸

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IMPROVING SSU AND THE CLINICAL TRIAL CONTINUUM

Craig Morgan

Workflow-based technology in the clinical trial continuum encourages process optimization, helps break down silos, enhances performance quality, and has a measurable effect on the electronic trial master file.

The focus on technology as a driver of performance improvement in clinical trials is intense, but despite years of valiant efforts, study execution remains far from optimal. For study start-up (SSU), one of the most complex parts of clinical trials, the data are dismal: Contract cycle times have doubled from an industry median of 1.5 months in 2009–2011 to more than three months in 2014–2015.¹ Nearly 50% of clinical trials are behind schedule, with slow patient enrollment cited as the top reason.² Research also suggests that for Phase II and III trials, a lengthy 16.7 months is typically required to initiate all approved investigative sites.³

These statistics are not surprising, given the findings of a new SSU process survey conducted by the Tufts Center for the Study of Drug Development (CSDDD), in which 35% of respondents still rely on spreadsheets to launch trials, 2% use paper-based systems, and 19% were unsure, as this function is outsourced to a contract research organization (CRO).⁴

While technology remains critical, as emphasis shifts to process optimization it may be only part of the solution. Since the introduction of electronic data capture in the 1990s multiple providers have entered the marketplace, offering point solutions* to improve quality in clinical trials. Two decades later, however, stakeholders have learned that point solutions can hinder the flow of data across the continuum,⁵ causing already entrenched silos to dig in further. The need to move to the bigger picture—the overall process—should resonate with stakeholders responsible for SSU management.

Although there is no industry-wide definition of SSU, a series of steps—from site identification to contract and budget negotiations to site initiation—are generally associated with starting a study. To improve performance quality for these elements, two factors are needed: an end-to-end solution and support from top management, i.e., the chief executive officer, chief information officer, chief medical officer, and others who comprise the so-called C-suite.

An end-to-end solution with workflows that aggregate data from disparate sources can draft documents in the correct format from the start and release them downstream into the trial master file (TMF) or electronic trial master file (eTMF). This approach can break down silos that have long performed in isolation with little understanding of what the next

department needs to fulfill its regulatory obligations and achieve targets measured by performance metrics.

As for the C-suite, the importance of buy-in from upper management cannot be overstated. Such input provides the critical impetus and strategic insight to align with the sponsor's goal for developing better therapies more quickly. Without management direction, efforts to jump-start overall performance optimization tend to flounder as departments retreat to their silos.

In short, tools are essential, but they don't create a master craftsman. Real expertise comes from combining experience with the authority and talent to influence the way studies are conducted from an operational perspective. Research suggests that organizational issues become strategic and of interest to upper management once they have proven relevance to performance.⁶

This article focuses on how workflow-based technology encourages process optimization and how these improvements enhance performance quality. Purpose-built SSU solutions can identify the documents needed to conform

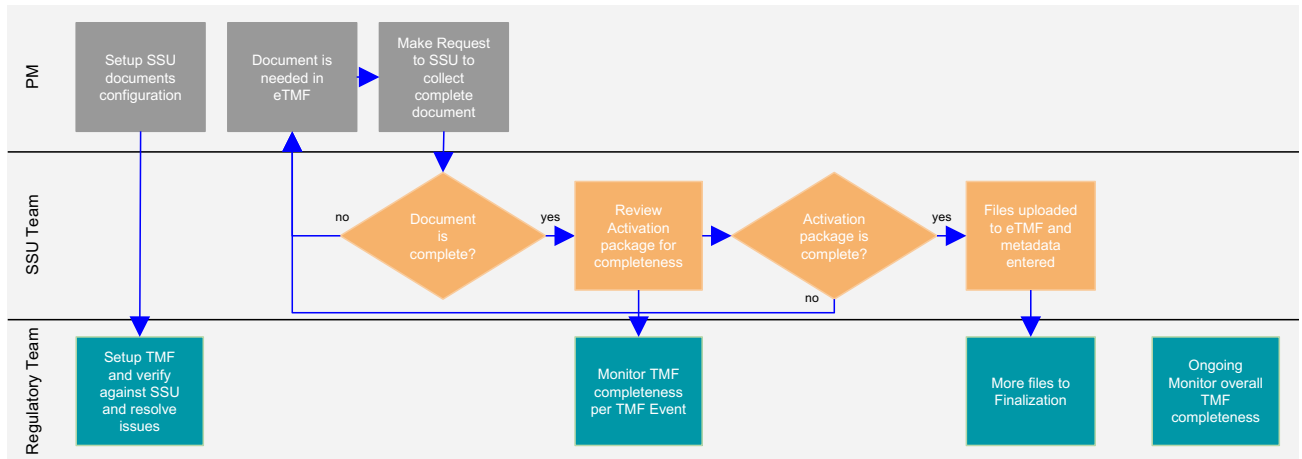
Where's your focus?

Transforming these clinical trial elements¹⁷ can lead to quality improvements:

- Contractual agreements between sponsors, institutions, and investigators
- Investigator recruitment
- Participant recruitment plan
- Quality control systems
- Data collection, management, and analysis
- Data standards
- Regulatory approval to conduct a clinical trial (e.g., IND in the United States)
- Coordination of global investigators and research sites

* According to *PC Magazine Encyclopedia*, point solutions “[solve] one problem without regard to related issues. Point solutions are widely used to fix a problem or implement a new service quickly.”

FIGURE 1



to downstream regulatory requirements, and can also signal bottlenecks or breakdowns in study execution. This approach helps to avoid rework, delays, and cost overruns; improves cycle times; and facilitates audit readiness.

IMPROVING THE PROCESS

The need to improve the clinical trial process, starting with the SSU, is a long-standing industry battle cry. A seminal 2012 report from the Institute of Medicine (IOM) confronted this issue head-on by encouraging transformation of the clinical trials enterprise through quality improvement efforts.⁷⁻⁸ The report contains a lengthy discussion on infrastructure improvements, identifies key elements (see sidebar on page 66), and recommends the following:

- Use “creative destruction” to replace old clinical trial business models with newer forms that complement advances in technology.⁷
- Trade outmoded mechanisms for newer technologies such as web-based clinical trials and smartphones.⁸
- Engage in more strategic planning and consider new organizational structures for entities that conduct clinical trials.⁸

Since the IOM report was published, process improvement has emerged as a hot-button issue, as evidenced by the expanding volume of literature on the subject. Some articles, for example, confirm the widely acknowledged challenges linked to contract and budget negotiations. Martinez et al. found those tasks to be the most time-consuming part of the study activation process and to be widely variable due to lack of standardized processes.⁹ Using a simulation model, they determined that increasing the efficiency of contract and budget development would reduce activation time by 28%.

Other articles describe the need for an organized Six Sigma approach to improve SSU processes, in which steps are carefully defined and continuous improvement becomes standard practice.¹⁰ For SSU, those steps involve accessing process, people, data, and systems for activities that range from site selection to site activation.

More recently, the survey of 591 clinical trial stakeholders conducted by the Tufts CSDD in Q1 2017 determined that a mere 8% of sponsors and 14% of CROs are extremely satisfied with their SSU processes. By comparison, approximately 40% are either somewhat or completely unsatisfied with those processes.⁴ Not surprisingly, respondents reporting that they are extremely satisfied have cycle times 57.5% shorter than those that claim to be completely unsatisfied.

BETTER QUALITY, FEWER SILOS

While the industry tries to implement processes that improve SSU quality, regulatory efforts may be the driving force. The November 2016 release of the first new good clinical practice (GCP) guideline in 20 years was a major step forward.¹¹ Put forth by the International Conference on Harmonization (ICH), the guideline, known as ICH-GCP E6(R2), is an addendum to the original statement from 1996. It includes a new section focused exclusively on risk-based quality management. It states that the sponsor should implement a system to manage quality from the start, and throughout all stages of the trial process. The new section also addresses topics such as critical process and data identification followed by subsections focused on risk factors, namely risk identification, risk evaluation, and risk control.

The guideline acknowledges that technology has advanced to the point that it can support processes and generate data that provide actionable insights into risks and study bottlenecks. As described in the new guideline:

Evolutions in technology and risk management processes offer new opportunities to increase efficiency and focus on relevant activities. When the original ICH E6(R1) text was prepared, clinical trials were performed in a largely paper-based process. Advances in use of electronic data recording and reporting facilitate implementation of other approaches. . . . Therefore, this guideline has been amended to encourage implementation of improved and more efficient

TABLE A: SSU PROCESS CYCLE TIME—A THREE-YEAR PERSPECTIVE

	Sites	Very or somewhat shorter, %	Very or somewhat longer, %
Sponsors	Repeat	18.9	27.5
	New	15.9	35.0
CROs	Repeat	36.1	15.3
	New	23.9	15.5
Centralized SSU	Repeat	35.9	17.1
	New	27.9	20.7
Decentralized SSU	Repeat	17.7	27.9
	New	13.5	33.3

Source: Tufts Center for the Study of Drug Development, 2017. Used with permission.

approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human subject protection and reliability of trial results.¹¹

Application program interfaces (APIs) are an example of technology that has greatly increased clinical trial efficiency. These tools integrate cloud-based eClinical solutions such as electronic data capture, the investigator portal, the data warehouse, and the clinical trial management system. APIs allow sponsors and CROs to link stakeholder data across the globe, irrespective of the systems they are using, optimizing the data flow across the clinical trial continuum and eventually releasing it into the eTMF.

Unfortunately, entrenched silos such as site identification, clinical development, data management, contracting, and regulatory affairs have long stymied these data flow efforts because they often have minimal understanding of what is needed downstream. This approach is often dubbed the “throw it over the wall” mentality, meaning that once a specific department has completed its work, it is tossed to the next department in assembly-line fashion.¹²

This awkward management style is a root cause of problems with the TMF and eTMF. Information about the standardized taxonomy and metadata provided in the TMF reference model is not typically shared with SSU team members, so they are frequently unaware of which documents are needed or the required format for release into the eTMF. Since start-up generates almost half of the artifacts found in the TMF—data files, documents, digitized content, and media—this can create challenges for the regulatory group tasked with mapping documents to the TMF and indexing the metadata.¹³

Fortunately, technology provides the opportunity to rethink the inefficiencies of silos. Some stakeholders want to move away from vertical silos and

WORKFLOW-BASED TECHNOLOGY IN THE CLINICAL TRIAL CONTINUUM ENCOURAGES PROCESS OPTIMIZATION, HELPS BREAK DOWN SILOS, ENHANCES PERFORMANCE QUALITY, AND HAS A MEASURABLE EFFECT ON THE ETMF

“think horizontally.” This method uses automation and workflows to integrate operational data across all functions, making it easier to extract meaningful insights from those data.¹⁴ Some also believe that bringing interdependent functions together using technology and critical teams will help navigate the highly complicated global regulatory maze.¹⁵

EMBRACING WORKFLOWS

Optimizing study conduct starts with embracing a workflow-based process that defines the documents needed for the SSU. This method boosts quality by preparing documents that are accurate, complete, and in alignment with the eTMF format established by a sponsor’s or CRO’s regulatory team, enhancing audit readiness.

The 2012 Tufts CSDD study highlights sponsors' and CROs' strong need for improvement.⁴ Both had lengthy site start-up cycle times—in the range of 4 months for repeat investigative site CROs and 5 months for sponsors; times were even longer for new sites. The study also revealed that site start-up process cycle times were substantially longer than they were just 3 years earlier, particularly for sponsors (Table A). Companies with centralized SSU functions did, however, see strong improvement.

Given these statistics, a workflow-based platform that facilitates quality efforts is a sensible option. The tool's integrated data from several e-clinical solutions provides an end-to-end continuum that allows properly formatted documents and structured artifacts to flow into the eTMF. With the help of this tool, moreover, documents eventually needed for the eTMF can be defined up front, during SSU. This is a major advantage because within those documents more than 400 draft and supporting artifacts can be structured, resulting in a final set of approximately 60 artifacts that will be released into the eTMF.

CASE STUDY

A recent case study details how a workflow-based tool helped a large CRO improve eTMF quality. The company had a history of uploading site documents and associated metadata into the eTMF manually.¹⁶ With the complexities of SSU and global regulatory requirements, determining when all necessary documents appeared in the eTMF required multiple quality control checks, which proved a tremendous drain on resources. In addition, as the CRO scaled clinical trials, the efficiency and quality of data entering the eTMF created audit risk and increased costs for full-time equivalents.

To manage this problem, the CRO implemented a tool that guides SSU workflows, documents, and submission collections with mappings to the TMF reference model. Using an API, artifacts and metadata were delivered to the eTMF only when specific business conditions or events occurred. As a result, the CRO was able to handle an estimated 20% increase in studies with the same staff levels, while also reducing the number of rejections per study site for artifacts where either the wrong version had been used or associated metadata were missing. Figure 1 depicts this workflow.

PLAN EARLY AND BREAK DOWN SILOS

As clinical trial stakeholders ramp up efforts to optimize the SSU process and begin the arduous task of dismantling silos, there is a growing recognition that technology is a critical component. Without it, sponsors and CROs will continue to experience the measurable ramifications of poor quality: delays, cost overruns, poor communication, and lack of audit preparedness. These problems can be avoided with the expanded use of workflow-based tools and performance metrics.

Such initiatives to improve quality are in early stages, but with the availability of solutions, transformational process changes can finally begin to happen. Planning up front for correctly formatted documents, artifacts, and associated metadata that will eventually be released into the eTMF will bring big changes to the typically inefficient chain of study execution. This is reflected in statistics that document just how intractable study start-up problems have become. Despite the presence of many point solutions, for example, 8 months remains the average time frame for moving from previsit to site initiation.³

Significantly, with the use of integrated information from disparate data sources, issues will be identified early on, rather than waiting until they reach

the eTMF. This is because regulatory metrics derived from documents arriving in the eTMF are developed too late to provide proactive insight. But with a real-time workflow tool, insight from performance metrics can offer the transparency needed to take action in real time. By embracing this approach, complemented by support from key decision makers, it is possible to move the needle on process change and increase the likelihood of more predictable cycle times, better adherence to study budgets, and audit readiness.

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About the author

Craig Morgan is a technology and life sciences management professional with more than 15 years' experience in the application of informatics to drug discovery. He leads the marketing and brand development functions at goBalto, working with sponsors, CROs, AROs, medical device manufacturers and sites to reduce cycle times and improve collaboration, oversight and risk management in clinical trials. Craig is a certified project manager with the Project Management Institute and holds degrees in analytical chemistry, information systems and business administration.



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INDEX

BWT Pharma & Biotech GmbH	5
Commissioning Agents, Inc.	Inside back cover
COPA-DATA	3
CPFS (Capital Projects and Facility Services)	37
CRB	1
Elettracqua Srl	11
Fluor Corporation	Inside front cover
Intelligen Inc.	9
Letzner Pharmawasseraufbereitung GmbH	7
Mar Cor Purification	29
Picarro Inc.	25
Stilmas SpA	Back cover
UBM Sinoexpo	41

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Research compiled by Scott Fotheringham, PhD

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