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DATA INTEGRITY IN THE TRENCHES

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ON THE COVER Data integrity has been and continues to be an inherent aspect of global GMP regulations governing electronic and paper-based records in pharmaceutical manufacturing.

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By Jim Breen

ISPE's New Year: Our Story in Action


Jim Breen

On sitting down to write my first Chair's column, I reflected on the events at our Annual Meeting & Expo in November. First, I want to commend the entire ISPE organization, and offer particular thanks to the 2018 Annual Meeting planning committee, for hosting a very successful and complex event. This year's gathering drew over 2,400 attendees, the second-largest total in the Annual Meeting's 27-year history. It demonstrated ISPE's ability to deliver value, knowledge, and networking to the pharmaceutical industry. Plenary speakers—Lars Fruergaard Jørgensen (CEO, Novo Nordisk), Chris Chen (CEO, WuXi Biologics), and Kevin Nepveux (VP, Pfizer)—represented the best of the best in an industry where technology and business models are changing daily.

Presenters also reminded us that our efforts improve patients' lives. Team Novo Nordisk Ambassador Becky Furuta shared her touching and powerful story. Nick Leschly (CEO, bluebird bio) showed us that much is being done (and more will be done) to save lives.

STRENGTHS AND FOCUS AREAS

The 2017 financial report presented by ISPE Treasurer Fran Zipp showed a strong and thriving organization, demonstrated by a 32% increase in revenue since 2009. We launched the ISPE Foundation in 2018. Mike Arnold, Foundation President, reported that while target funding had been set at $45,000, by early November generous donations had exceeded $172,000. ISPE has also invested in the foundation to support a special focus on our Workforce of the Future.

In 2019, we will maintain our focus on critical areas of the industry such as Women in Pharma®, Young Professionals, Facilities of the Future, and critical technology topics like gene and cell therapy to help our members prepare for the future. Board Treasurer Tom Hartman discussed ISPE's strategic plan in development for 2020–2022 that will address the changing technological landscape and continue to help members to address and remain engaged in the industry. Our Board of Directors will also work to drive collaboration and engagement globally with our chapters and affiliates.

THE FUTURE IS BRIGHT

I look forward to seeing you at ISPE events this year such as our Facilities of the Future event in February in San Francisco; Aseptic Conference in North Bethesda, Maryland, in March; the Europe Annual Conference in Dublin in April; and the June Process Validation Workshop in Boston. All these events will feature industry-leading topics and will have key thought leaders in attendance. For more information, visit the Conferences page at ispe.org/conferences.

I also wish to thank outgoing Chair Tim Howard for his leadership in 2018 and look forward to his continued support in 2019.

Finally, as we embark on a new year, I am reminded of how Becky Furuta at Team Novo Nordisk explained the challenges and celebrations in her life: "We all create our own story in our life by our actions." My challenge to all ISPE members is to work together to create ISPE's story: expand our influence; engage new, existing, and potential ISPE members; and remind everyone of the importance of our industry and how we improve people's lives each day.

Jim Breen is 2019 ISPE International Board of Directors Chair; Vice President, Lead Biologic Expansion, Janssen Pharmaceutical; and adjunct professor at Drexel University. He has been an ISPE member since 2000.

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VISION TO REALITY

2018 ISPE 2018 Annual Meeting & Expo Highlights

Over 2,000 attendees from more than 28 countries gathered in Philadelphia for the 2018 ISPE Annual Meeting & Expo on 4–7 November. Highlights below show the many ways that presenters captured the conference theme of "Vision to Reality": in strides against disease, ISPE's advancements over the last year, ISPE's plans for the future, and the impact of ISPE members' work on patients' lives.

DAY ONE

At the opening plenary on Sunday, 4 November, Tim Howard, Immediate Past Chair, ISPE International Board of Directors, noted some of the industry challenges that have emerged since the 2017 Annual Meeting concluded: globally, 18 million people received a cancer diagnosis, 9.5 million people died from cancer, and 5,600 people were diagnosed with ALS—a disease that is always fatal, he noted.

While these numbers present challenges for the industry, Howard noted that "technology is progressing at a rate that is unprecedented," with developments such as chimeric antigen receptor (CAR) T-cell therapy, supply chain advancements, and other groundbreaking developments that members would hear more about during conference presentations and sessions. "ISPE will play a critical role in developing these," Howard said.

A Word from the President

John Bournas, ISPE's CEO and President, explained that the conference theme "Vision to Reality" holds great meaning for ISPE. "Although we are a nonpro t association and not necessarily involved in the delivery of advanced therapies, we do provide an enabling platform for visions to one day become a reality."

The contributions of ISPE's 18,500 members around the world, including its 38 a liates and chapters, are part of that platform, he said. And as Bournas noted, "it really all starts at the student level. We have over 70 ISPE student chapters at universities around the globe, from newly established ones such as Thailand, the University of the Philippines, Virginia Tech, Georgia Institute of Technology, to 11 others now being formed, such as Stanford University, University of South Australia, University of Maryland College Park, University of Pennsylvania, and Villanova, among others. We also have strong collaborations with leading ISPE member academics, who have paved the way, such as Dr. Antonio Moreira.

The commitment to education connects with the workforce of the future in both pharma engineering and the wider industry, and Bournas noted the growth of Young Professionals, with more than 27 Young Professional groups around the world and over 60 events in just the last year.

"We hope to fully harness the energy that exists within this segment of the membership to help us drive toward some of the strategic goals that we envision for the next four years."

Lars Fruergaard Jørgensen

A Leap Forward in Drug Development

Lars Fruergaard Jørgensen, President and CEO of Novo Nordisk A/S and Honorary Conference Chair, gave a presentation exemplifying the spirit of Vision to Reality by describing the company's path to a groundbreaking new treatment for patients with diabetes.

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In "From Vision to Reality: Delivering Next-Generation Diabetes Treatment," he recalled the company's commitment to patients and defeating diabetes. Novo Nordisk began in 1921, when August and Marie Krogh were granted permission to produce insulin in Scandinavia. Today Novo Nordisk provides nearly half the world's insulin and is using its skills in diabetes treatment to develop therapies for growth hormone de ciencies and hemophilia.

"We have stayed true to our purpose to discover and develop innovative biologics and make them available to patients around the world," he said.

Jørgensen noted that pricing and a ordability "is part of our social responsibility. The triple bottom line is a lens we use for decision-making." He illustrated this by noting that a 10-ml vial of insulin can be purchased in the United States for $25.

"Aiming high," he noted, is necessary to get fast market access. Innovation is central to aiming high, and Jørgensen discussed an innovative drug in development that does just that. There is great need for other ways beyond injectable insulin to address the tremendous global health challenge of diabetes, which affects 425 million people globally and is projected to a ect over 700 million in the next 30 years.

Despite numerous treatment options, patients are not meeting desired outcomes. Only half of the world's 425 million diabetics are diagnosed; of those, half receive care. Among those, only about half achieve treatment targets, and just half of those (6% of the original total) achieve desired outcomes.

Fear of injections and a lifetime of insulin treatment create barriers for many patients. To help address this, Novo Nordisk decided that an oral insulin drug was needed. This is where the company's approach of aiming high came into play because it was said that this could not be done.

Novo Nordisk now has an oral semaglutide in phase 3 trials, with 8 of 10 planned trials completed, and 9,356 patients enrolled through all phases. The technology combines insulin and glucagon to treat type 2 diabetes. This appears to be a promising therapy to reduce glucose levels and to help with weight loss, he noted. As the oral semaglutide tablet dissolves, other ingredients in the tablet protect the semaglutide molecule and transport it into the bloodstream. The new product is being tested against Victoza, Novo Nordisk's injectable GLP-1 analog. The company's goal is to complete the trials and submit the drug to the Food and Drug Administration (FDA) in 2019, with the hope of launching by 2020.

How to manufacture the new drug will be the next challenge. Jørgensen noted that a million square feet are needed for the tablet's manufacture. While pills are usually produced in small facilities, more room is needed to produce the amount of semaglutide needed. Novo Nordisk will use its $2 billion site in Clayton, North Carolina, to manufacture the active pharmaceutical ingredient (API).

"We are quite serious in terms of doing innovation. We are investing $2 billion in manufacturing, but we are investing another $2 billion in the program. We believe we know how to do this. I believe this will become a de ning new treatment for type 2 diabetes."

Kevin Nepveux

New Technologies Bringing Change

In today's market, new modalities require new manufacturing technologies, as therapies are developing in parallel with technology, said Kevin Nepveux, Vice President, Launch Excellence, P zer Global Supply, in his plenary presentation, "Manufacturing and Supply: Vision becomes Reality," on the rst day of the Annual Meeting.

Nepveux cited some of the major drivers behind the need for new technologies, including continued pressure on costs, personalized medicine leading to products with smaller volumes, and new modalities being explored, including gene and cell therapy and mRNA vaccines. Large molecules have "grown up," with more than half the R&D and a lot of revenue devoted to them. Other drivers of change include lean, agile manufacturing and biosimilars with more complex molecules. Changes in regulatory expectations also mean that end-stage testing is no longer enough to ensure quality. Social responsibility is important, too: "green," "sustainable," and "carbon footprint" are terms you see in many annual reports, he said.

In response to these drivers, P zer—a research-based pharma company with a mix of large- and small-molecule plants—is moving to continuous manufacturing and real-time process control, and increasing its dependence on process analytical technology and online measuring systems. The company is building a gene therapy plant in Sanford, North Carolina, and plans to produce a promising investigational therapy, developed in partnership with Spark Therapeutics. A continuous solid oral dose platform is about to launch; Nepveux noted that P zer hopes to produce 60%–80% of its solid oral product on that platform.

Regulators are providing opportunities for accelerated review for products with compelling clinical data: "The product development process used to take 10 years," Nepveux said. Now programs are on seven- and even ve-year cycles. "The increased R&D productivity coupled with tighter timelines puts signi cant pressure on new product development assets, but it is a great problem to have, as it means patients are getting new medicines faster."

Nepveux emphasized that P zer's people are central to its success. "Our people make it possible," he said, also noting the contributions of suppliers who provide the raw materials—as many as 400 raw materials are required to manufacture a single dose of some vaccines.

The move from batch to continuous production requires more

and different skills, he noted, requiring colleagues with deeper science and technical backgrounds. The skills necessary for a successful pharmaceutical manufacturing operation are changing, too, he said. “We need geologists, statisticians, microbiologists, control engineers—some positions that didn’t exist 30 years ago.”

P zer’s ownership culture, reinforcing that individual achievements impact results, supports this new reality. The company’s employee engagement score of 85% is among the highest in the industry, he said, and exempli es its “Head, Heart and Guts” leadership: “head” behaviors include being decisive and focused, “heart” is connected and inspiring, and “guts” is courageous and resilient.

“In line with ISPE’s goal to transform the industry to better ensure availability of quality medicines to patients, we see opportunities for continued collaboration with regulators; academia, students, and new hires; and other companies, in the pharmaceutical industry and beyond,” he said. “This is a great time to be working in the pharmaceutical manufacturing community.”


Becky Furuta

Patient Viewpoint

Becky Furuta, Ambassador, Team Novo Nordisk and Health Care Policy Consultant, gave the nal plenary presentation on the opening day. In “How Diabetes Drives My Success,” she explained that she chose to live her life as an athlete, a member of the Team Novo Nordisk bicycle racing team, which is elded completely by athletes who have type 1 diabetes. Today Furuta is ranked 21st out of 463 professional female racers in the United States.

Cycling was an accidental discovery when illness sent her family into poverty and Furuta sought a way to cope with the devastating changes. Her bike took her all over Colorado roadways—including the dangerous Million Dollar Highway—but Furuta took comfort in the way cycling calmed the turbulence in her life and showed her how to nd adventure in her life’s circumstances.

“Diabetes can be stigmatizing, but nothing is more marginalizing in your life than poverty,” she observed. “It changes expectations by others and of yourself. What separates so many people from their potential is the story they tell themselves.” So she changed the story: instead of being a homeless kid, she was a talented athlete. “The bike was someplace I could be empowered and strong and capable.”

Furuta was a competitive bicycle racer until a diagnosis of type 1 diabetes during her second pregnancy challenged her progress. At rst, a doctor told her that her racing days were over, but Furuta refused to give up the sport she loved. She found a new doctor who worked with her so that she could continue to cycle, although she did stop racing for a while. When she decided that she was ready to return, she read an article about a team that had six diabetic riders. Her letter to them to learn about how they were able to perform as racers with diabetes led to an invitation to join the group. “It was the most amazing experience of my life! I realized I was racing at a much higher level, and realized it was truly the opportunity of a lifetime.”

A year after she joined the team, Novo Nordisk came on as a sponsor. “It is still amazing to me that people had so much faith in us, and in what’s possible with diabetes. I can race a bike to tell people it is possible to dream as big as you want to. And do really amazing things!”

She urged attendees to “Delight in how you impact patients every day! I have the opportunity to live, and live bigger and better than I ever could have dreamed, thanks to the pharmaceutical industry.”

DAY TWO

Nick Leschly

Innovation and Energy

The second day of the conference, on Monday, 5 November, opened on a dynamic note. “There’s a tremendous amount of energy here,”

James Breen, Jr., Incoming Chair of the ISPE International Board of Directors, told attendees as he opened the morning plenary. "I want to keep the momentum going."

The first plenary session speaker, Nick Leschly, CEO of Massachusetts-based bluebird bio, shared the story of the company's birth and progress as he spoke with humor and passion about gene therapy.

To demonstrate what drives him, Leschly presented a touching video about a young boy who died at age 10 from cerebral adrenoleukodystrophy (CALD), a rare and deadly genetic disease. One of bluebird bio's first four products, all of which Leschly hopes will be approved by 2020, includes a lentiviral vector-based therapy for CALD that has halted disease progression in 15 of the 17 children tested with the therapy.

Bluebird is using the same vector to develop treatments for thalassemia and sickle cell anemia. Another therapy, based on the CAR T-cell therapy bb2121, shows great promise for multiple myeloma, extending survival from 3–5 months to nearly 18 months. "If you can harness the immune system, if you can galvanize it, you can get a tremendous response," Leschly explained.

Bluebird's quest is for one-time transformative, or curative, treatment. The faces behind the diseases drive the company's work. "Now we have a genome-editing platform. We want to galvanize technology to go after diseases," Leschly said. In the future, combination therapy platforms will be used to cripple tumors, he predicted.

The company recently opened a new manufacturing facility in Research Triangle, North Carolina. The key factor in choosing this location was the workforce talent available there. "We have to have the best people. They can't just apply their trade. They can't be standard Lego® pieces here," he explained.

The drive for bluebird bio is more than innovation: It is about disruption, Leschly said. He defined innovation as doing the same things a little better; disruption is making things that make old things obsolete.

Staying the course through the ups and downs of gene therapy development is not easy but for Leschly and the bluebird bio team, there is no other option. "Walk, fall down, get up, and walk again," was how Leschly characterized the process. "Many people would have shut this program down, but we didn't have a choice—and it's what we love."

Leschly concluded with a discussion about the pharmaceutical industry's social responsibilities in drug development. "Gene therapy began with 40 years of agony and failure," he said. "Now it works, but there are no rules. It's expensive and inefficient, and the business case is unknown.

"Drug pricing used to be, 'What will the market bear? What can you get away with?' And you do have to charge something that rewards your risk," he conceded. "But value-based payment over time is the solution. Don't be shortsighted. Ground to something meaningful," he urged the audience.

Chris Chen

Biologics Boom

Chris Chen, CEO of WuXi Biologics (Shanghai) Co., Ltd., shared his thoughts on making biologics in the second plenary presentation. He acknowledged that like Leschly, his story is somewhat disruptive as well. WuXi is making biologics more affordable and available to patients more quickly. Like Leschly, Chen sees great opportunity ahead.

"I want to accelerate and transform how biologics are discovered, developed, and produced," he said. WuXi, which Chen noted operates the world's largest bioreactor, is a contract development and manufacturing organization.

The company's WuXi City facility, the 2014 ISPE Facility of the Year Awards (FOYA) Overall Winner, consists of two parallel upstream cell culture bioreactor lines with flexible working volumes of 50- to 2,000-liter bioreactors and one downstream purification production line. It is the most advanced such facility built in China, and the first in the world to be capable of utilizing 100% disposable equipment for drug substance manufacturing.

"In 2011, when I started WuXi, I said this is the way to go," Chen said. "It's entirely disposable and we don't need an autoclave." The facility took 18 months to build and was completed in 24 months.

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2018 ISPE International Honor Award Recipients

- Student Poster, Undergraduate: Cy Rodriguez, University of the Philippines, Philippines A□liate
- Student Poster, Graduate: Martin K. Burns, PhD Candidate, Stevens Institute, New Jersey Chapter
- A□liate and Chapter Excellence Award: DACH A□liate
- Committee of the Year: International Young Professionals Committee
- Company of the Year: AstraZeneca
- Max Seales Yonker Member of the Year Award: Máiréad Goetz
- Richard B. Purdy Distinguished Achievement Award: Charlotte Enghave Freurgaard, PhD
- Joseph X. Phillips Distinguished Achievement Award: Joseph Famulare
- Facility of the Year Awards Overall Winner: Shire, Los Angeles Building 8 Project

Disposable bioreactors and new investment in continuous puri cation platforms enable integrated bioprocessing for a proof-of-concept commercial facility.

Continuous manufacturing can use smaller, modular facilities with smaller and/or single-use bioreactors to allow for a simpli ed process ow and logistics, enable high operational exibility, and fast technology transfer. Parallel production lines ("scale-out") can meet increased production demands. "You can grow as demand increases. It also gives clients exibility," Chen said.

WuXi is now building a second facility with double the capacity in [Ireland]. "Mfr 1 [China] was really a test," said Chen. "Mfr 2 [Ireland] is our vision of scale-out and continuous processing. Now we're ready to do something big."

The facility, which should be operational in 2021, will help WuXi make biologics even more affordable and available, especially for patients in China. "We can make 8 tonnes of antibodies, and we can make them as low as $15 per gram. This will allow us to change the industry and make biologics much more cost competitive," Chen said.

DAY 3

Achievements and Honors

The ISPE International Honor Awards Committee acknowledged exceptional e orts, recognizing individual volunteers, a liates and chapters, students, the company of the year, and the Facility of the Year Awards (FOYA) Overall Winner during the Membership and Awards Breakfast on Tuesday, 6 November.

The annual event is also an opportunity for the ISPE International Board of Directors to share information about strategy, achievements, and plans for the year ahead.

Outgoing Chair Tim Howard, Vice President, Commissioning Agents International, opened this year's breakfast by introducing the new board and thanking past members for their service.

Past Chair Mike Arnold, Senior Director Strategic Relationships, P zer Inc., followed with a review of one of the year's most signi cant events: establishment of the ISPE Foundation. Thanks to generous donations, the foundation was able to award 14 grants for travel to the 2018 ISPE Annual Meeting & Expo its rst year.

Target funding for 2018 had been set at $45,000, Arnold said, but donations have already far exceeded that initial amount. To date the foundation has received over $162,000, and several donations made that week added another $10,000.

Fran Zipp, incoming Board Vice Chair and President and CEO, Lachman Consultant Services, presented the treasurer's report. The nancial decline following the 2008 recession is now on the upswing, she said, so much so that ISPE was able to invest this year in the ISPE Foundation, a new strategic plan, and new technologies. "Our net income is slightly lower as a result, but it'll help us in the future," she explained.

Howard returned to review other important events of 2018. He extended special thanks to ISPE's past presidents, many of whom were in attendance. ISPE's new continuity initiative calls on the current board to engage with past presidents as they work to develop ISPE's new strategic plan. Another new enterprise came from the North American task team: a community of practice for chapters and a liates. Membership in the group will be available to all chapter and a liate o cers and board members.

Howard noted that last year the board modi ed its bylaws to allow direct board appointments to address critical needs. The board appointed Chris Chen, CEO, WuXi Biologics (Shanghai), Co., Ltd., to the board. "With his knowledge, we expect to improve our reach to the Asian market greatly," Howard said.

Howard concluded his talk by passing the ceremonial gavel to Jim Breen, incoming Chair, and VP Project Lead Biologics Expansion, Janssen Pharmaceuticals.

A New Year Begins

"This is an exciting time to be in the pharmaceutical industry," Breen said. "Technology is changing, and the future looks bright. Your work improves patients' lives, and we do a great service to the industry and the world.

"ISPE is the intersection of engineering and technology, but it's more than that. ISPE allows you to network. You can meet people from around the world. And get a lot of good friends. I want you to get involved more than you have."

Fran Zipp reported on the Women in Pharma® committee and its many activities—mentoring, education sessions, and perhaps most important, social and networking opportunities. For 2019 Zipp will be the group's board liaison, and Christa Myers will assume the chair.

Joanne Barrick, incoming Board Secretary and Advisor, Global Validation Support, Eli Lilly and Company, reported on the restructuring of regulatory committees that will better de ne their members' roles and responsibilities and give the Regulatory Steering Council increased strategic focus. The Guidance Document development process is also being restructured to produce predictable and timely document delivery. In addition, she noted that in the past year access to ISPE Good Practice Guides had become free for all members. Training is undergoing a three-year transformation plan that will permit better integration with Guidance Documents and Communities of Practice.

Tom Hartman, incoming Board Treasurer and VP, GMP Operations, GlaxoSmithKline, discussed ISPE's refreshed strategic plan, necessitated by the organization's diverse population, growing membership, and geographic diversity, as well as the industry's transition to new technologies. During the past year, ISPE partnered with McKinsey and Accenture to conduct a survey that will inform the new strategic plan.

International Honor Awards

John Bournas announced the 2018 award honorees. Among the most signi cant awards of the morning were:

Máiréad Goetz

Charlotte Enghave Fruergaard

The **Max Seales Yonker Member of the Year Award**, which recognizes extraordinary commitment to ISPE service, was presented to Máiréad Goetz, Global Head Analytical Science & Technology, QC, OpEx, Novartis Pharmaceuticals, and leader of the ISPE Advancing Pharmaceutical Quality Team for the past two years. Her other contributions include coordinating ISPE's e orts with the University of St. Gallen, cross-industry meetings in response to Food and Drug Administration (FDA) Guidance, and requests from ISPE a liates and chapters for presentations on the proposed program. She also played an important role in building a collaborative relationship with the quality culture team at the Parenteral Drug Association (PDA).

Thanking the judges and committee, Goetz commented on the great privilege of being part of a team in relentless pursuit of pharmaceutical excellence. "They're an incredible group of consummate professionals."

The **Richard B. Purdy Distinguished Achievement Award**, presented to members who have made significant, long-term contributions to the society, was presented to Charlotte Enghave Fruergaard, PhD, Partner, Compliance Consulting, NNE, for her sustained commitment to ISPE, wide breadth of contributions, and leadership positions that included International Board of Directors Board Chair (2012–2013), Nordic A liate Board Chair (2005–2007), and Annual Meeting Program Committee Chair (2017 Annual Meeting).

"Thank you to the committee and everybody," she said. "ISPE is a big family, and every Annual Meeting is like a family reunion.


Joseph Famulare

Sam Kitchell

I'm proud to stand here today. You believed in me, and you helped me, and you made a dream come true. Thank you."

The **Joseph X. Phillips Distinguished Achievement Award**, which is not given every year, honors an ISPE member who has made a signi cant contribution to the industry. This year's award was presented to Joseph Famulare, Vice President, Global Quality Compliance and External Relations, Genentech, Inc., for his significant contributions to ISPE, the Global Pharmaceutical Manufacturing Leadership Forum, and the entire pharmaceutical industry. A former ISPE board member, he contributed to or led several international regulatory initiatives, and is a respected conduit between the society and worldwide regulatory bodies. Famulare expressed heartfelt thanks to his colleagues, sta , management, and the regulators themselves as he accepted the award.

Tony Crincoli, Chair of the Facility of the Year Awards Judges' Committee, ISPE board member at large, and Vice President of Global Engineering, Glenmark Pharmaceuticals, presented the nal award: the **Facility of the Year Awards Overall Winner**. "The category winners and honorable mentions were selected from a variety of submissions from around the world," Crincoli said. "Each one was a standout in its category, and all exhibit the highest caliber of innovation and technological ingenuity." The award was presented to Shire for its Los Angeles Building 8 project.

This year's Facility Integration category winner, the Shire Building 8 project, involved the construction of a new 120,000-square-foot puri cation facility, which was integrated into an 11.6-acre campus with eight other buildings, space constraints on all sides, multiple underground utilities, and ongoing manufacturing operations in adjacent buildings.

Sam Kitchell, Group Vice President of Engineering at Shire, accepted the award. "ISPE recognized seven incredibly strong projects, and to stand out among them is truly an honor. A forum like this to do benchmarking is an important way to drive our industry forward." After thanking Los Angeles, their industry partners, and employees, Kitchell thanked their patients: "They inspire us to do our best work. We are a champion for people with rare diseases."

Jim Breen closed the ceremony with a dazzling video invitation to Las Vegas, site of the 2019 ISPE Annual Meeting & Expo. "See you next year," he said.

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By LeAnna Pearson Marcum

A NEW YEAR BEGINS FOR YPS

Happy 2019! The last time I saw many of you was at the ISPE 2018 Annual Meeting & Expo in Philadelphia, where I started my tenure as the ISPE International Young Professionals Chair.

When I began my involvement with ISPE in graduate school, I found not just a technical and professional community, but a family. I am currently part of the bluebird bio family as well—a member of the Quality Assurance groups as a QAV Manager at the Durham, North Carolina, site. In this amazing role I get to work with other talented individuals as we create bluebird's first gene therapy manufacturing facility. So far, this job has taken me on travels around the world and pushed me far past what I thought I could do. I have loved every moment of it!

YP BENEFITS

Being an ISPE YP has many benefits, including:

- Identifying, supporting, and sharing local affiliate and chapter programs that serve YPs and enhance their ISPE experience
- Providing guidance and best practices for affiliates and chapters as they establish new YP or student groups
- Interfacing with other ISPE Communities of Practice (CoPs) to increase YP and student involvement
- Providing YP input to continuing ISPE initiatives

YP CHANGES

We were honored to receive the Committee of the Year award at the Membership and Awards Breakfast during the ISPE 2018 Annual Meeting & Expo. As 2019 begins, I want to build on this momentum. As Young Professionals we span both age range and experience levels. While you can be a new graduate, you can also be someone who is new to the industry and looking to make more professional connections. We have grown in the past year and will continue to grow in the year to come. If you are looking to attend a YP event or are interested in starting a YP Group, contact me at Lpearson@bluebirdbio.com or post on the YP Online Community at http://cop.ispe.org/p/co/ly/gid=91.

JOIN US

As Walt Disney said, "The way to get started is to quit talking and begin doing." Please "begin doing" by joining us. We want your expertise and your thoughts on development and growth. Volunteering for a local or international spot on the YP Professional Committee can take as much time as you want it to.

When I first started, I just called into the meetings and listened. As I started to feel more comfortable, I decided to take on more responsibility, starting with smaller roles that eventually led me to my current position. The sidebar Open Positions lists several committees that are looking for YP members. You can choose one of these, or find another one that interests you. You can view ISPE's roster of CoPs here: https://ispe.org/communities-practice.

I have received much helpful guidance and feedback from both the YP leaders and the International Board of Directors; while I am much more assured of what I am doing, I still look to many of those people, whom I now call friends, for that same guidance from time to time. Let's be honest—we will always be growing in our careers, and nobody knows it all. I am and will always be humbled by the time that people have spent helping me navigate my early-career journey as the International YP Chair.

LeAnna Pearson Marcum is a QAV Manager with bluebird bio in Durham, North Carolina, and the 2019 ISPE International Young Professionals Chair. She has been an ISPE member since 2009.

Open Positions

- YP Community Secretary
- PE Magazine Committee
- iSpeak Blog
- Annual Meeting Planning: Europe or Asia–Pacific

Contact

LeAnna Pearson, IYPC Chair, at Lpearson@bluebirdbio.com

Kevin Chronley

FISHING FOR BIOPHARMA SUCCESS

Maritime discipline took the Boston Area Chapter President from a trawler to the boardroom.

It might seem odd to connect commercial fishing to the study of chemical engineering—and perhaps even more unlikely to connect commercial fishing to a career in the biopharmaceutical industry. But for Kevin Chronley, Vice President of Strategic Business Planning and Development at A\Z Corporation and ISPE Boston Area Chapter President, the lessons he learned on New England trawlers served as the foundation for success in college and career.

A native of coastal Narraganset, Rhode Island, Chronley worked hard on the boats to pay for his education at the University of Rhode Island. The rigors of that job, he realized, apply to his biopharma career too. "You've got to be tenacious. Put in the extra e ort. Get out there earlier, stay out there later. And then, when you come in exhausted, you've got to get up and do it all again."

Chronley, who holds the distinction of being the only person to serve as President of two di erent ISPE Chapters, rst led the New England Chapter from 2010 to 2013. He now heads the combined Boston Area Chapter, which merged with the New England Chapter in 2013. His seaside roots inspire his commitment to the region, demonstrated by the Geographic Outreach (GO) initiatives with hubs in Providence, Rhode Island; Portsmouth, New Hampshire; and Worchester, Massachusetts.

CORE ELEMENTS

Describing the three pillars of ISPE as education, networking, and resources, Chronley explained his deep appreciation for these core elements. Like the self-discipline he learned on shing trawlers, Chronley knows they were also key to his success in college. Dr. David Schilling, a professor and mentor that Chronley and his classmates a ectionately called "Coach," helped him come to this understanding.

"I was fed up with the course work. I was making good money fishing, and thinking I would quit," Chronley recalled. "Coach pulled me aside and put it to me plainly. He said, 'I heard you were thinking about quitting. Look around at these old shermen with missing ngers. I think you'll regret dropping out of college. But look, if you want to succeed, you need to read the material, work together collaboratively with your classmates, and recognize resources that can be utilized to contribute to your objectives.' Looking back, I realize those are the same three pillars of ISPE: education, networking, and resources," Chronley explained. His gratitude to Coach Schilling is clear, as his career path has been an exciting one.

Chronley's initial pharmaceutical work with Ciba-Geigy (which merged with Sandoz in 1996 to form Novartis AG) evolved into a career in global chemical process manufacturing. This brought him to the Chicago area as Vice President of Operations for Hammond Group, a small multinational diversi ed chemical manufacturing rm. But it didn't take long for Chronley to return to New England. "I was in Tampa, Florida, on a February afternoon

Reinvent yourself relentlessly. Careers are a playground of opportunities—be an ongoing learner. It will either inspire improvement and innovation within your field, or it will stimulate evolution to new areas of interest.

in 2003 when I signed up to head to Engineered Technologies, Inc. And that same afternoon, I signed up to participate in the winter ISPE conference, because I knew ISPE would provide access to those three keys: education, networking, and resources."

INDUSTRY CHANGES

Chronley is excited by the trajectory he sees in the industry. "When I first entered the market in the early 1980s, the industry was primarily small-molecule pharmaceuticals addressing high-volume therapeutics for common diseases. Today the commercial focus of biologic drug development is categorically 'orphan' or personalized drugs." These therapeutics will improve quality of life and longevity, he added. "Innovation is delivering health care solutions for some of the most common and treacherous diseases, as well as those for smaller populations."

As an example, he noted a presentation by Dr. J. Christopher Love (Koch Institute for Integrative Cancer Research at MIT) at the ISPE Boston Area Chapter 25th Anniversary Gala. "He talked about the evolution of manufacturing, and he laid out a vision for small, appliance-sized biologics-process devices that could custom-produce drugs for individual patients at a pharmacy. That kind of technology could well be on the horizon."

It's an exciting prospect, but having the right people with the right skills is key to realizing this innovative future, according to Chronley—and that's where ISPE plays a crucial role. "There's a gap of trained human capital in our industry. ISPE is instrumental in developing careers in biopharma. ISPE brings a value proposition with the benefits we provide, including scholarship and mentoring for young professionals." He couples this observation with his encouragement and advice to emerging leaders. "Reinvent yourself relentlessly. Innovate. Careers are a playground of opportunities—be an ongoing learner. It will either inspire improvement and innovation within your field, or it will stimulate evolution to new areas of interest."

Chronley knows that in biopharma, as in any industry, there's no substitute for discipline and commitment. The grit that saw him through long cold days on heaving fishing trawlers is the same that sustained him through college—and what keeps him working hard today. But working hard isn't enough, to hear Chronley tell it. One also must work smart, and that includes making the most of education, networking, and resources. "Through those three pillars," Chronley explained, "ISPE facilitates the requirements for a successful, growing, ever-changing career."

—Paul J. Cumbo, MS, M.Litt.

By Raj Vora, PE

TEAMWORK UNLOCKS SUCCESS

Lessons from the Lacrosse Field

Across industries, the trend is toward speed to market. Whether it's meeting consumer expectations for instant service or being the first to bring an innovation to shelves, companies have plenty of incentives to make products and services available faster.

This has generally been a positive development for stakeholders throughout the architecture/engineering/construction delivery chain. Consumers get the products they want sooner. Companies and their shareholders often see better results. Contractors and suppliers—as well as the people they employ—reap nancial rewards. Traditional work ows also become leaner and more e cient and drive the entire industry forward.

Speed to market can be so appealing that it's easy to assume anything that looks leaner is automatically better. At its heart, lean production isn't about doing more with fewer resources, however; it's about bringing the best resources together, optimizing them, and breaking free of legacy workflows that have not kept pace with technology. Creating a team that looks lean but retains blind spots might actually lead to more waste.

As manufacturing changes, all of us with roles in that evolution—especially in construction and design—should be careful to

While the rationale behind trying to “lean up” construction delivery in manufacturing is sound, the logic behind omitting a construction firm needs some examination. The best way to obtain sole-source contracting remains true design-build or methods like CM/GC that integrate constructors with designers early in the process.

focus on what really constitutes lean project delivery. As the life sciences world also begins to focus on smaller, more nimble facilities, however, there are already signs that the goal of speed to market is causing some to lose sight of the best ways to build.

CREATING A CHAMPIONSHIP TEAM

As a longtime lacrosse player and fan, I admire Bill Tierney—one of the most successful coaches in NCAA Men’s Division I lacrosse. After long-term success at powerhouse Princeton University, Tierney led the University of Denver’s team to the semi nals ve times during his seven-year tenure. Tierney, who clearly created high-caliber teams, is also the source of a quotation that’s especially applicable to my work in construction: “Every game is so important, especially in a year like this with so many upsets. You can’t lose focus. After last year, I think the reminder is still clear enough.”

Construction and design may not be as ashy as college lacrosse, but having a team with the right skills and dedicated focus is the key to success in both ventures. Despite this, there is a growing trend of owners moving away from traditional construction partners and utilizing their design teams as their construction managers.

It sounds like a great lean solution, right? It seems like a chance to have fewer cooks in the kitchen, and create a more streamlined process from benchtop to business and a single-source contract solution.

This approach might sound good on paper, but project owners who follow it risk losing some of the things a partner with a core construction business brings to the table:

Technical building expertise: Too often, construction is viewed as simply executing what is on a set of drawings. In reality, contractors and construction managers have decades of field knowledge that brings amazing designs to life. In addition, complex projects with a variety of mechanical, electrical, plumbing, and process systems or cleanroom space requirements present potentially costly pitfalls. A specialized construction rm not only knows how to avoid them, but how to anticipate them.

Local market knowledge: Construction managers’ deep knowledge of and experience with local subcontractor markets can bring value throughout the construction chain that other rms cannot. In addition, local labor markets vary widely, from availability of craft and union agreements to local processes for permits. Challenges with even one of these areas can a ect project schedules and budgets.

Lessons learned: Construction rms with years of experience know where the pitfalls are, and often have the in-house expertise to help avoid them. Making the same mistake twice (or more) is the antithesis of lean delivery. As in any team sport, a rookie’s long-term success often depends on learning from seasoned veterans, the ones who already know how to avoid common errors.

A WINNING SYSTEM

While the rationale behind trying to “lean up” construction delivery in manufacturing is sound, the logic behind omitting a construction rm needs some examination. The best way to obtain sole-source contracting remains true design-build or methods like CM/GC that integrate constructors with designers early in the process. Some owners take things a step further and “lean forward” with integrated project delivery (IPD). What appeared to be a fad several years ago is now a very real project delivery system within the global life sciences industry.

Our industry has spent so much time calling these approaches “alternative delivery” that it masks their wide adoption. Putting construction, design, and engineering partners together creates the industry equivalent of a championship sports team, and allows each rm to not only focus on its strengths but also to work together toward the common goal of customer outcomes. In IPD, where each entity signs the same contract and shares the same stake in success, that cohesiveness is even more formal.

It’s natural for any project owner to want a superstar on the team. To yield the best results—a team that doesn’t just make the playo s, but can win it all—stars and key supporting players have to work together.

Project owners don’t need to cut corners in the name of speed to market. The design and construction process is not a boxing match or marathon in which an athlete is competing only for himself or herself; it’s a team sport. Putting the right team together and letting individual talents build the best workflows will ultimately bring facilities online faster and be more replicable across the industry.

About the author

Raj Vora, Life Sciences CML, DPR Construction, Inc., has nearly 20 years of experience in the A/E/C industry, with emphasis on life sciences. He has been an ISPE member since 2002.

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DATA INTEGRITY IN THE TRENCHES

A Look into the QC Laboratory

James B. Powers, Jr., and Doreen Newhouse

Pharmaceutical Engineering magazine's March–April 2016 Special Report [1] highlighted the increasing importance of data integrity for companies throughout the global GMP-regulated industry. This is especially true during health authority inspections. [2–4] Pharmaceuticals, biotech, and API manufacturers—as well as contract manufacturing organizations (CMOs) and contract laboratories—have been "in the trenches," addressing improvements to strengthen data integrity and data management over the data life cycle.

Much of the focus on data integrity (DI) by health authorities during GMP inspections has been related to quality control (QC) laboratory operations. In this article we will look at both the regulatory context and the industry response. Additionally, since the QC laboratory analyst is a key GMP role that touches data integrity, we will take a deeper look at the challenges of sustaining data integrity in that environment. We believe that a holistic approach to data governance that includes people, processes, and technology will provide the road map to sustainable data integrity.

HOW DID WE GET HERE?

Data integrity is not a new requirement. It has been and continues to be an inherent aspect of global GMP regulations. An analysis of data integrity deficiencies in FDA Warning Letters issued from 2008 to 2017 revealed both an increase in numbers and global scope as well as consistency in the findings. [2–3] When the period was expanded from 2005 to 2017, the top five types of deficiencies related to basic GMP records requirements were: [4]

- Missing or incomplete records
- Deficient system access controls (e.g., shared logins)
- Mishandled chromatography samples and data, including reprocessing, reintegration, and manual integration without proper controls
- Deleted or destroyed original records
- Audit trail deficiencies

Guidance

In response to these trends, global health authorities and professional organizations began to publish data integrity guidance documents in 2015. [5–16] These documents emphasize key principles related to robust data integrity, e.g., data life-cycle management, data governance, and "ALCOA+"* principles.

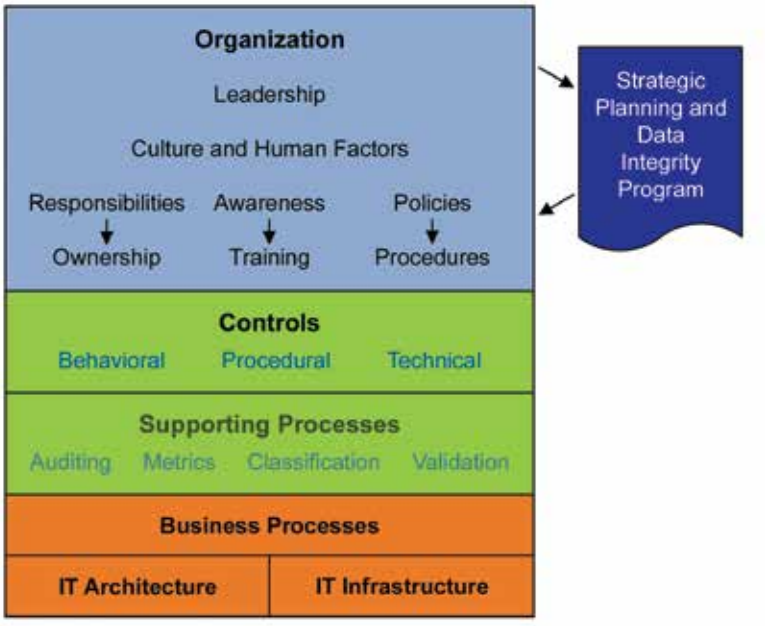
It is important to understand that preventing deliberate falsification is only one aspect of data integrity risk management—albeit a significant one. Human error and other challenges, which we will discuss later in this article, are also contributors.

Terminology

Inconsistent definitions are another factor. When comparing global regulatory guidance about data integrity, it becomes clear that terminology is not always used in a consistent way. Industry organizations have helped provide greater clarity on expectations and "how to," but inconsistencies in interpretations of the term "data integrity" remain. An analysis of "data integrity" definitions in guidance documents compared to those published in international standards for electronic records found that in most of the

* ALCOA is a framework of data standards designed to ensure integrity: attributable, legible, contemporaneous, original, and accurate. ALOCA+ also includes complete, consistent, enduring, and available.

Figure 1: Data governance elements—data protection over the full life cycle



Source: International Society of Pharmaceutical Engineering. GAMP® Guide: Records and Data Integrity. ©ISPE 2017. All rights reserved. Reprinted with permission.

We believe a holistic approach to data governance that includes people, processes, and technology will provide the road map to sustainable data integrity

guidance documents the term is used primarily to mean "data reliability" or "data quality." [17] The recently published *GAMP® Guide on Records and Data Integrity* provides a framework for consistent terminology and key concept de nitions. [16]

Leadership

Health authorities agree on management's responsibility to assure that the pharmaceutical quality system (PQS) governing the GMP environment provides e ective data integrity risk management. Figure 1 illustrates the key elements for e ective GMP data governance. [14] This holistic approach includes the organizational components of leadership and culture; controls that encompass people, process, and technology; and supporting processes such as metrics, IT architecture, and infrastructure. The purpose of such an approach is to assure that product manufacturing and testing can be reliably reconstructed from the records. Achieving reliable ALCOA+ data attributes can be considered an output of a robust data governance system such as this.

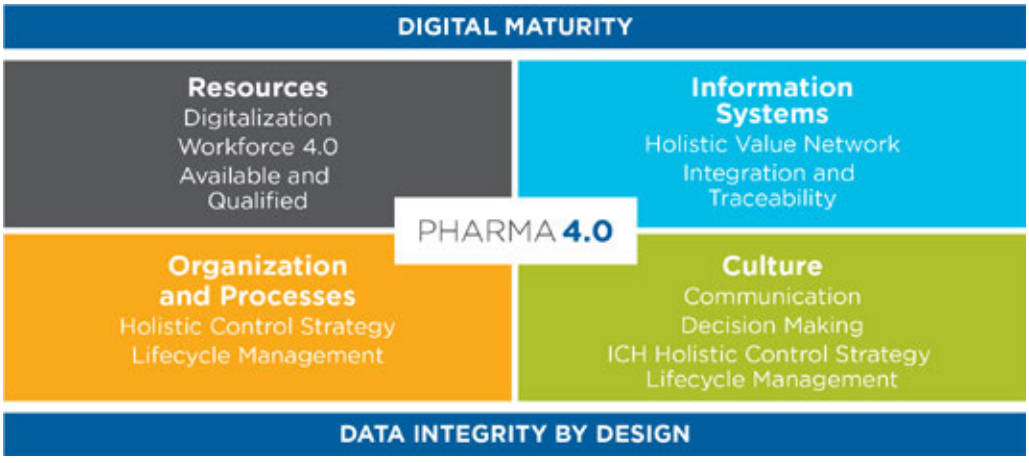
Pharma 4.0

The transition currently underway to adopt Pharma 4.0 principles and practices emphasizes digitalization of pharmaceutical manufacturing and supply chain operations in alignment with the PQS. [18] Figure 2 illustrates the four quadrants of the Pharma 4.0 operating model and its key enablers: digital maturity and data integrity by design. Although an in-depth examination of these enablers is beyond the scope of this article, we will explore aspects of how the transition to Pharma 4.0 may a ect the role of the QC laboratory analyst and the QC laboratory of the future.

DATA INTEGRITY PROGRAMS

In response to the increased regulatory focus on data integrity, many companies have established data integrity programs. During our preparation of this article in late Q3 2018, we interviewed 11 global pharmaceutical leaders responsible for such programs. Their companies represented top 20 pharmaceutical companies,

Figure 2: Pharma 4.0 Operating Model and Enablers



one generic company, and one API supplier. We wanted to gain a broader view of the challenges and learnings resulting from these e orts, as well as the leaders' perspectives on the 3- to 5-year horizon for these data integrity programs.

Several themes emerged regarding data integrity program scope:

- Most companies focused initially on QC laboratory systems and operations, then began to transition e orts to manufacturing operations, third-party CMOs, vendors, and other areas. In most cases, the corrective and preventive actions (CAPAs) generated relative to QC laboratories were still in progress.
- Most programs emphasized technology enhancements to connect and integrate laboratory equipment and systems to achieve full compliance and to minimize human error.
- Although increasing data integrity training was a common aspect of program scope, fewer companies reported a focus on building cultural excellence as part of sustaining data integrity enhancements.
- Data integrity maturity in the group of companies interviewed ranged from those struggling with limited program scope to a fully mature remediation program that has since transitioned to integrated permanent roles and practices embedded with the PQS.
- Most of the companies are in the trenches at di erent stages of detecting and remediating gaps. They expect this to continue into 2019 and beyond.

Common challenges included:

- Laboratory informatics products and tools meet system compliance requirements (e.g., 21 CFR Part 11, EU Annex 11) but fall short when it comes to meeting data integrity operational needs. Needed tools include 1) standard reports and queries for e ective and e cient reviews of data audit trails and 2) retiring spreadsheet calculations and manual transcriptions of results in favor of (master data) database con gurations.
- Balancing subject matter expert resources between daily business, data integrity enhancements, and other urgent priorities. One company, for example, shifted its focus to cybersecurity, which they perceived as a greater risk.
- Capital and labor costs for new equipment and systems and long timelines for implementation and integration.

We also noted that some companies joined with others to share learnings in informal forums. Key topics included audit trail review practices and health authority expectations during inspections.

The challenges described by the companies we interviewed indicated that most were in the trenches—i.e., focused on data integrity program CAPAs to strengthen systems and processes. Most have not yet envisioned sustaining data integrity in a future QC laboratory beyond the landscape of integrated systems.

Because the QC laboratory and QC laboratory analyst role remain primary focus areas for regulatory inspections, data integrity observations, and remediation e orts, the next sections focus on the role of the QC laboratory analyst and the data integrity challenges and risks they face every day.

QC LABORATORY ANALYST

While QC laboratories in the regulated industries operate reasonably smoothly, they can still face data integrity issues. For purposes of illustration, we have created a fictional analyst named Fabian, whose daily QC laboratory workflow is detailed, tedious, and sometimes dependent on factors that are hard to control (missing

samples or reagents, equipment failures and outdated analytical test methods). Although we will focus on a day in the life of this analyst, the information presented is relevant to other roles and functions as well, including R&D laboratory scientists, lab supervisors, and manufacturing. The pressures described in this section can occur in any laboratory over time.

Figure 3 shows the long list of complex tasks that are typically part of Fabian's day. He must complete large volumes of laboratory paper and/or electronic documentation for each sample tested. Like most QC laboratories, Fabian's productivity is measured (samples/tests completed per day) and monitored. His work is reviewed for accuracy and correctness. Documentation gaps and laboratory errors result in time-consuming investigations and CAPAs. Controls added to monitor, detect and lower data integrity risks have increased the workload of Fabian and his colleagues in the past several years. Despite this, at the end of the day, Fabian sometimes feels that his completed work is not fully trusted by his peers, company or organization leaders, auditors, or regulators.

Pressures and Challenges

Being a QC laboratory analyst is tough and tedious! Pressures come in many forms. Some are obvious; others are subtler but equally signi cant. This pressure can increase the risk to data integrity by planting seeds for data integrity failures and fraud, especially when combined with opportunity (to adjust/modify data) and rationalization (justifying fraudulent actions). Figure 4 illustrates a few of the pressures that today's GMP laboratory analyst (and laboratory leaders) often encounter.

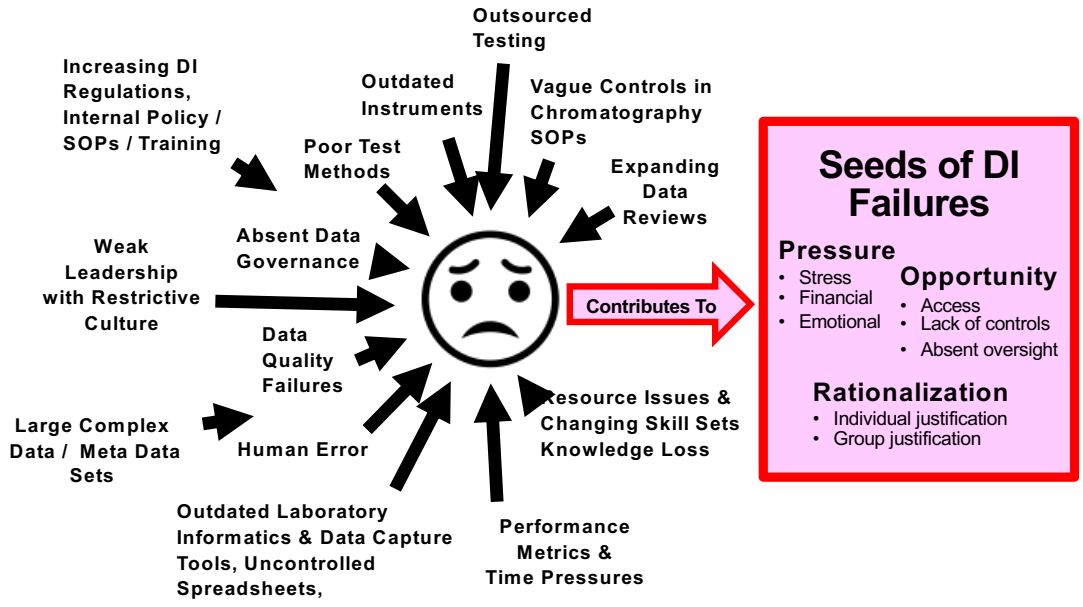
Poor and Outdated Test Methods

QC laboratories sometimes use outdated test methods (i.e., analytical, micro, environmental monitoring, sterility, container closure, immunology) typically found with mature products. The cost and time required to update these methods—including associated change controls and multi-country registration lings—can put the brakes on needed changes in some laboratories. [19] Mergers, acquisitions, and outsourced manufacturing and testing can cre-

Figure 3: QC laboratory analyst daily tasks

1. Receive sample from production
2. Record sample chain of custody in paper logbook and spreadsheet/system
3. Transfer and register samples in LIMS
4. Prepare sample labels and safety info
5. Transfer samples to testing laboratories
6. Review emails and plan workday
7. Print test documentation/worksheets
8. Collect reference standards; record metadata
9. Collect glassware and consumables
10. Collect/prepare reagents/solutions; verify expiry dates; record metadata
11. Perform daily balance check
12. Prepare equipment and instruments, verify calibration; record metadata
13. Weigh samples and standards
14. Prepare samples (dilutions/filtration); record metadata
15. Run system suitability/calibrations; record metadata
16. Run tests/instrument (overnight); record metadata
17. Attend daily shift huddle
18. Discuss change in sample priority with lab planner; switch to an urgent sample or di erent methods?
19. Capture and record test results and metadata on paper or system
20. Save all raw data files
21. Perform calculations and capture on paper or use spreadsheet
22. Update test status on wipe board
23. Review data for errors
24. Attend training session due to previous laboratory errors (CAPA)
25. Manually enter data to LIMS/SAP
26. Manually enter data into spreadsheets for trending
27. Review data compared to specs
28. Manually trend data
29. Update sample tracking spreadsheet
30. Review peer's test results and calculations for errors
31. Request OOS/LI if errors are found
32. Update usage logbooks
33. Save all sample, standard, and reagent preparations pending data review
34. Review documentation and audit trails
35. Wait for peer data verification
36. Correct errors found during data review (paper and e-Records)
37. Wait for supervisor data review
38. Correct errors found during supervisor review (paper and e-Records)
39. Receive decision: data valid
40. Clean work area
41. Stage dirty glassware for cleaning
42. Stage sample for waste disposal
43. Update sample chain of custody
44. Respond to any investigations
45. Repeat testing/remeasurement
46. Wait for results of investigation
47. Close records; file all paper data packs and notebooks

Figure 4: Laboratory analyst pressures



ate virtual and fragmented supply models and take the focus o updating old analytical methods. Another problem is test methods whose performance relies on undocumented "tribal knowledge." Analyst turnover and the use of temporary analysts in response to mergers, acquisitions, and cost reductions can accelerate the loss of this tribal knowledge and a ect test method execution. All of these situations can lead to data integrity issues.

QC laboratory analysts can nd themselves in no-win situations when they are required to use outdated test methods that generate errors and/or data quality issues. These pressures can lead to atypical behaviors, such as channeling testing to just one or two analysts, and increasing the risks of data fraud and data integrity breaches.

Weak Chromatography Procedures and Controls

While many QC laboratories rely on chromatography testing as a primary analytical technique, many standard operating procedures (SOPs) and training materials contain vague language that is subject to interpretation. Examples include no controls about disabling audit trails, or the use of manual interventions or integrations; no requirement to process samples in a certain order (system suitability, data acquisition, data analysis); no requirement to include all injections made while testing; and no sample or standard naming conventions.

Vague chromatography SOP controls can yield data integrity issues and place further pressures on the QC laboratory analyst, a concern discussed in depth by Newton and McDowall: "Management is responsible for creating a robust chromatographic procedure, and foundational policies that accompany it. These must be incorporated into training that is received by every analyst to assure consistency in practice." [20]

Work Volume, Performance Metrics, and Time Pressures

While work volume for the QC laboratory analyst typically uctuates, both high- and low-volume workloads can be stressful. Analyst performance is typically measured in several ways, including: performance (e.g., samples and/or tests per unit of time, roles completed per unit of time, batches tested per analyst, percentage of samples completed on time vs. demand), and quality, typically measured as right- rst-time (RFT) testing. If not managed properly, such metrics can induce behaviors that increase data integrity risks and underreporting of laboratory errors. [21–22]

Human Error

Although QC laboratory analysts are human and occasionally make mistakes that can lead to laboratory errors and inaccurate test results, regulators make no distinction between inadvertent human error and intentional fraud, since both have the same e ect on data integrity, product quality, and patient safety. [21] Fear of retraining and disciplinary consequences can lead to additional pressures on the laboratory analyst.

Large and Complex Data Sets

Laboratory data complexity has increased signi cantly over the past few decades, requiring more time and e ort to collect, analyze, review, and report. Simple wet chemistry testing and single-point assays have given way to complex high-performance/ultra-performance liquid chromatography analysis, which is sometimes paired with gradient columns, diode array detectors, and mass spectroscopy analysis. Large-molecule/biological products require complex plate-based analysis, biochemical testing, and genomic testing.

The growth of CMOs and contract laboratories, combined with the diversi cation of laboratory informatics tools, has added complexity to recreating records for a batch of drug product. The digital laboratory record could include elements from multiple suppliers, manufacturing processes, CMOs, and contract and internal laboratories, each with a mixture of instruments, raw data, audit trails, and analyzed and reported results. The expanded size and increased complexity of laboratory raw and processed data records put additional burdens and pressures on the laboratory analyst.

Expanding Data Reviews

Until recently, most QC SOPs contained few requirements to review laboratory record audit trails. Time, skills, and resources required have increased over the past few years as cGMP data integrity expectations expanded. "Data review" now includes test results, (multiple) audit trails, metadata, calculations, supporting static data (speci cations), trends, unreported data, repeat testing, chromatography integration parameters, etc.

The QC laboratory analyst acting in a peer or dedicated role performs the bulk of these reviews, which add new tasks to the laboratory work- ow. The percentage increase in laboratory analyst work related to expanding data integrity controls, while hard to quantify, is estimated at 10%–15%. Despite this, resources often have not expanded enough to meet the additional data review requirements; this adds more pressure on the QC laboratory analyst.

Outdated Instruments and Informatics

Cost constraints may lead to chronic underfunding or deferred funding for needed instrumentation and software updates. Outdated instruments are sometimes tied to the outdated test methods discussed previously. Older instruments can fail due to poor service, lack of parts, lack of knowledge for proper operation and/or skills required to x them. Outdated laboratory instruments with dedicated software typically do not have provisions for 21 CFR

Part 11 requirements (individual sign on, electronic records, electronic signature requirements, and support for audit trails).

Laboratory informatics tools (software applications) age along with the instruments used to acquire data. Outdated tools such as laboratory information management systems (LIMS), chromatography data systems (CDS), and stand-alone instrument systems have data integrity gaps that may include no or limited audit trails, limited user and data controls, security gaps, absent vendor support, no support for electronic records or electronic signatures, and performance and data loss gaps. These problems are further exacerbated by outdated instruments running old software on older stand-alone PCs that are not connected to a local network for data storage and whose operating systems contain added risks, including local uncontrolled data storage, direct access to modify date and time, unsupported operating systems, and no security updates.

Analysts pressured to "get the work done" even when instrument failures repeatedly disrupt testing schedules may explore workarounds or improvise to complete their work assignments. This may include recording additional information in instrument paper logbooks to make up for the lack of audit trails.

Rapidly Evolving Informatics

The number and scope of QC laboratory informatics tools available have expanded signi cantly (Figure 5). Twenty years ago, many laboratories employed basic LIMS and CDS to perform QC testing as illustrated in the left half of Figure 5. The right side of the g-ure illustrates the growing set of laboratory informatics tools, each with a broad set of functionalities that can collect, analyze, review, and report test results: robust LIMS and CDS, electronic laboratory notebooks, scienti c data management systems, and advanced analytics (e.g., genomic analysis tools and plate-based automation for immunology testing). Each system has its own analytical/electronic/paper record with its own set of audit trails and data life cycles that must be formally quali ed (e.g., GAMP validation), documented, analyzed, reviewed, reported, and managed. QC laboratory analysts need a broad set of skills to manage test results in multiple laboratory informatics systems.

Data Quality

In a review of recent data quality research across di erent industries, Redman wrote: "We estimate the cost of bad data to be 15% to 25% of revenue for most companies."[23] Yet while laboratory test result accuracy (one of the As in ALCOA+) is assumed, RFT documentation (RFTDoc) error rates for paper-based laboratory records typically range between 20% and 50%. This may be surprising to those who are unfamiliar with laboratory operations. The documentation corrections generate rework and stress for laboratory analysts.

While many QC laboratories and the analysts working in them produce quality work, the pressures can elevate data integrity risks and sow potential seeds of failure—or even fraud. Proactive steps are needed to reduce and mitigate these risks.

Trust takes years to build, seconds to break, and forever to repair

—Anonymous

KEY ENABLERS

The discussion below lists elements that contribute to a holistic and sustainable future QC laboratory environment with lower overall data integrity risks (Figure 6).

Establish Cultural Excellence

Engage QC laboratory analysts and supervisors in designing the future state to promote environments in which analysts feel comfortable sharing errors and quality issues. Encouraging cultural excellence within the laboratory and across the site, including strong leaders with a quality vision, quality mindsets, leading quality metrics, transparent reporting, and Gemba walks that cover both process and the data life cycle (as described in detail in ISPE's *Cultural Excellence Report*). [24]

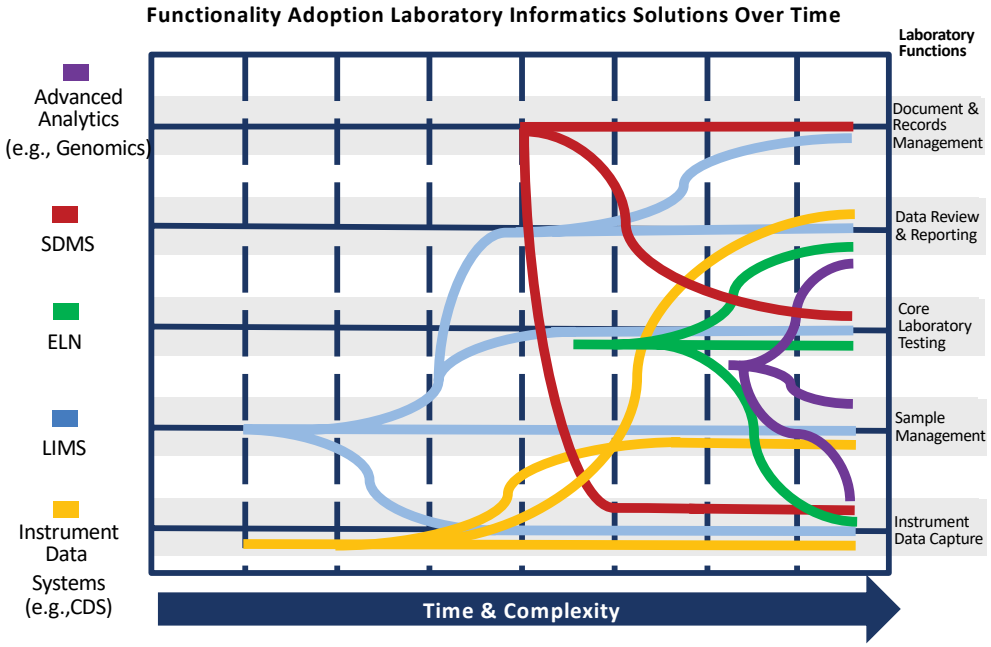
Improve Test Methods

Improving or replacing outdated and/or awed QC test methods is a critical step in providing reliable and trustworthy QC test results. Asking for analyst input and participation can identify test methods with high failure rates, weak robustness, low productivity, and safety issues. A quality risk management (QRM) approach can screen test methods, develop a business case, and prioritize what to work on rst. Test method mapping is used to identify undocumented "tribal knowledge" and improve existing SOPs. New test methods with updated analytics, instrumentation, and informatics are sometimes required. A regulatory assessment is recommended for minor changes such as wording clari cation to determine if a regulatory ling is required. Where significant changes are made, a regulatory filing assessment is required.

Update Testing SOPs and Controls

Clear, straightforward de nitions, requirements, and controls for QC testing provide a trusted environment for testing, while robust, objective testing SOPs are essential for mitigating data integrity risks. The Parenteral Drug Association Technical Report No. 80, "Data Integrity Management System for Pharmaceutical Laboratories," is recent guidance that details common chromatography

Figure 5: Laboratory informatics system evolution



E1578-18 Standard Guide for Laboratory Informatics, Figure 2, copyright ASTM International, 100 Barr Harbor Drive, West Conshohocken, PA 19428. A copy of the complete standard may be obtained from ASTM International, www.astm.org.

data processing and peak integration gaps that should be de ned and controlled in SOPs. The report also discusses microbiology testing data integrity risks that should be mitigated with strong SOPs, and includes testing for environmental monitoring, sterility, and bacterial endotoxins. [15]

Update Test Instruments

Updated laboratory instruments with improved technical controls for user account security, electronic records, and electronic signature requirements are critical for a productive and compliant laboratory. Equally important is full control of instrument parameters—including metadata capture—and control of all records generated throughout its data life cycle. Replacing outdated instruments with modern 21 CFR Part 11–compliant instruments and enabling appropriate GMP con guration lowers overall data integrity risks, reduces laboratory errors, increases reliability, and improves the work environment.

Manage Work Volume

High- or low-volume work combined with day-to-day variability comprise a big part of the pressures on today's QC laboratory analyst. Detailed data analysis and leveling solutions combined with internal customer lead-time requirements and standard work roles that are constructed and veri ed by laboratory analysts can distribute work evenly among analysts and workdays. With QC analyst participation, the result is a fair day's work for all on a consistent and repeatable basis.

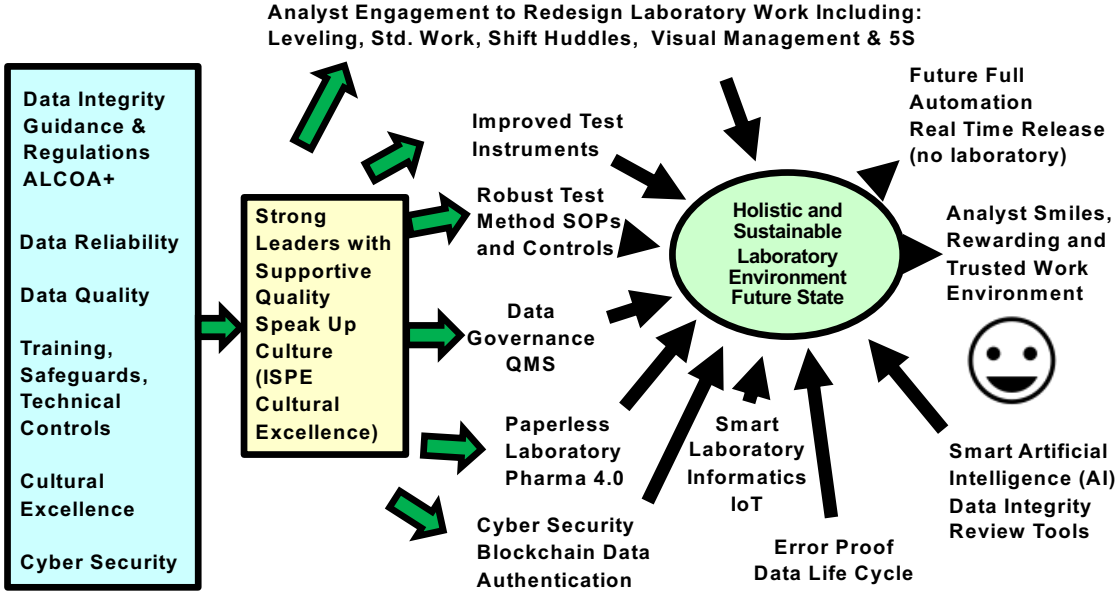
Go Beyond Human Error

An understanding of human behavior as described in James Reason's book *Human Error* [25] is the rst step in moving away from blaming and retraining analysts for laboratory errors. Root causes described as "human error" need to be traced more deeply to fully understand their origins. Examples include failures in systems, processes, and organizations; awed defenses (faulty temperature sensor in stability chamber) and error precursors (rst time performing test upon return from medical leave). Human error programs work best when incorporated into the investigation and CAPA quality systems. Given cognition limitations and published studies on human error rates, [21] an organizational culture that values and practices openness is critical to reach root causes and determine preventive measures. The full use of laboratory informatics to interface instruments and systems will signi cantly reduce human error (and data integrity risks) related to data entry, transcriptions, and other manual activities.

Expand Data Reviews

The level of detail required for comprehensive reviews of QC laboratory data continues to expand, but tools to assist the laboratory analyst with data reviews have been slow to enter the market.

Figure 6: Sustainable Laboratory Future State



Pharmaceutical companies have started to develop their own informatics tools, including simple user interfaces that with a click of a button run queries to look for data integrity issues such as alteration of raw data, repeat testing of the same sample, incomplete or missing records, substitution of test results, use of manual integration or reintegration/reprocessing of chromatography peaks, substitution of calibration curves, trial injections, non-contemporaneous dating (backdating, predating), and data deletions. A formal de nition of what is in the laboratory record (including metadata and audit trails), combined with clear de nitions of which elements are included in the review process, is a best practice. Review-by-exception approaches continue to be employed on a limited basis for low-risk test results.

Update Laboratory Informatics

Laboratory informatics have become an important element in planning, preparing, capturing, analyzing, trending, reporting, and storing laboratory test results. The ASTM E1578 Standard Guide for Laboratory Informatics was updated in 2018 to include the subjects of data integrity, arti cial intelligence, blockchain, and cloud-based platform-as-a-service and software-as-a-service tools.

Integrating informatics tools within the laboratory, with other business systems, and in some cases with external partners, has expanded the landscape and complexity of implementing and sustaining these critical tools. The large yellow circle on the left side of Figure 7 shows examples of informatics tools that can be found in today's laboratories. The blue circle on the right side shows examples of internal business tools that may exchange data with the laboratory informatics tools. The figure as a whole illustrates both the complexity and overlap between laboratory informatics tools, business systems, and external organizations.

Hospital and clinical settings that use laboratory information systems (LIS) are increasingly active in the development, production, and testing of chimeric antigen receptor (CAR) T-cell and gene-based therapies. The intricate, decentralized supply chains needed for these therapies centered on the patient (patient-manufacturer-patient) further increase the complexity of managing and reviewing their digital records. Fortunately, innovation in this space is moving forward rapidly with new processes and evolving laboratory informatics to support clinical investigations. These tools stitch together and help manage the many dispersed elements that encompass the data life cycle for CAR-T or gene-based therapies. [26]

Turning on technical controls for existing laboratory informatics solutions (i.e., LIMS/ LIS/CDS) will go a long way in reducing data integrity risks. Laboratory informatics tools provide complete record capture with minimal human data entry, thus lowering the risk of data integrity failures. As they are adopted, laboratory analyst skills required to use these tools for advanced analytic analysis of laboratory data continue to grow. Laboratory informatics vendors are also slowly developing additional technical tools to help laboratories address expanding data integrity needs.

FUTURE APPLICATIONS

Artificial Intelligence

While artificial Intelligence (AI) is in its infancy within laboratory environments, the idea of using AI to detect and lower data integrity risk is promising. AI learning includes looking at data sets, links between data, search algorithms, and variables to find new insights. AI has the potential to digest laboratory data quickly and make decisions as laboratory transactions are processed. To enable AI benefits for data integrity, AI should be integrated with laboratory informatics applications (i.e., LIMS, CDS, and Internet of Things [IoT] devices).

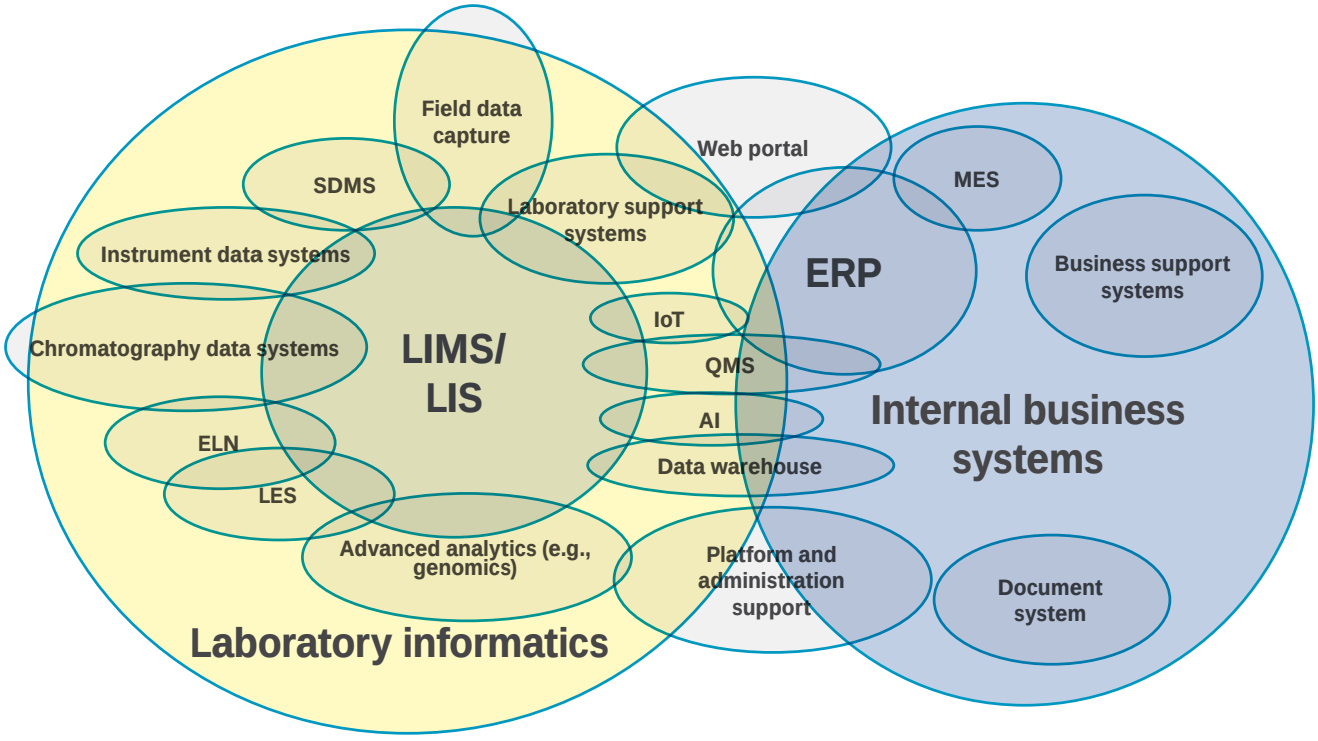
Laboratory informatics applications are beginning to embrace AI by defining, learning, and utilizing data ontologies (concepts, categories, and the relations between them) to support laboratory functions. Analyses of complex data sets such as genomics utilize AI for searches and pattern recognition. Smart tools with limited AI capabilities can assist with supportive laboratory functions and testing.

Looking to the future, laboratory informatics vendors have an opportunity to incorporate elements of AI to accelerate and improve the expanding data review requirements that support data integrity. Potential examples include: verifying data accuracy, verifying that data capture/entry is contemporaneous, recognizing outliers in a consistent flow of data from sample receipt to sample destruction, reviewing audit trails for data integrity risks, and examining data patterns for copied data, missing data, duplicate testing, manual integration of chromatography data, and test injections for chromatography testing. Future application of AI tools in laboratory environments may help laboratory analysts conduct routine testing, relieve data review workloads, and restore trust in laboratory test results.

Internet of Things

Manual recording or transcription of laboratory data remains a data integrity risk. Current practice for connecting instruments to a laboratory informatics solution is either by direct connection or through middleware. These interfacing methods remain costly and time-consuming. IoT offers a path to greater instrument connectivity with less human interaction and lower data integrity risk. Implementing IoT in the laboratory comes with its own considerations, including communication methods, security, validation, and quality of data.

Figure 7: Laboratory informatics systems integration model



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Partner, government, and organization interactions

Blockchain

Blockchain is an evolving form of data encryption that provides secure identity management and authentication of records. Blockchain is in the early phase of adoption in laboratory and medical data systems, with a focus on completed final reports (i.e., certificates of analysis), instead of individual laboratory transactions. Blockchain technology operates in a decentralized way over multiple computer servers using cryptography, distributed ledgers, smart contracts, hashed IDs, and tokenization to provide a dynamic repository of traceable and secure transactional records. Organizations are beginning to use blockchain to track and trace entire supply chains from raw materials to nal products delivered to patients. Laboratory communities are starting to experiment with blockchain to improve data portability, integrity, auditability, and security.

Transaction data stored in a blockchain is almost impossible to change or hack. Data integrity is critical for clinical trials (and all GMP laboratories), and blockchain technology provides trusted records with strong data integrity. [27] Blockchain also has the potential to change how data audits (internal and external) will be performed in the future. Another clinical application may allow data records to be shared between collaborating partners across networks. The application of blockchain technology may also help restore confidence in both the work performed and the laboratory analyst.

Cybersecurity

Cybersecurity risks overlap with data integrity risks, since connected laboratory instruments with global informatics tools and data-rich environments are potential targets for cyberattacks in the laboratory as well as the greater organizational landscape. Our

Analysts pressured to "get the work done" even when instrument failures repeatedly disrupt testing schedules may explore workarounds or improvise to complete their work assignments

interviews with data integrity leaders con rmed that formal controls must be in place and actively monitored to mitigate cybersecurity risks.

Dozens of rms worldwide were hit in the June 2017 "NotPetya" malware attack, which began as an attack on Ukraine (attributed to Russian actors) and then spread rapidly through multinational corporations (including health care companies) with operations or suppliers in Eastern Europe. Major manufacturing and laboratory operations were disrupted as entire systems, databases, and data les became inaccessible, creating signi cant disruptions and - nancial losses. [28]

NEXT STEPS

Sustaining data integrity for the long term requires diligence and creativity to keep the principles of ALCOA+ fresh in the fabric of the daily work and to help establish "a way of working" culture that values trust, integrity, and an openness to sharing failures.

The steps required to implement a holistic and sustainable future state laboratory environment that values trust and integrity vary with the organization and laboratory's maturity level. While a detailed description of the future state implementation methodology is beyond the scope of this article, the high-level steps include:

- Laboratory analyst participation
- Holistic assessment of the current laboratory state
- Mindset and behavior assessment to understand the current organizational culture
- Detailed data life-cycle review
- Technical assessment of critical laboratory processes with high data integrity risks (chromatography, micro, others) and implementation of corrective measures
- Business, QRM, and regulatory assessment and remediation of laboratory test methods and SOPs
- Business, QRM, and regulatory assessment and remediation of laboratory instruments
- Detailed data assessment of laboratory work volume followed by a detailed leveling design supported with visual management tools and metrics
- Iterative implementation of leveling and ow solutions combined with standard work role cards
- Laboratory informatics and data governance assessment, followed by future-state design using paperless laboratory and instrument integration, plus GAMP methodology for data governance and validation
- Adoption of advanced IT technologies (where appropriate) including blockchain and AI to help restore trust in laboratory data.
- Human-error training supporting laboratory investigations, CAPAs, and laboratory work ow design
- Development and implementation of cultural excellence—including process and data life cycle Gemba walks—and smart metrics to stimulate human behavioral changes and sustain data integrity.

CONCLUSIONS

Corporate data integrity programs remain in the trenches after more than three years of assessment and remediation efforts. These programs have produced many assessments and remediation deliverables, but they have not necessarily yet achieved the cultural excellence needed to sustain data integrity. Although many companies have included a focus on people in their data integrity programs, major activities in this area have been conducting awareness and SOP training. Only a few have reported including a focus on developing, monitoring, and improving organizational culture as a key element in their transition to holistic, ongoing data governance.

Some companies are struggling to sustain data integrity and are looking at alternate approaches. Continued focus on strengthening culture, improving the integration of data governance within the PQS, and embracing the Pharma 4.0 enablers of data integrity by design and digital maturity will be essential to creating the QC laboratory of the future. Behavioral change-management campaigns that strengthen culture via tools such as Gemba walks and data integrity process-risk analyses were rarely mentioned by the companies we interviewed.

The challenges and pressures faced by QC laboratory analysts to meet data management expectations contribute di culties in managing data integrity risks as well as operational e ciency and e ectiveness. We noted several key themes, including outdated tests methods and instruments; increasing work complexity and volume, especially for data reviews; performance metrics and time pressures; human error; data quality; large and complex data sets; and outdated informatics tools.

Over the past 15 years, laboratory informatics vendors have gradually improved their products to comply with 21 CFR Part 11 requirements. Current product offerings, however, fall short in some areas of what QC laboratories need to support the new operational focus on data integrity. Several companies have taken on internal IT projects to develop data review tools that support the

QC laboratory. The adoption of smart analytics and AI tools in the QC work ow o ers the potential to transform the data life cycle from capture to review, speeding overall data analysis and detection of data integrity issues. Updated laboratory informatics, AI, and blockchain tools also carry the potential to reinject trust into laboratory test results and the work of the laboratory analyst. Renewed e orts between laboratory informatics vendors, regulators, and the pharmaceutical industry are needed to address these critical business needs.

In this article we focused on the role of the QC laboratory analyst in recognition of the critical role the analyst has in assuring product quality and patient safety. The connection between a corporate culture of data integrity and the resulting bene ts to product quality and patient safety cannot be overlooked. Additional work is needed to create laboratory environments that restore trust in analysts and their test results as well as customers' faith in safe and readily available products. This requires engaged and supportive leadership that will collaborate with QC laboratory analysts to implement the best practices and minimize the pressures discussed.

The QC laboratory analyst needs our help to create a new laboratory environment that delivers consistent high-quality test results that are trusted and valued by our customers.

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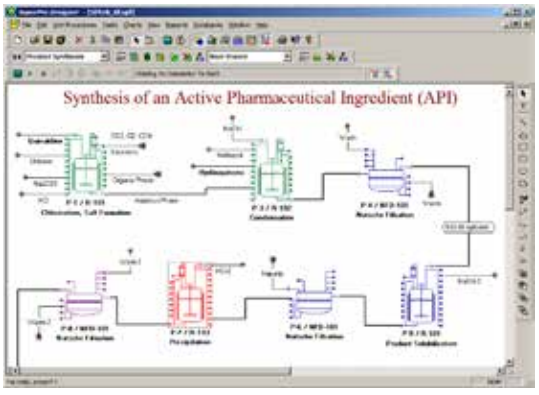

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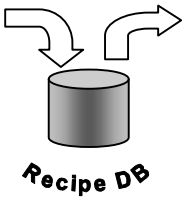

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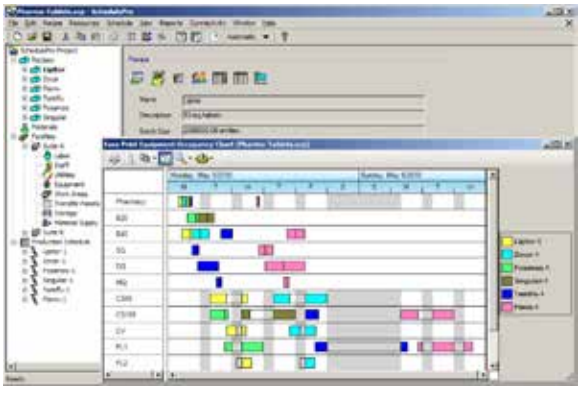

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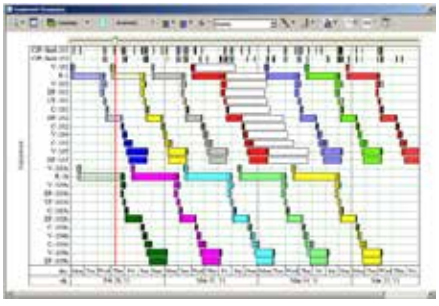

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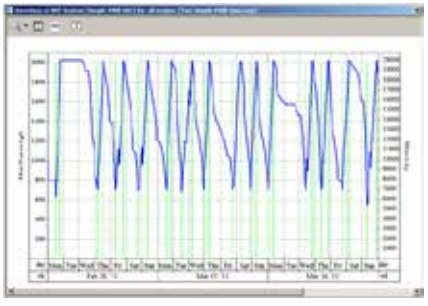

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DATA INTEGRITY
Beyond the Lab

Nuala Calnan, PhD, and James Davidson, PhD

The 2018 ISPE Quality Manufacturing Conference, held 4–6 June 2018 in Arlington, Virginia, included a well-attended session entitled "Data Integrity—Beyond the Lab," which reaffirmed continued focus from both industry and regulators on this critical element of assuring product quality and patient safety.

The program, chaired by James Davidson, PhD, Vice President, Science and Technology, Lachman Consultant Services, Inc., included a variety of perspectives shared by Paula Katz, FDA regulatory attorney and former director of the agency's Office of Manufacturing Quality; Aidan Harrington, PhD, Senior Consultant, DPS Group; and Nuala Calnan, PhD, Senior Associate, Lachman Consultant Services, Inc. The session concluded with a lively audience participation session, in which contributions from both the podium and the floor confirmed that concerns related to data integrity challenges and risks extend beyond the lab, onto the manufacturing shop floor, and into the supply chain.

TIP OF THE ICEBERG

Katz reminded participants that ensuring data integrity is an important component of industry's responsibility to ensure the safety, efficacy, and quality of drugs, and of the FDA's ability to protect public health. Data integrity underpins cGMP, the minimum standard required to assure product quality, and lapses can obscure other problems. [1] Data integrity issues unearthed during an inspection raise a red flag about the integrity of other quality practices, the level of control and oversight by management, and the levels of qualification, training, and access of frontline staff who may consciously or unconsciously impact data quality and integrity.

Data integrity continues to be a factor in a significant portion of OMQ Warning Letters (WLs), she said. Sharing FDA data for FY 2017 and Q1 2018, Katz showed that data integrity shortcomings appear in just under 50% of all WLs issued. Furthermore, data for FY 2015–FY 2017 show that the detection of data integrity issues during regulatory inspections continues to rise, confirming that they remain a global challenge for the industry. This is despite the fact that five years have elapsed since the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) announced its expectation regarding self-inspection and data integrity in a December 2013 news item [4].

DEEP AND WIDE PERSPECTIVE

An examination undertaken by the authors of recently published data integrity deficiencies from both FDA WLs and EU Statements of Non-Compliance shows that a much broader range of ALCOA+ issues extend well beyond the lab, including:

- Data quality, security, or integrity issues with batch production and control records
- Record review practices in general
- Falsified management oversight on follow-up and closeout of commitments given in earlier inspections
- Incomplete or falsified recording, review, and closeout of deviations and investigations in aspects of the pharmaceutical quality system
- Control and use of automatic, electronic, and computerized systems across the plant
- Falsified cold-chain records*
- Falsified contamination control data associated with the production areas
- Falsified cleaning records for production equipment

This litany of failures highlights the need for a broader industry perspective when examining potential weaknesses in production systems and business processes, including an honest review of how they operate within their organizations.

* See "QP Not Present in Company: Prohibition of Supply," EU NCR Report 2017090955 by the Danish Medicines Agency for EuroPharma. This indicates that not only are inspectors seeking data integrity infringements "beyond the lab" but they are also looking at it beyond the shop floor and into the supply chain. https://www.gmp-compliance.org/gmp-news/qp-not-present-in-company-prohibition-of-supply

THE ROLE OF CORPORATE CULTURE

It could be said that industry's response to date has largely focused on weaknesses in the technology platforms and systems in use—most specifically in the quality control laboratory—by driving data integrity programs that focus on gap assessments of physical equipment and computerized systems to identify mitigation requirements. What has perhaps been overlooked in the pressure to complete the assessment work is the signi cant role that the prevalent culture within an organization can play in identifying and preventing data integrity risks.

Organizational culture directly in uences day-to-day behaviors and actions, giving rise to data quality and integrity outcomes that matter to the patient and ultimately to the business. Furthermore, responsibility for the health of an organization's culture lies rmly with its leadership. When leaders have a clear understanding of the desired culture and behaviors, they can consciously and more e ectively in uence employees by their own behavior. Leaders can achieve this by how they allow, reward, and model the desired behaviors for their associates. [5]

One of the rst steps for success is to ensure that both corporate and site leadership are aware of and uent in the increasing regulatory expectation for good data governance. They are then more likely to in uence their organization toward the necessary actions. A clearly communicated good data governance program enables the entire organization to understand the desired state of protecting patient safety, ensuring product quality, and understanding the role of data integrity. Leaders should share this message broadly and frequently within the organization, both formally and informally. It is essential that they return frequently to the message to sustain behaviors and rea rm the importance of data quality to overall product quality.

Leaders are also responsible for promoting an environment that is open and free from blame or fear, where ideas to improve quality and data integrity compliance are welcome, and where employees are not afraid to voice data integrity concerns. Many integrity breaches are not intentional, and if employees discover vulnerabilities, they should not be afraid to raise and address them. This "speak-up" culture is a key success factor that mobilizes the entire workforce to seek out and identify potential data integrity issues. This spreads the burden and increases opportunities for success, rather than leaving the task to the data integrity subject matter expert team.

DATA GEMBA

During the June conference, Dr. Nuala Calnan presented a very practical and e ective way to drive the message right down to the shop oor, the lab bench, and the warehouse: Consider introducing the practice of routine data Gemba walks as a means to discuss and highlight data integrity risks. Gemba is a well-known operational excellence practice (which may be either formal or informal) of regular management visits to the shop oor to observe, assess, listen, and coach employees on issues of quality improvement.

Gemba walks confirm that desired quality behaviors are practiced on a day-to-day basis, and that opportunities for continuous improvement are routinely identi ed and implemented, as appropriate. They o er a safe way to raise "speak-up" concerns or issues, and maintain focus on the importance of data integrity to overall quality outcomes for the area. Data Gemba can be planned either for a physical area or by walking the data life cycle of a critical record through the facility and engaging frontline staff to share their insights. They offer a much broader, alternative perspective than that found by executing asset register assessments on a system-by-system basis.

The new *GAMP® RDI Good Practice Guide: Data Integrity—Key Concepts* [6] includes a data Gemba checklist template that o ers both leader self-learning and coaching questions that can be used during a data-integrity-focused Gemba walk.

Nuala Calnan

James Davidson

UNDERSTANDING THE DAM DATA!

A fundamental consideration in the proactive communication of data integrity risks is to ensure that everyone in the organization understands what is meant by the term "data" with respect to good data governance and data integrity. A common problem is that the raw data (or result le) is backed up and available, but metadata and associated audit trail les are not secured as part of routine backups. When we talk about "data," therefore, it is helpful to think about it as the "DAM" data (raw Data, Audit trail, and Metadata). This can serve as a reminder that ALCOA+ principles should ensure that all aspects of the raw data, audit trail, and metadata are complete, consistent, enduring, and available.

This can be a challenge for many older plant oor computerized systems, where backup and archive procedures may capture raw data, but the metadata and associated audit trail for that record are often stored in di erent areas of the system architecture or le structure. It's important to remember that the goal of retaining and securing data is to be able to recreate the associated records; this cannot be achieved if the metadata and the audit trail are not also retained and linked to the raw data.

Some older SCADA,* building management, and stand-alone systems such as PLC-controlled autoclaves, fridges, and freezers also present challenges in terms of capability to meet audit trail review requirements.

AUDIT TRAIL REVIEW EXPECTATIONS

At the June conference, Dr. Aidan Harrington, Senior Consultant, DPS Group, explained that audit trails need to be "available, convertible into a generally intelligible form, and regularly reviewed." [2] Because audit trails tell us WHO did WHAT, WHEN, they should be capable of doing so automatically and contemporaneously. Harrington also noted that audit trails should ideally also tell us WHY the user undertook the action. In principle, he said, audit trails have two purposes:

1. They provide a history for the data, which helps decide if the data can be trusted.
2. They should deter wrongdoing.

Harrington added a cautionary note, however: Without adequate review, audit trails provide no meaningful deterrent. For many of the older systems mentioned above, ensuring that the audit trail is both accessible and available for routine review presents real challenges for industry.

In looking across the range of regulatory guidance on audit trails, from CFR 21 Part 11 [9] right through to the latest MHRA GxP guidance, [7] Harrington pointed to the confusing variety of terms used to describe how frequently audit trails should be reviewed: "regularly," "adequately," "periodically," and "routinely." Navigating a path through these options requires a robust risk assessment to determine the review period relevant to the intended use of the system in question.

Evaluating the di erent purposes of such reviews should also be part of the risk assessment. A likely scenario could include routine review of the data audit trail associated with a critical record (e.g., reviewing audit trails for nonconformance events associated with each batch record created). Beyond that, there may also need to be periodic checks of the audit trail or technical system logs, which are random or targeted to con rm correct, ongoing system operation by all user groups who have access to a given system, e.g., user, reviewer, system administrator.

Recent guidance documents [7–8] acknowledge that reviewing audit trails on many legacy systems will present a burden that is not sustainable in the longer term. They recommend that a more appropriate way to manage this burden may be to establish validated exception reports that identify and document "predetermined 'abnormal' data or actions, that require further attention or investigation by the data reviewer." [7] The PIC/S guidance goes further to recommend that "companies should endeavor to purchase and upgrade software that includes electronic audit trail functionality." [8] Until such time as the systems in use have been upgraded or replaced, it is important not to neglect the expectations for audit trail review and to implement practical "alternative arrangements to verify the veracity of data, e.g., administrative procedures, secondary checks and controls." [7]

THIRD-PARTY AND OUTSOURCED SERVICES

Finally, it is crucial that the control measures implemented for critical data are not myopically applied only to systems and personnel within the boundaries of the organization. Given the fragmented and complex nature of current pharmaceutical supply chains, it is essential that traditional supplier quality agreements be updated to re ect clear roles and responsibilities related to each data life-cycle activity. Furthermore, supplier and third-party auditing programs should routinely include evidence of good data governance in the day-to-day practices.

It is clear that the extent and impact of data integrity expectations has well and truly extended beyond the lab. Make sure, therefore, that your e orts across your product life cycles are prioritized according to your actual risks.

* Supervisory control and data acquisition systems

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DATA INTEGRITY:
A Vertical Journey

Alessandro Linciano and Antonio Buendia

Data is an important factor that is reshaping the pharmaceutical industry and triggering significant innovation. Vertical integration of equipment can represent an optimal solution to manage the increasing flow of data e□ciently, innovate the manufacturing environment, and fulfill data integrity (DI) requirements. Regulators and health agencies are strongly enforcing DI-related requirements [1–2] and therefore have increased focus on how companies are managing data over its entire life cycle.

Guidelines and regulations [3–5] can help companies avoid unacceptable DI risk to product quality, patient safety, and public health. Original equipment manufacturers (OEMs) and equipment suppliers are updating their portfolios to deliver to market-compliant solutions. However, the lack of standards and increasing customer pressure on OEMs could lead to heavily customized and ine cient stand-alone solutions.

We suggest that vertical integration [6] of equipment represents a pragmatic and realistic concept that can dramatically simplify equipment speci cation and improve e ciency, reduce risk, facilitate training, and optimize support for equipment and personnel in the working environment. Vertical integration allows the segregation and specialization of functions as data reports, data storage, and data generation. This allows machines and personnel to focus on producing high-quality medicine in an e cient manner.

We also present a lter integrity tester case study to highlight the di erences between stand-alone solutions and vertical integration.

DATA INTEGRITY REQUIREMENTS AND THE CURRENT TECHNOLOGY LANDSCAPE

Big data, digitalization, arti cial intelligence, cloud computing, Industry 4.0: These are just few of the buzzwords of this new industrial revolution. Data are embedded in our everyday life, representing a fundamental part of our work. Every day we perform tasks with data: We create, update, share, connect, upload, analyze, manipulate, secure, and store data. The way we manage data can make a signi cant di erence.


Alessandro Linciano


Antonio Buendia

Every day we make decisions and base the quality of products on data, understanding always that mishandling might compromise patients' access to safe medication. But how can we guarantee that a safe environment and a strong culture will properly manage data, ensure high quality standards, and improve e ciency, especially when the businesses constantly pressures the manufacturing environment to optimize cost? DI requirements represent an environment in which solutions and ideas can evolve and be developed to manage, control, and compliantly use this increasing ow of data.

Figure 1: Holistic data integrity approach

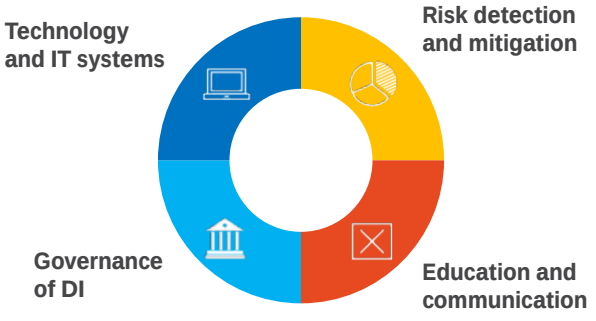


Figure 2: Stand-alone system vs. vertical integration

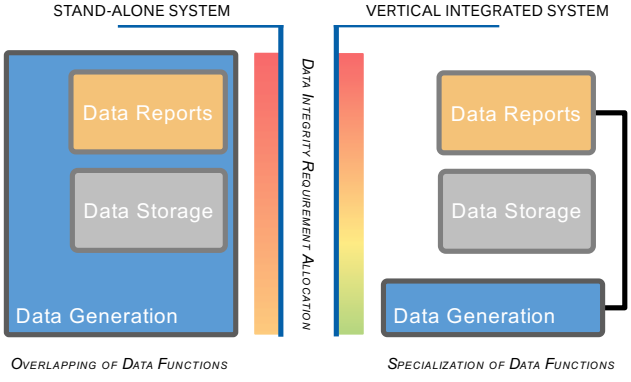


Image provided courtesy of Pall Corp., Sotax, Belimed, IMA, and Fette

The Novartis Data Integrity Program supports associates in all aspects of the business with solid DI governance by proactively detecting and mitigating risk, facilitating communication, promoting education with di erent tools and learning levels, and improving technologies and systems. DI cannot be managed in silos: Our approach can ensure success not only in developing and implementing DI-compliant solutions, but also in controlling and sustaining them (Figure 1).

The well-known ALCOA+ acronym defines a framework of standards designed to ensure data integrity. ALCOA refers to data that is attributable, legible, contemporaneous, original, and accurate; the "plus" adds complete, consistent, enduring, and available. These attributes can be translated into process and technical requirements and later into technical features.

In addition, guidelines such as the ISPE *GAMP® Guide for Records & Data Integrity* [7] have been published to help companies address the DI expectations of regulators and health agencies. OEMs and equipment suppliers are currently updating their portfolios to deliver compliant equipment to the market. Discussions are still ongoing, however, and the lack of standards across the market might lead to customized stand-alone solutions driven mainly by companies' subjective interpretation of DI requisites.

Historically, the stand-alone concept has been the most common equipment-design approach used in the pharmaceutical manufacturing environment, allocating the tasks to generate, store, and report data internally. All processes, as well as business, technical, and regulatory requirements should be ful lled by the equipment or system. When this is not feasible, procedural controls should compensate.

Considering each piece of equipment as an autonomous and an independent "island" can lead to complexity and ine ciency on a crowded manufacturing shop oor. At the same time, new technologies offer solutions and opportunities that were previously restricted to speci c areas or businesses. Recent progress on networks, historians, data lakes, interfaces, and connectivity protocols has been impressive. [8] Some of these technologies enable vertical integration of equipment systems and processes.

Vertical integration solutions are already on the market and achievable through standard components. Once a company has de ned a strategy for selecting and adopting upper-level systems, equipment only needs the required interfaces to communicate with them. These systems allow the separation and specialization of such functions as data reports, data storage, and data generation. DI requirements can also be tailored to the systems. Conversely, stand-alone equipment could be designed to have all these systems built-in and fully integrated, with the goal that requirements should be ful lled by the equipment (Figure 2).

A lter integrity tester case study will compare the stand-alone concept to vertical integration.

CASE STUDY

Stand-Alone Systems

Regulators and health agencies have recently increased their focus on lter integrity testers, particularly for DI requirements. Access controls and audit trail functionalities are often the major gaps identi ed during inspections.

Filter integrity tests represent a critical unit operation commonly employed in the pharmaceutical industry. They are subject to detailed requirements such as the FDA "Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice" guidance. [9] A satisfactory result provides assurance that the nal product is sterile and therefore acceptable for human use.

As part of the normal use of testing equipment, an operator performs a test on a lter (data generation), data are stored internally (record), and the operator usually collects a summary of test results (report). Depending on the features of the model, these activities can be fully or partially automated. However, ensuring integrity of the data that are generated, stored, and extrapolated is fundamental.

In a high-level automated filter integrity tester, ALCOA+

Figure 3: Stand-alone system

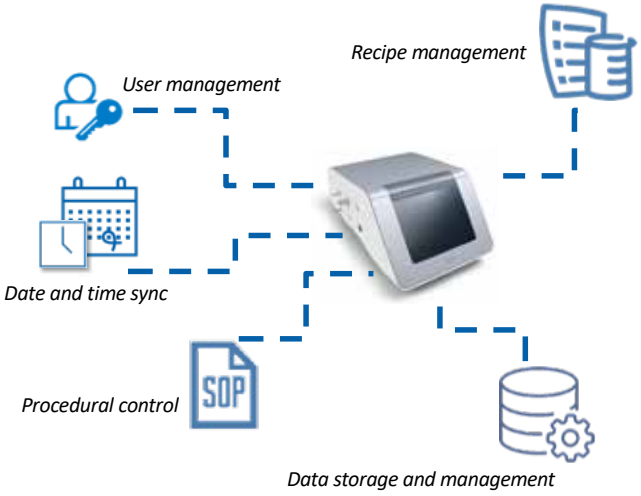


Image provided courtesy of Pall Corporation

Figure 4: Vertical integration

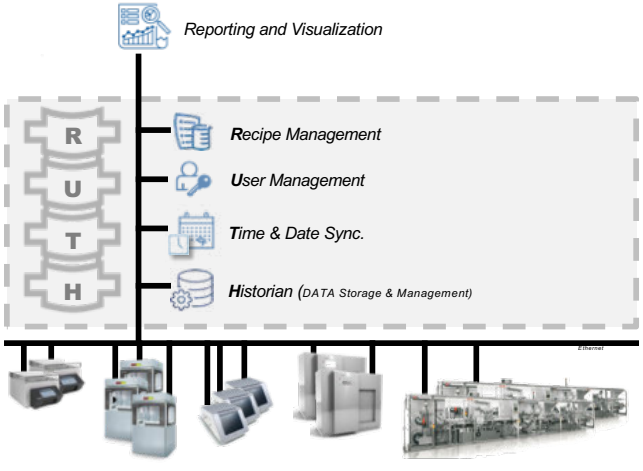


Image provided courtesy of Pall Corp., Sotax, Belimed, IMA, and Fette

standards might translate into advanced access control characteristics such as unique user IDs and passwords, and access privileges designed to separate duties. Adequate recipe (transactional data) management, date–time settings, and a local storage system capable of containing all data generated should also be embedded. Equipment software should guarantee an integrated audit trail and customizable reporting functionalities. An SOP should also be associated with the equipment (Figure 3).

In a single manufacturing plant, several lter integrity testers are often operative. Allocating all of these requirements in each stand-alone unit might lead to a fragmented, ine cient, and expensive process that is complicated to qualify and maintain within the working environment. Risk of data manipulation, probability of mistakes, training requirements, and need for supervision must be considered and properly managed for each piece of equipment.

This stand-alone concept can be applied to all equipment on the shop floor, with variances influenced by specific process requirements and technological limits. The complexity can increase with equipment, software, and functionalities from different manufacturers. Large manufacturing networks across multiple countries and technological platforms can add additional levels of complexity.

Equipment standardization can reduce the variety of models, vendors, and systems, but variation cannot be eliminated. Vertical integration allows equipment and software from di erent manufacturers to operate together e ciently while achieving compliance with health authority regulations. Each vertically integrated unit is connected to a centralized "backbone" system where good practice (GxP) data and associated management controls are incorporated.

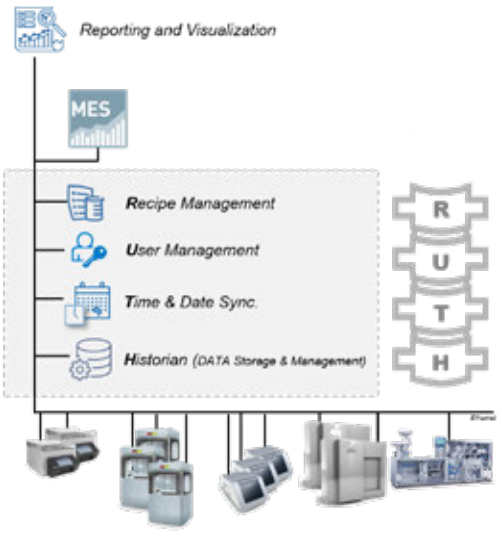
Though it may be considered similar to a distributed control system, vertical integration does not rely on central operator control but on interfaces that allow the automatic exchange of data. The bene t of vertical integration can be explained using the example of our lter integrity tester.

As part of a standardization program, Novartis, in association with Pall Life Sciences, developed a lter integrity tester unit that leverages industry standards (domain controller, OPC connectivity, [10] historian, storage, etc.) to integrate the working environment vertically. Upper-level systems were selected and standardized. The unit is accessed via unique user login credentials, with passwords that are automatically maintained and authenticated (Figure 4).

Recipes are managed by the central management system and recalled from each unit during operation. Date and time are centrally synchronized. Data is stored in a centralized system (historian). The operator can use the equipment to perform the test (data generation), transmit the data to the historian (record), then use a third application to generate an electronic summary and present it on the screen (report).

Vertical integration reduces DI risks at the equipment level, and permits compliance e orts to be focused on a few standardized upper-level systems. In a certain way, adopting the vertical integration concept makes the equipment "lighter," leaving it as only a data generator. Maximum bene t can be achieved once the concept is applied to all equipment operative in the manufacturing plant.

Figure 5: RUTH “backbone” allows e cient vertical integration



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It’s important to know who was running the equipment and who performed which operation

Vertical Integration

The vertical integration concept defines a new and important equipment characteristic: The interface is enabled to extract data in a way that allows it to be handled by the upper-level systems. The number of interfaces required is directly linked to the question “Do we need to extract *all* the data from the equipment or just di erent data sets with di erent characteristics?” The RUTH (recipe, user, time, history) concept o ers an answer to this question and de nes the data that needs to be extracted (Figure 5).

Recipe

The “recipe” is transactional data related to manufacturing order, initial equipment setup, or orchestration (interaction with other pieces of equipment). Recipe data con gurations are controlled, approved, and stored in a standard recipe management (SRM) system that controls the creation, change, and approval of master recipe data by authorized operators, based on their roles. The SRM maintains the different versions and storage of master recipes. Prior to starting a process, the operator initiates the SRM to set the batch information and selects the recipe to use in the equipment. Only one recipe is available in the equipment at any time. The historian is the connecting link between the SRM and equipment for data transfer. It maintains the recipe data transaction associated with the batch produced.

User Authentication

It’s important to know who was running the equipment and who performed which operation. The domain controller maintains and automatically authenticates a central list of unique user accounts and passwords, with privileges de ned by login to limit activities. Additionally, it allows for a single control of all users and password policies across all the machines, so any kind of “reporting”—viewing who logged in, when, and why—can be done easily. Operational executions, entries, and actions are linked to user ID logins and recorded in the historian.

Time

Time refers to when relevant events occur. It is synchronized to central time at the domain controller. Date and time for the equipment reference to the domain controller system time to assure accuracy across equipment.

History

The historian is the heart of vertical integration design and the only source of data storage. Equipment process events and data changes can be reconstructed through its records. Con gurations and records are audit-trailed and protected from any change. Data is distributed to report generation systems and can be extracted by other reporting and data visualization systems to support various plant operations for GxP and non-GxP usage.

CONCLUSION

The vertical integration concept can dramatically reduce the e ort to meet regulatory requirements and expectations in an e cient and advanced way. A single and harmonized RUTH “backbone” speci cation can allow an easy and e cient vertical integration of every piece of equipment. ALCOA+ data requirements can be ful lled almost entirely by the backbone, reducing overall e ort and cost to develop, implement, qualify, and maintain the equipment in the working environment. Because energy is not being used to manage silos of data, vertical integration frees both machines and personnel to focus on what they need to do: produce high-quality medicines in an e cient manner.

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SOUTH AFRICAN PHARMACEUTICAL INDUSTRY

Workforce Appraisal and Proposed Development Strategy

Dr. Mothobi Godfrey Keele and Douglas W. Oliver DSc, PhD

The past two decades have changed the pharmaceutical sector and health care delivery in both developed and emerging economies. The increasing use of generic medicines globally, [1] the consolidation of manufacturing into centers of excellence—mainly in Asia—and evolution of supply chains have been driven by rising demand for health care, decreasing budgets, and pressures to drive medicine prices down. [1–2] The emphasis on improved health outcomes—especially for women, children, and those with HIV/AIDS—further increased demand for medicines, particularly in emerging economies on the African continent.

The global pharmaceutical market, valued at $1.1 trillion in 2017, [3] is expected to grow to $1.4 trillion by 2020, representing a 4.2% compound annual growth rate (CAGR). Sub-Saharan Africa is expected to lead the trajectory at a rate of 7.5% CAGR. [3] The South African pharmaceutical market was valued at $3.2 billion in 2017, making it the biggest in Africa (ahead of Nigeria, Egypt, and Kenya). [4]

The Department of Trade and Industry (DTI) reports, however, that the country's import penetration rate for pharmaceuticals (the ratio of pharmaceutical imports to exports) is a staggering 65% [5] and growing disproportionately. According to Quantec, a leading consultancy on economic and financial data, the pharmaceutical trade deficit totaled $15.35 billion between 1993 and 2017. [6] This led to the pharmaceutical industry being the fifth leading driver of the national trade deficit.[5]

South Africa's pharmaceutical trade deficit can be attributed to a considerable shrinkage of the country's pharmaceutical manufacturing capacity: 37 plants closed in the late 1990s and early 2000s. [5] The country's weak pharmaceutical industry is due to factors such as a lack of access (perceived or real) to capital, tariff structures that favor low-cost imports, and an insufficiently skilled labor force. The latter was well documented in a 2011 study commissioned by the DTI to investigate the human capital outlook within the domestic pharmaceutical industry. The study highlighted considerable constraints as well as the lack of a coherent, evidence-based, demand-driven skills development strategy for the sector. [7]

POLICY DEVELOPMENTS

Following the advent of democracy in South Africa in 1994, the 1996 Constitution declared that access to adequate health care (including medicines) is a human right and describes the state's responsibility to ensure that sound regulations and laws promote affordability and improve access to health care (including medi-

cines). The key policy objective of the 1997 "White Paper for the Transformation of the Health System in South Africa" was to promote equity and accessibility to health services. Pharmaceutical care was dealt with extensively in a document called the National Drug Policy (NDP), part of the White Paper addenda that guided the recalibration of the policy frameworks from the previous segregated health care system.[8]

As depicted in Table A, wide-ranging legislative reforms were enacted on both the demand and the supply sides of the pharmaceutical industry to promote access to medicines. Inadvertently, some of the legislative reforms had a profound impact on the pharmaceutical human capital in the country.

Section 22F of the Medicines Act, for example, allows generic substitution; the Patents Act amendment allows generics to be registered while the original patent is still valid. These pro-generic legislative reforms led to an in ux of generic drug applications at the Medicines Control Council (MCC), then the South African regulatory authority. The increase in drug applications created considerable challenges for the council's ability to process applications, resulting in drug registration backlogs. These delays deny patients timely access to a ordable, high-quality, safe, and e cacious medicines. [9–10]

RECONFIGURATION OF THE PHARMACEUTICAL LANDSCAPE

Key developments in the South African health care system are likely to have a considerable impact on the pharmaceutical workforce. These include the National Health Insurance (NHI), the South African model of universal health coverage, which has been in a pilot phase since 2012. [11] The NHI is intended to remove barriers to health care access, including medicines. This is expected to signi cantly increase the consumption of medicines, and will likely exert pressure on the supply side of the fragile market, which relies on pharmaceutical imports.

The South African Health Products Regulatory Authority (SAHPRA) has been established to recalibrate the local pharmaceutical industry. Introduced in 2018, SAHPRA replaced the 50-year-old MCC, which had not kept up with legislative changes. Registration delays spanning an average of three years or longer had become an industry norm owing to the in ux of registration applications.[9] SAHPRA is expected to improve e ciencies and reduce timelines for medicine registrations. This goal is unlikely to be realized, however, unless agile skills development and retention strategies are adopted by the agency and in industry.

SKILLS DEVELOPMENT STRATEGY PROPOSAL

In its Industrial Policy Action Plan (IPAP), the South African government has designated the pharmaceutical industry as a priority sector and has installed several mechanisms and measures that seek to increase local production of pharmaceuticals.[5] To adequately address this challenge the DTI, in partnership with the United Nations Industrial Development Organization, convened a multi-stakeholder consultative forum in 2015 to establish a cutting-edge skills development strategy for the sector. Contributions were solicited from a broad range of actors—policymakers, academicians, pharmaceutical manufacturers, the regulatory body, and various national government departments.


Mothobi Godfrey Keele


Douglas W. Oliver

In aligning with Agenda 2030 (the United Nations' Sustainable Development Goals), National Development Plan for South Africa, and the South African Pharmacy Council, the meeting developed its own version of Vision 2030. Industry stakeholders envisioned the South African pharmaceutical industry in 2030 as "a globally competitive pharmaceutical manufacturing industry that is able to supply the majority of its requirements for cost e ective high-quality medicines."

As depicted in Table B, a broad range of strategic skills development objectives were proposed at the forum. Some of the most critical were industry concerns about the ill-preparedness of pharmacy graduates for pharmaceutical manufacturing.

LEGISLATION AND REGULATION

South Africa's pharmaceutical industry employs pharmacists in a wide range of positions such as production, regulatory affairs, quality assurance, responsible pharmacists, etc. National regulation dictates that pharmacies, including manufacturing pharmacies, should be under a custodianship of a responsible pharmacist (RP), [12] the equivalent of a "qualified person." [13] An array of sta ng types will be required to prepare RPs and other pharmacists for their roles in the pharmaceutical industry, even as the NHI and SAHPRA are likely to have a profound e ect on the pharmaceutical workforce.

It is imperative that new cadres of pharmacy personnel such as pharmacy technicians, pharmacy technical assistants, [14] and specialist pharmacists [15–16] account for the competencies required by the pharmaceutical industry. Additionally, because the pharmaceutical industry is a knowledge economy, such recon guration must support Industry 4.0. Mechanisms are required to ful ll the role that the now-defunct Regulatory Science Institute was earmarked to fulfill. Professional associations, academia, regulatory authorities and other critical stakeholders should collaborate to craft a cutting-edge skills development strategy, then oversee its execution and swift implementation.

Table A: Legislative framework for the South African pharmaceutical industry

The Constitution of the Republic of South Africa, 1996	
Section 27(1)	Everyone has the right to have access to health care services (Bill of Rights)
Section 27(2)	The state must take reasonable legislative and other measures, within its available resources, to achieve the progressive realization of each of these rights (Bill of Rights)
White Paper on the Transformation of the Health System in South Africa	
Goals & Objectives	To promote equity, accessibility and utilization of health services
	To extend the availability and ensure the appropriateness of the services
National Drug Policy of the Republic of South Africa	
Health Objectives	To ensure the availability and accessibility of essential drugs to all citizens
Economic Objectives	To lower the cost of drugs in both the private and public sectors (by developing specific strategies to increase the use of generics in South Africa)
National Objectives	To support the development of the local pharmaceutical industry and the local production of essential drugs
Medicines and Related Substances Act (No. 101 of 1965 as Amended)	
Section 15C	Made provisions for parallel importation of medicines that are still under patent to South Africa for public sector
Section 18A	Forbids supply of medicines in terms of bonus, rebates, and incentives schemes
Section 18B	Forbids the sampling of medicines
Section 22A	Control of medicines and scheduled substances
Section 22C 1(b)	Empowers the government, through the MCC, to prescribe the standard for manufacture of medicines in South Africa: PIC/S
Section 22F	Makes it mandatory for the pharmacists to inform patients of generic equivalents of the prescribed drug
Section 22G	Made a provision for the introduction of the transparent pricing system for medicines based on single exit price
Section 22G(2)	Made provisions for regulation of dispensing fees and capping of logistics fees
Regulations Relating to a Transparent Pricing System for Medicines and Scheduled Substances, Medicines Act (No. 101 of 1965)	
Regulation 5(2)(e)	Made provisions for benchmarking of pharmaceutical (innovator products) prices internationally
Regulation 14(5)	Made provisions for use of pharmacoeconomic studies in support of price
Patents Act (No. 57 of 1978)	
Section 46(1)	Stipulates a duration for which a patent remains in force as 20 years
Section 69(A)	Provides for limitations to intellectual property by allowing registration of generics prior to patent expiry
Regulations in terms of the Medical Schemes Act (No. 131 of 1998)	
Regulation 8	Makes a provision for implementation of cost-containment strategies such as the use of formularies and reference price lists

SUMMARY AND CONCLUSION

Aligning the current legislative framework, recalibration of the enablers and drivers of health care, along with increased demand for pharmaceuticals has the potential to create opportunities for advancing the South African pharmaceutical manufacturing industry. Actions aimed at cutting-edge skills development in the face of the changing pharmaceutical landscape are urgently required. The development of a focused and e ective sector strategic plan should encompass key stakeholders such as the national government, academia, pharmaceutical manufacturers, and the regulator. The realization of the right to health care and access to medicines in South Africa and elsewhere is contingent on adequate empowerment of the pharmaceutical workforce.

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Table B: Proposed skills development strategy for the South African pharmaceutical industry

Strengthen the teaching capability of academic institutions by e□ecting dual appointments	
Rationale	There are considerable shortages of skilled academics with prior exposure to the pharmaceutical industry
Strategies and inputs	Allow placements of academics in industry and provide a platform for industry experts to spend time in academia
Opportunities and barriers implementation	Will facilitate knowledge transfer to students enabling them to be ready for their critical roles in industry
Stakeholders	Industry, government, academia, SETAs
Assist academic institutions with financial resources and placements for WIL	
Rationale	WILs are a critical component of academic training aimed at adequately preparing students for employment
Strategies and inputs	Make SETAs a liaison between companies and training institutions; allow SETAs to fund the cost of logistics such as transport
Opportunities and barriers implementation	Obtaining access to the workplace is a key challenge for universities
Stakeholders	DHET, SETAs
Introduce modules on quality systems in undergraduate sciences curricula	
Rationale	The level of regulation the pharmaceutical industry warrants requires graduates with an appreciation for and understanding of quality systems
Strategies and inputs	Training institutions to introduce modules on topics such as ISO systems and total quality management
Opportunities and barriers implementation	Training in quality systems will assist industry to become globally competitive at the International Conference on Harmonization level
Stakeholders	DHET, SAPC, SACNSP, and providers of training in science, pharmacy, information technology, engineering, etc.
Strengthen regulatory systems through postgraduate specialization programs	
Rationale	Increase the pool of experts to strengthen regulatory authority operations
Strategies and inputs	Place pharmacists at the regulator for community service following academic internship
Opportunities and barriers implementation	The current pool of external experts that are used by the regulator are aging
Stakeholders	Regulatory Science Institute, MCC, SAPC

DHET = Department of Higher Education and Training

MCC = Medicines Control Council

SACNSP = South African Council for Natural Scientific Professions

SAPC = South African Pharmacy Council

SETA = Sector Education and Training Authority

WIL = work integrated learning

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HOW NEW TECH CAN PROPEL AFRICA to the Forefront of Health Care

Patrice Matchaba

The Fourth Industrial Revolution could completely transform health care.

From big data to genomics, the fusion of technological breakthroughs in the physical, digital, and biological spheres is changing the most fundamental tools and techniques of medicine and public health. Already, IBM's Watson Project is combining unprecedented amounts of clinical and social data to transform drug trials and disease management systems. DNA sequencing is now a mainstream part of medical care in countries across the world.

As a physician, I see one common denominator to the coming changes. This is an increasingly patient-centric approach to health care. Better information and more customizable technology means more personalized tools and methods for promoting wellness.

The developed world's health systems, many of which are focused on 20th-century paradigms of care, could have trouble adapting to a world of "bottom-up" care. But in Africa, where health systems are now rapidly developing, the Fourth Industrial Revolution in health care could take hold.

For all the resources and technological advantages of the rich world, many health care systems in Europe and North America are mired in old ways of thinking. They focus on costly secondary and tertiary care and they emphasize treatment rather than prevention. Their rules and processes make it di cult to take full advantage of new and ubiquitous technologies, like the smartphone in all our pockets. All this is understandable. Highly industrialized countries have longstanding ways of doing business in the health sector. Legacy systems are hard to transform.

African countries have an opportunity to be the trailblazers of a 21st-century paradigm of care. Already, countries on the continent are heavily focused on preventive care. Think mass drug administration for parasitic diseases, malaria chemoprophylaxis, and prophylactic antiretroviral medication to prevent HIV infection.

Africa already uses technology to manage human resource constraints, such as text services that enable doctors to support Trained Birth Assistants at a distance. Across the continent, mobile phone-based services like SMS for Life have transformed supply chains for malaria drugs and other medications, substantially reducing treatment stock-outs.


Patrice Matchaba

These transformations are necessary. With rising economies and urbanization, noncommunicable diseases (NCDs) present new challenges to Africa's emerging health systems. For example, NCDs like diabetes and heart disease are now responsible for at least 40% of deaths in South Africa. In just over a decade, such diseases are projected to be the leading cause of mortality in Africa.

We believe that addressing Africa's "dual-disease burden" of both NCDs and infectious diseases will require developing and adopting low-cost and high-quality medical systems that encourage people to manage their own health. Mobile technologies and new breakthroughs in customized care will help us succeed.

Transformations are already happening in countries like Ghana, where the ComHIP program aims to shift the point at which patients with high blood pressure access health care to the community, rather than the regional hospital, which is often crowded and far away. Across Africa, mobile devices and telemedicine support community nurses in decision-making and ensure seamless connection with community health care workers and physicians, as needed. SMS and voice messaging are used for patient education, reducing risk factors for cardiovascular disease, and supporting adherence to therapy. Rwanda recently became the rst country in the world to incorporate drone technology into its health care system, for delivering blood for transfusions. Tanzania now implements a similar model.

But not all smart solutions are high-tech. Rwanda's capital Kigali has a car-free day every month to promote prevention and

African countries have an opportunity to be the trailblazers of a 21st-century paradigm of care

wellness through walking and cycling. Few European or American cities have been able to achieve this.

Of course, the dual burden goes beyond Africa. Asian and South American countries are grappling with aging populations and the lingering challenges of infectious disease. They are also pioneering programs that can serve as models for Africa and the rest of the world. Only a third of Indian citizens have access to modern health care. Roughly two-thirds of the country live in rural areas. In this context, Novartis created a program called Arogya Parivar ("healthy family" in Hindi) to recruit and train locals in remote villages to become "health educators." These individuals help inform communities about good health, disease prevention and the importance of seeking timely treatment. Local teams work with doctors to organize health camps in remote villages. These are mobile clinics that provide access to screening, diagnosis and therapies. The program is also piloting an e-health-care project linking villagers to physicians in primary health care facilities. This brings quality health care services closer to remote communities.

Arogya Parivar was so successful that we have since replicated the program in Kenya and Vietnam. Since 2010, outreach in rural areas through these programs has brought health education to more than 30 million people and direct health benefits to three million patients through diagnosis and treatment. These systemic innovations will be enhanced by the emergence of new cross-cutting health technologies.

Many African governments are aiming for universal health coverage based on an e cient, equitable, and innovative primary care system. This is good news. As European and North American health care systems face extraordinary demand from rapidly aging populations, we may see them adopt lean innovations pioneered in Africa and other parts of the developing world. In the emerging age of personalized "bottom-up" care, developing countries have a powerful opportunity to lead.

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ISPE SINGAPORE CONFERENCE

Record-setting 1,000 participants from 25 countries

Pierre Winnepenninckx and Shanshan Liu

The 2018 ISPE Singapore Conference and Exhibition, 30–31 August, drew over 1,000 participants, a record attendance for the 18 years of the conference. Attendees included Southeast Asian delegations from Indonesia, Thailand, and Vietnam. Over 65 speakers shared thought leadership, best practices, and real-life experiences. The event also featured the region's first Women in Pharma® panel session, held in conjunction with the conference.

Pierre Winnepenninckx

Shanshan Liu

OPENING PLENARY

Ferry Soetikno, Chief Executive Officer, Dexa Group, Indonesia, shared his insights on ensuring the supply of quality medications beyond domestic markets. With its patient- and quality-centric ethos, Dexa's vision and achievements have extended beyond Indonesia. The company's products include nonsterile oral dosage forms, sterile injectables, topicals, OTC and herbal preparations, and consumer products. The company's products are marketed in Asia, Africa, and the Pacific. It has two cGMP facilities, one of which has been approved by the MHRA (UK), TGA (Australia), and Darmstadt.

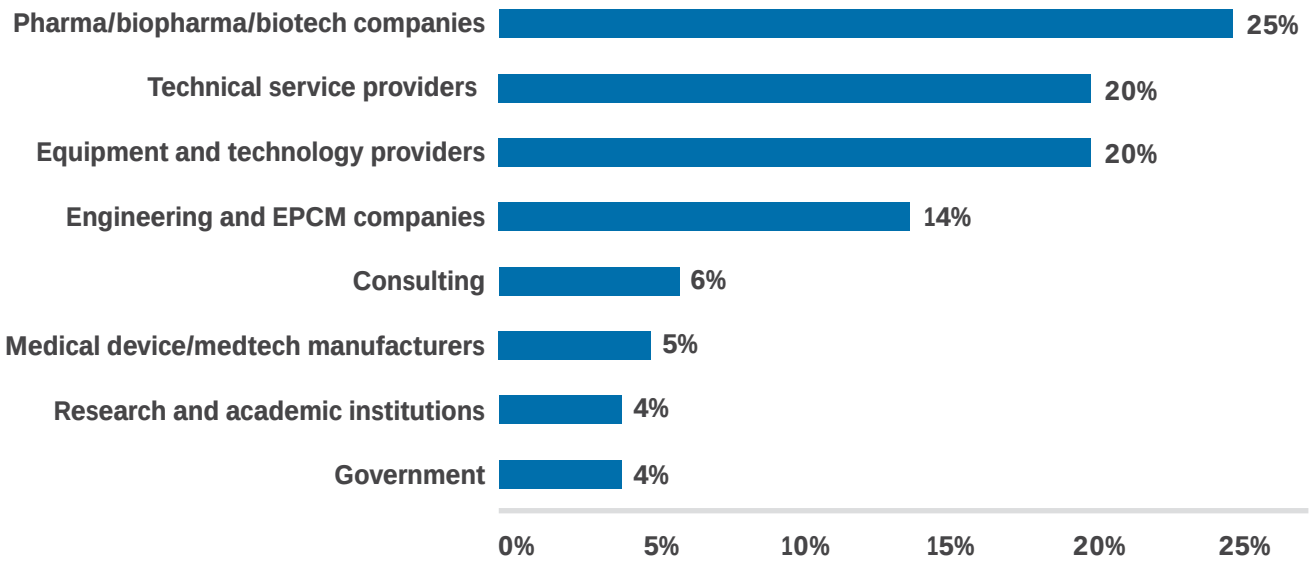
ISPE 2017–2018 Board Chair Tim Howard pointed toward strategic plans, which focus on globalization and regulatory harmonization. Drug shortages will require continuous vigilance, aided by regulatory and industry efforts on quality metrics and quality culture. He announced an upcoming APAC regional conference for 2019.

The importance of quality and culture was underlined by the plenary panel discussion: "Driving a Quality Culture through Leadership," moderated by Conference Chair Pierre Winnepenninckx, CEO and Founder, No Deviation Pte, Ltd., and led by Chong Meng Chai, Head of Mammalian Manufacturing, Lonza Biologics, Singapore; Vincent Loret, Site Director, GlaxoSmithKline, Singapore; and Dr. Jincai Li, Vice President, Drug Substance Manufacturing (MFG1), WuXi Biologics, China.

Chai cautioned the audience not to assume that established systems and workflows are always robust. He stressed the importance of leaders staying connected to the shopfloor to reduce the gap between work as they imagine it and work as it actually happens. This was supported by Loret, who emphasized the need to "walk the talk." He said this drive should come from leadership and not external facilitators.

The panel agreed that key performance indicators (KPIs) should drive positive behaviors and solutions, but warned against using

Figure 1: Attendees by industry



KPIs to reduce deviations, since that could lead to adverse behaviors such as hiding deviations and cosmetic corrective and preventive actions. Applied correctly, KPIs enable tracking and help transform "non-right- rst-time" incidents into improvements.

While all the panelists said they do a Gemba walk once a week, they wished to do so more often because of the energy it gives people and the encouragement it provides to identify problems and propose solutions. The session concluded with a discussion on the critical importance of trust, openness, and transparency by demonstrating the positive consequences and improvements they produce.

STERILE AND ASEPTIC OPERATIONS

Maurice Parlane, ISPE Australasia Board Director, Centre for Biopharmaceutical Excellence Director, and Principal/Director of NewWayz Consulting Ltd., New Zealand, spoke on risk assessment (RA) in aseptic processing. The typical linear 1–5 scale used in the failure modes and e ects analysis may not be the best representation of risk ranking, he said. There are many factors to consider and a reality check with the monitoring system should be done. Since RA focuses on the probability of occurrence, does a ranking of 4 (very probable) mean it is two times more likely to happen than a risk ranking of 2? A logarithmic or weighted scale could be a better approach.

PROCESS VALIDATION

Hazem Eleskandarani, Global Director, Commissioning & Quali - cation, Johnson & Johnson, USA, explained that process validation (PV) is demonstrated through design. PV and commissioning and qualification (C&Q) are not two separate steps but are integral parts of a continuous process, known as commissioning quali ca- tion validation (CQV). This aligns with the second edition of the *ISPE Baseline® Guide Volume 5: Commissioning and Qualification*, currently in development (publication expected in 2019). CQV should not wholly be the quality team's responsibility but should also fall to subject matter experts.

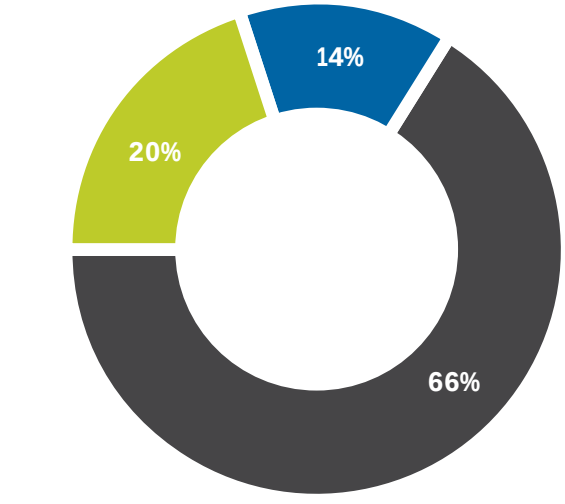
Eleskandarani also discussed the critical design elements of an integrated CQV process:

- Trained personnel working on the end-to-end process
- Execution plan or road map
- Follow regulatory guides
- Work with the quality team throughout (not only at the end)
- Know and adhere to policies and procedures
- Use the right materials and resources
- Follow proper C&Q of facility and equipment for a smooth PV
- Create accurate and timely documentation

Maurice Parlane also moderated the panel discussion "Transitioning from Project to Validation" with panelists Paul Si, Head Project Management Asia, Novartis, Singapore; Melis Tay, Operations Start Up Manager, AbbVie, Singapore; and Michael Lee, Senior Vice President, Mab Venture Bio Company, China. All agreed on the importance of the 3Ps: project, process, and product. Eleskandarani added that clearly defining the objectives from the start and making sure the whole team is aware of the objectives give a sense of ownership, helping both teams and individuals integrate them into their own objectives.

In the case of how involved the project management should be in process validation, both Lee and Eleskandarani agreed that the hando from project to operations varies with project and should be a gradual process. Si said that a part of the operations team could be integrated into the C&Q team at identi ed points during

Figure 2: Attendees by region



* Bangladesh, China, India, Indonesia, Japan, Korea, Malaysia, Pakistan, Philippines, Thailand, and Vietnam

the C&Q time frame for recipe testing done by the operations team. Lee emphasized that the users (operations) are the clients and the project management team should take their input into account and not shrug o their comments.

With deviations, Si noted that prede ning the stage at which it is a punch-list item and at which it is a deviation would save time and allow the team to be more focused on solving the problem. Eleskandarani said that knowing the objectives, using factory acceptance tests to draft SOPs, and doing test runs with the equipment and automation systems, among other actions, would smooth the process and increase people's knowledge and expertise. "Practice makes perfect," he said.

LOGISTICS AND DISTRIBUTION

Participants in this track agreed that as more regions, including Asia, adopt and require serialization, its key bene ts and enormous potential of end-to-end tracing—even to patient level—with fully attributable information will become apparent. Serialization will also expedite recalls, help prevent identify theft and counterfeiting, improve complaint management, and aid deviation investigation.

Main challenges include long timelines for successful implementation, varying standards and systems, and making regulations mandatory. In initial stages complaints may increase due to the need for all parties, such as wholesalers and pharmacies, to be ready.

Blockchain and integrating databases were also discussed.


Women in Pharma® panel

WOMEN IN PHARMA®

The rst WIP event organized by the Singapore a liate was moderated by Shanshan Liu, VP of ISPE Singapore. The panel of female leaders and role models in the pharma industry were: Sook Peng Chua, ASEAN Regulatory and Quality Compliance Director, Johnson & Johnson, Singapore; Christine Moore, Global Head and Executive Director, GRACS CMC–Policy, Merck Sharp & Dohme Corporation, USA; Dr. Vasiliki (Vee) Revithi, former head of EOF/Greece, GMDP Inspectorate, Greece; and Michelle Peake, Senior General Manager, PT Kalbio Global Medika, Indonesia.

They shared their experiences, stories, and aspirations in both careers and personal lives during the interactive session, including insights on planning a successful career path, keys to opportunity, career barriers, and work–life balance. Male audience members also participated actively, gaining awareness of and committing to making the industry more diverse and inclusive.

SINGLE-USE SYSTEMS

This track was well balanced between insights from suppliers, manufacturers, and service providers. All emphasized the signi - cance of close collaboration between supplier and end user to implement single-use systems. Sessions presented pros and cons associated with single-use systems, as well as considerations in choosing single-use over traditional stainless steel systems. Aside from saving on capital costs and utility consumption, one bene t of single-use systems is the possibility of "scaling out" to avoid the risks associated with "scaling up."

Participants also shared the latest technology in buffer systems. While this may sound simple, significant challenges and planning are involved. To simplify the complex in-line-dilution bu er skid, the single-use version is in development.

Issues with leachables, extractables, and absorption are still major concerns for single use. The selection of various materials, how surface/volume ratio varies the impact of bag material, and even

quality variations in the same material from di erent suppliers or even di erent batches from the same supplier, were addressed.

Dr. Jincai Li, Vice President, Drug Substance Manufacturing (MFG1), WuXi Biologics, China, presented a case study of transferring a stainless steel production line to a single-use production line. The company expects to achieve a DS capacity of 220 kiloliters globally by 2021, re ecting the growing roles of the Asia market and Asian manufacturers in the pharma/bio world.

REGULATORY AFFAIRS

Regulatory updates were followed by a discussion moderated by Bob Tribe, former Chairman, PIC/S, Australia, and Asia–Pacific Regulatory A airs Advisor, ISPE. Regulatory members were:

- Dr. Vasiliki Revithi, former Good Manufacturing and Distribution Inspectorate Head, Ethnikos Organismos Farmakon (Greek National Organization for Medicines)
- Meow Hoe Boon, 2018–2019 PIC/S Chair who shared on "GMP Harmonisation & GMP Inspection Reliance from a PIC/S Perspective"
- Hock Sia Chong, Health Sciences Authority, Singapore who presented on "ASEAN MRA on GMP Inspection: Bene ts to ASEAN Economic Community"
- Vladimir Orlov, State Institute of Drugs & Good Practices, Russia, who spoke on "Foreign Medicines Inspections in 2017: Overview of Results"
- Dr. Achiraya Praisuwan, Thai FDA who gave "Regulatory Updates: Thai FDA"

Some highlights of the panel discussion were:

- China FDA showed considerable interest in PIC/S and is expected to apply for membership in the next year or so. CDSCO, India, also showed interest in PIC/S, but it was not known whether they would make an application.
- The Russian regulatory authority recently made a pre-accession application for PIC/S membership.
- There was strong support for the PIC/S "Inspection Reliance" initiative, as it will avoid unnecessary duplication of GMP inspection work.
- With the recent publication of version 14 of the PIC/S GMP Guide, it is common practice for PIC/S member authorities to give manufacturers a 12-month transition period to adjust to the new requirements. However, some PIC/S member authorities have been very slow to adopt new versions, with several authorities still using version 8 as their legal requirement.
- Although the ASEAN mutual recognition agreement (MRA) on GMP inspection currently applies only to medicines, it will soon be expanded to include APIs, biologicals, and herbals.
- As of August 2018, the US FDA had to complete the assessments of 14 EU member states by 15 July 2019, per its MRA with the EU. If those assessments are not completed by this date, the MRA will not proceed.

Regulatory a airs discussion panel

About the authors

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ISPE Briefs

Three New ISPE Guidance Documents Debut

ISPE has released three new Guidance Documents:

Good Practice Guide: Single-Use Technology provides a road map for e cient implementation of single-use technology (SUT) with minimum disruptions to existing operations. From this Guide, users will learn how to select single-use components and design functional systems, when and how to perform e ective extractables and leachables studies, how to evaluate suppliers of SUT, and about the interrelated tasks for implementing SUT. Available on the ISPE website at https://ispe.org/publications/guidance-documents/good-practice-guide-single-use-technology

GAMP® RDI Good Practice Guide: Data Integrity – Key Concepts provides detailed practical guidance to support data integrity within a regulated organization. Positioned under the *GAMP® Guide: Records and Data Integrity and aligned with GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems*, this guide provides detailed guidance in four core areas: data governance, data life cycle, risk management approaches, and critical thinking. Available on the ISPE website at https://ispe.org/publications/guidance-documents/gamp-good-practice-guide-date-integrity-key-concepts

ISPE Japan A liate *Pest Control Manual* (English translation, version 4) expands on the Japan A liate's previous *Pest Control Manual*, and o ers advice for both new and aging GMP facilities. It proposes plans to incorporate pest control best practices into the project schedule for new construction, and includes advice on integrating pest control requirements during all phases of construction, training construction sta , and determining areas that should be inspected, both during and at the end of construction. Available on the ISPE website at https://ispe.org/publications/guidance-documents/japan-a liate-manual-pest-control

Purchase these and other Guidance Documents on the ISPE website at https://ispe.org/publications/guidance-documents

SINGAPORE AFFILIATE GMP WORKSHOP HELD IN COOPERATION WITH DRUG ADMINISTRATION OF VIETNAM

Just six months after meeting with the Drug Administration of Vietnam's (DAV) Drug Quality Management Division, the ISPE Singapore Affiliate held its first GMP Workshop from 18 to 20 October in Ho Chi Minh City. About 150 participants attended from more than 65 companies and sites in Vietnam. The event was jointly organized with the Ministry of Health's Centre of Training and Supporting Pharmaceutical, Cosmetic Enterprises.

The agenda covered pharmaceutical quality systems, data integrity requirements and regulatory expectations, quality risk management (QRM) principles and practice, managing GMP deviations using QRM, quality improvement, CAPA, and product quality reviews. Additional sessions included bioburden control, cleaning and disinfection, HVAC, and water system treatment.

Based on positive feedback, future events and programs to develop skills and knowledge for both industry members and regulators will follow. The a liate also signed on 20 DAV regulators as ISPE members.

NEW REGULATORY RESOURCE

ISPE members can now access a carefully curated collection of regulatory updates. Each month, ISPE's Regulatory Quality Harmonization Committee's Europe–Middle East–Africa Regional Focus Group publishes a list of select updates that includes regulations, guidelines and other documents, and news about Brexit. Available on the ISPE website at https://ispe.org/initiatives/regulatory/updates

We'd like to feature your group in an upcoming ISPE Briefs!

Share the highlights of training programs, conferences, social events, or other activities with ISPE members. Article length is 250–400 words; photos should be 300 dpi or > 1 MB. Send both to Susan Sandler, Editorial Director, at ssandler@ispe.org.

Connecting Pharmaceutical Knowledge

ISPE's Core Members are pharmaceutical professionals who use expert knowledge to create high-quality, cost-effective GMP solutions. ISPE delivers technical and operational solutions to support our Members across the global pharmaceutical and biopharmaceutical industry in the manufacture of quality medicines for patients.

Attend one of our conferences, and find out what you've been missing.

2019 ISPE SCHEDULE OF EVENTS

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Facilities of the Future Conference
7–8 February | San Francisco, CA USA

Aseptic Conference
18–19 March | Bethesda, MD USA

Biopharmaceutical Manufacturing Conference
18–20 June | Boston, MA USA

Process Validation Workshop
20–21 June | Boston, MA USA

2019 ANNUAL MEETING & EXPO
27–30 October | Las Vegas, NV USA

Regulatory Conference
5–6 December | Bethesda, MD USA

EUROPE AND ASIA

2019 EUROPE ANNUAL CONFERENCE
1–4 April | Dublin, Ireland

Europe Biotech Conference
September | Belgium

Pharmaceutical Manufacturing Conference
September | Singapore

Europe Pharma 4.0 Conference
November | United Kingdom

ISPE.org/Conferences

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BLOCKCHAIN
for Pharmaceutical Engineers

James Canterbury, Steven Thompson, and Arthur D. Perez, PhD

This article discusses how blockchain technology may disrupt the way we collect and manage data within regulated processes. The first section is a nontechnical summary of blockchain's features, including a description of what it is (and what it is not). This sets the context for the next section, in which we discuss several blockchain use cases currently being piloted by life sciences companies. In the final section we explain how you and your organization can leverage blockchain technology.

If you haven't heard of blockchain yet you probably will soon. The technology behind the cryptocurrency craze has been gaining momentum since early 2016 and shows no sign of slowing down. Blockchain is now making its way into life sciences companies across many different operational disciplines. *PE* magazine published a feature article in the July-August 2018 edition titled "Blockchain: The Next Disruptor in Clinical Trials." [1] While this is certainly a great use case, it is only one of many that are being pursued within the industry. Before we look at blockchain applications in life sciences, let's begin with a primer on what it is.

BLOCKCHAIN

What It Is

To many people, blockchain and cryptocurrency (bitcoin being the first and best known) are synonymous. The former, however, is the underlying technology and the latter is an application of that technology. While the two are related, it's important to understand that the volatility of the cryptocurrency market does not mean that blockchain technology is volatile. It is still evolving, though, and as with many new technologies there is currently much hype and speculation about how it will change the world. This initial excitement and speculation will fade as the technology matures. But blockchain is a fundamentally new way of sharing and trusting information, a new communication protocol for exchanging data between computer systems. If successful, it will become the foundation for many technologies, in much the same way as TCP/IP (Transmission Control Protocol and Internet Protocol) did when it was introduced in the 1980s, allowing for the development of the now-ubiquitous Internet. [2]

What do pharmaceutical engineers need to know about blockchain? That depends on a lot of factors, many of which are still being explored by the communities who are evolving blockchain protocols. But there are a few fundamental concepts that are likely here to stay, and they will shape the way we redefine our processes to capitalize on this technology. To put this in context of a pharmaceutical manufacturer let's consider the simple distribution model in Figure 1.

In this example we can think of each transfer of the finished good as a transaction on the blockchain. To manage and track those movements we will use foundational blockchain elements:

Transactions: Blockchain networks are peer-to-peer transactional systems. This means they track exchanges between parties that use the network as a medium of exchange. Among other things, this allows transactions to be time-stamped based on the network protocol (i.e., outside the control of any one individual). While blockchains are considered databases and some additional information can be included in each transaction, they are not large data stores, nor are they organized in typical relational tables with rows and columns.

Distributed ledger technology: All blockchains are a form of distributed ledger technology (DLT)—but not all DLTs are blockchains.

- The "ledger" part of DLT is simply an ordered listing of transactions, not unlike your credit card statement. As we'll explain in more detail later, these ledgers are "append only"; new records can only be added to the end of the ledger, and once added cannot be changed.
- "Distributed" means that instead of having one source maintain your list of transactions (e.g., your credit card company) many sources maintain the list.
- "Technology" refers to the protocol that defines how the distributed ledgers will be kept in sync. It does this through a mechanism called "consensus." Different DLTs have different ways of reaching consensus.

DLTs create a redundant and resilient network that no longer needs a central authority to maintain the integrity of a transaction list. Of course, it also introduces concerns around how public this information is and who can see what; people do not make it a habit of publishing their credit card statements, for example. This is where cryptography comes in.

Cryptography is at the core of blockchain functionality. It is both how we secure transactions (using public and private keys) and is a part of how we make sure that only authorized individuals can view certain information about transactions.

One of the most utilized tools in cryptography is hashing, in which an algorithm (a piece of computer code) generates a unique identifier for just about anything digital. A hash of the letters "ISPE" using an SHA256 algorithm looks like this:

```
E7AE003CF0974DEC21E4BB10C0EB3ECD1B-
C389471C8CDA83798AA825C51C04B9
```

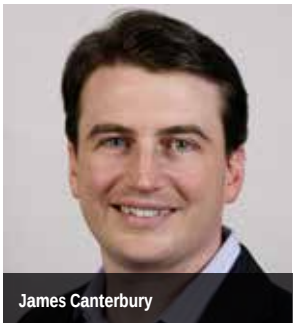
Hashing is one-way encryption; if you have only this hash there is no way to gure out what it means. If you were given "ISPE" and knew the algorithm that was used, however, you could reproduce the same hash. Most hashes are very sensitive. Even a minor change in the original input produces an entirely di erent hash ; for example, the hash of "ISPe" using the same SHA256 algorithm:

```
481A9F91046AEF67E2D2407C05C3E6EE-
C52894108794324A2B2A1DBF0CBBB880
```

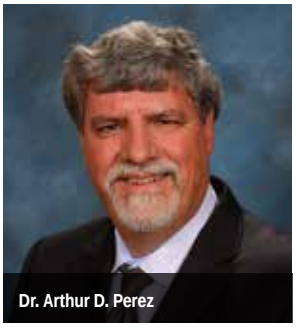
There is currently a lot of development around privacy within blockchains, and this is an area that is expected to generate significant advances in the near future.

Hashing of hashes: One thing that sets blockchain apart from traditional distributed computing systems is the concept of "hashing of hashes" to make an immutable chain. Blockchains group transactions into "data blocks" based on when the transaction was posted. Once veri ed, a hash of each transaction is generated to prove that the data was not altered. The blockchain protocol then combines each transaction hash into a tree structure (allowing us to search the blockchain faster) and creates a hash of all the transaction hashes it contains. When the next block of transactions is created, the hash of the previous block is included in the overall block hash, e ectively "chaining" the blocks together. Because a change in the source data would result in an entirely new hash, changing a past transaction would invalidate the hash of that block and invalidate the hash of every block that occurred after it. This is known as being "tamper evident" and it leads to the next blockchain element.

Immutability: Once a transaction (and any data associated with it) is stored in a blockchain, it cannot be altered without others knowing about it (since the ledgers are distributed). Any change will be evident, since records can only be appended to the end of the blockchain. Rewriting history would require a massive coordinated e ort to change all of the ledgers simultaneously. This does not mean that transactions posted in error cannot be corrected; it just means they must be reversed by a subsequent transaction, and there will always be a record of that reversal. It would be better to prevent those mistakes by implementing rules or controls on your blockchain. This is where smart contracts come into play.


James Canterbury


Steve Thompson


Dr. Arthur D. Perez

Smart contracts are pieces of logic—business rules—that can be deployed on a blockchain. They act as an "account" where transactions can be sent when certain conditions are met (de ned by the contract logic). They can generate "events," which are typically another transaction. Most blockchains that support smart contracts deploy them in a way similar to posting a transaction—that is to say, once the contract code is written and posted to the blockchain it cannot be changed. In life sciences companies, many controls that exist in our systems could be pushed into smart contracts. This would allow rules to apply across disconnected systems. A smart contract might prevent inventory movement once the expiry date has been reached, for example. The expiry date could be set by the manufacturer but the inventory might be managed by a wholesaler or dispensary. Accomplishing this in today's world would require a set of interfaces or electronic data exchanges.

Tokenization: Transactions within a blockchain are often an exchange of value between two accounts; to keep track of that value blockchains use tokens. "Fungible" tokens, used in cryptocurrencies and mobile pay phone apps, can represent a utility or can simply be a store of value; they are non-unique and interchangeable. Of particular interest to life sciences, however, companies are "non-fungible" tokens (NFTs). These represent unique assets such as serialized unit of a drug or a uniquely identi ed medical device. NFTs can be created, transferred, associated with other another, and consumed (destroyed). Product provenance can be captured on a blockchain by tracking the movements and changes to an NFT. The "tokenizing" process creates and maintains the tokens on a blockchain;

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this is likely where a lot of e ort will be placed as companies begin to use blockchain as an exchange medium for assets. You can see how this works by tracking the asset on the blockchain in Figure 2.

What It Isn't

Having noted some of what blockchain is, here are a few things that it is not.

Blockchain is not a silver bullet, nor is it a unique stand-alone solution. Blockchain will most likely be a backbone that connects systems or business partners, but existing systems will still play a role and will need to be integrated into the blockchain to trigger events or record important information. Leveraging blockchain may introduce additional data-sharing requirements to store and secure o -chain data.

Blockchain is not bitcoin. Bitcoin is the longest-running blockchain experiment, a cryptocurrency that uses a blockchain network to pass value between accounts. It is unlikely that the rst production use of blockchain in life sciences will be tied to bitcoin or any other cryptocurrency.

Blockchain is not an application. While it is possible to build a new breed of distributed applications on top of a blockchain, the blockchain itself is not an application—it is a protocol-based network. Many blockchain network protocols such as Ethereum (an open blockchain platform), allow smart contracts to be executed within the network itself. Because the network can execute logic it can be thought of as a virtual world computer, though this still would not be an application.

Blockchain will not store all your data. This must be underscored when considering use cases for blockchain. Though it is a distributed database, it is not a database in the traditional sense. It is designed to store a ledger (or an ordering) of transactions, each one being only a few bytes of information. Most blockchains incentivize users to keep transactions as small as possible. When transactions become too large, or when there are many transactions, latency is introduced into the blockchain (making it less functional). As technology advances, current scalability issues will be addressed, but the underlying principles of small data will still be applied. This means that blockchain integration points will not look like the electronic data interfaces currently utilized in life sciences companies today.

POTENTIAL USES

While there are many fascinating predictions on how blockchain can be applied within the life sciences (a quick Internet search of "blockchain for pharma" will provide enough reading material for several days), the following features will probably drive the rst production uses of the technology.

Anti-censorship and data integrity: This is blockchain's *raison d'être*—the purpose for which it was created: the need for records that cannot be manipulated or repressed.

Chain-of-custody, asset tracking, and immutable audit trails: This can be serialization, but that will likely just be a byproduct of a network that can track the exchange of assets between parties. The reliability and transparency of that tracking will change the way we account for the value of our assets, determine legal ownership/custody, and calculate tax due to movements between tax jurisdictions (just to name a few).

Proof of existence: Time stamps certify events on the blockchain in the order in which they occurred—if an asset were posted 100 blocks back, you would know that the asset had to have been in existence at that time.

Connecting the Internet of Things without integrating it all. Blockchain is both a network and a database. This means that it can be used to store and share data from many sources, including IoT sensors and existing systems, without needing to "connect" those sources in a traditional sense. As pointed out above, blockchain is not meant to store big data, so designs must specify what is captured and posted.

Data privacy and authentication: Blockchain goes beyond two-factor (username/password) authentication, providing a good mecha-

Figure 1: Simple distribution of a finished good

nism to store consent, or grant/revoke access. Interesting solutions are being built on top of blockchains that will allow people to better control their personal data. These solutions also o er a reliable way to track how organizations manage personal data, something that will be useful in supporting compliance with data privacy regulations.

USE CASES

A recent article published by McKinsey & Company [3] identi ed the strategic importance of blockchain by industry. Several of the health care use cases discussed have also been topics of discussion in recent GAMP® Community of Practice (CoP) forums.

Health care research: As medical information begins to be stored on blockchains in the form of transactions associated with individual patients and treatments, a rich and reliable data set will emerge that may change the way new drugs or incentives for preventive care are researched. This new way of recording history may also challenge many of our existing policies for data management.

> *Currently, blockchain is a double-edged sword. The features it is known for are also problematic for trading partners. For example, immutability is bene cial but can also go against a company's data retention policy where data owners have the right to delete their records. Visibility is key and so is privacy. Conversations between industry stakeholders and blockchain platform developers will be pivotal to work out balance between the need and the possible."*
>
> —Bob Celeste, Founder, Center for Supply Chain Studies

Identity and data security: With the potential of managing medical records on a blockchain come risks associated with data privacy and security. Several initiatives currently underway are exploring blockchain as a means to govern information exchange, verify digital identity, and authorize (or revoke) access to use personal data. This places the ownership (and control) of information back in the hands of the individual and may play a key role in connecting our ecosystem in a secure manner.

Blockchains will change the way we trust and share data between business partners

Blockchain is both a network and a database

Blockchain also holds great promise for the healthcare industry, in addressing current challenges like interoperability of data systems and data security. [4]

—Vas Narasimhan, CEO Novartis

Drug supply chain: With serialization and unique device identi - cation major factors in the pharmaceutical industry, certain distributed ledger solutions o er a tremendous bene t in proving the provenance of the drug supply chain. Many of these also incorporate IoT devices to register environmental factors that might a ect drug stability during transportation and storage.

We are looking to use the unique capabilities of blockchain technology to create a permissioned distributed network for the Pharma industry that will deliver a step function improvement in prescription medicine security. We believe the ability to curtail diversion and counterfeit is possible by creating a con dential chain of ownership as drugs change hands. It is exciting to work with industry leaders who are actively experimenting to see what this technology can do.

—Susanne Somerville,
Head of Pharma Solutions, Chronicled

Clinical trials: From managing patient registries to securing trial protocols and results in an immutable manner, blockchain use cases in the clinical trial space are plentiful. Blockchains can bridge communication, trust, and privacy gaps between contract research organizations, sponsoring organizations, and regulators.

Blockchain will do for a network of companies what the ERP did for an individual organization. In life sciences this is about creating both uidity and traceability within R&D and our drug supply chain; this will help keep patients safe while making the approval of new drugs more e cient.

—Paul Brody, EY Global Blockchain Leader

While there is much potential around the development of use cases that capitalize on blockchain, solutions for some of the industry's more intractable problems are still a few years away. As the technology is still evolving, it is crucial to capture the use cases now; this will help refine and incorporate requirements into open-source standards that will shape future blockchain transactions. One such standard is Ethereum Request for Comment (ERC)-721, [5] which defines a standard for transmitting NFTs (e.g., serialized drugs and devices) on an Ethereum blockchain. This touches on another interesting change that blockchain is introducing to life sciences companies—the application of open-source development to solve industry-wide problems.

There is a lot of power in open-source development, each successive application is built using the lessons learned from others within the community—this lets us avoid making the same common mistakes and lets us move faster with better quality. The trade-o is companies will need to be comfortable sharing their code and be willing to incorporate designs from the broader community.

—Will Entriken, Blockchain Developer

OPENING THE BLOCKCHAIN DOOR

So where will this lead the life sciences industry? Blockchains will change the way we trust and share data between business partners. This in turn will change the way that we ensure the integrity of that data when making decisions. From a regulatory perspective, companies will have to understand what that means and be able to explain it to regulators. As more and more control points are pushed into the blockchain via smart contracts there may be "business rules" set by external upstream suppliers that are enforced by internal systems. (Consider, for example, the expiry date example from the perspective of the wholesaler.) To understand and capitalize on these changes it is important to experiment with blockchains and "get your hands dirty" in these early days. The community of developers is hungry for use cases and practical applications of blockchain. The life sciences are rife with such use cases.

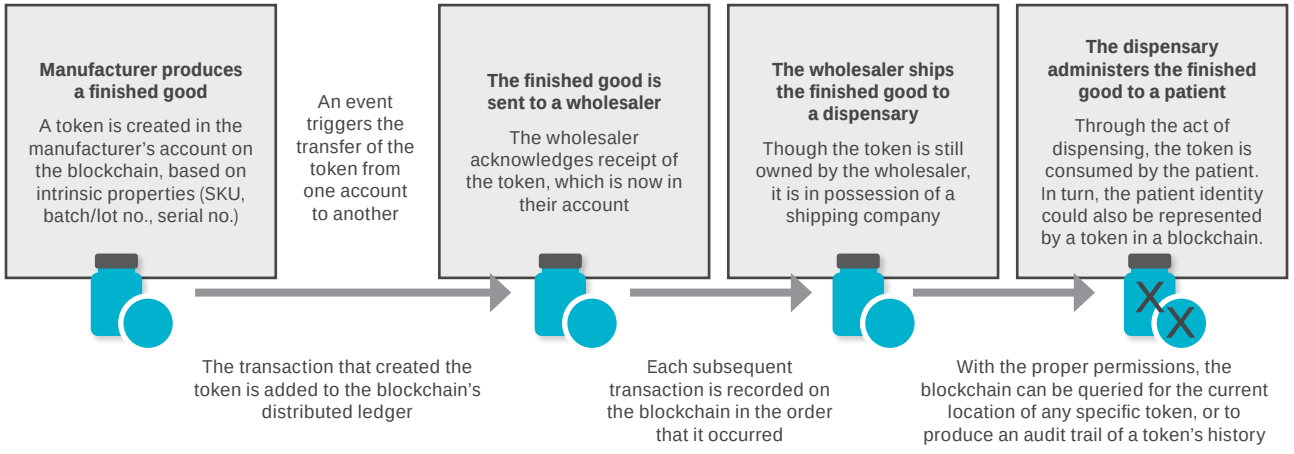
HOW TO GET STARTED

1. **Learn the ropes.** It's likely that your organization, or one of your business partners, is already running a blockchain pilot. The protocols themselves are generally free to download and many create easy-to-install test environments that come complete with step-by-step tutorials. The blockchain community tends to be a collaborative one; it may be as easy as reaching out.

2. **Educate yourself.** There are lots of great online do-it-yourself tutorials out there, though many will quickly take you down a technical track. Service organizations increasingly o er blockchain education sessions or sponsor workshops to help identify and design use cases.

3. **Build an application.** This may not be everyone's forte, but there is no better way to learn about what the technology is capable of than to try to make it do something. Whether you initiate a proof of concept within your organization, join an existing one, or even just experiment on your own, getting familiar with the nuts and bolts of blockchain now will serve you well in the future.

Figure 2: Distribution of a finished good tracked by a tokenized asset



4. **Join the GAMP Blockchain SIG!** Many of the authors of this article meet monthly to discuss the latest trends and developments and hear from industry speakers about their exciting projects. Through our CoP website we are also building an inventory of great reference articles and case studies within the life sciences.

Acknowledgments

The authors thank the GAMP Blockchain SIG for their help in drafting and reviewing this article.

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James Canterbury is a Principal working with EY's Advisory practice where he is part of the global blockchain team, and a leader within Risk Advisory focused on Life Sciences regulatory quality and compliance. Before blockchain he primarily managed projects that span from interpreting FDA regulations to privacy and security to financial controls. James holds a BS in industrial engineering from Penn State University and is a Certified Information Systems Auditor. He currently sits on the board of the NJ chapter of ISPE, is part of ISPE's GAMP® Americas steering committee, and leads the GAMP Blockchain Special Interest Group. He has been an ISPE member since 2015.

Steve Thompson has over 20 years of GxP experience in life sciences, including medical devices. Steve is Senior Manager of Professional Services for ValGenesis, Inc. He was certified as a Parenteral Drug Association (PDA) auditor, has held managerial positions at various levels within information technology and quality assurance for large corporations and start-ups, is a published author, and has presented at several conferences and industry associations. Steve has a BS in computer information systems. He has been an ISPE member since 2017.

Dr. Arthur "Randy" Perez earned his SB degree in chemistry from MIT and a PhD in organic chemistry from the University of Michigan. He worked at Novartis for 33 years in a variety of roles, including chemistry process development, API manufacturing, QA validation, and IT compliance. He has been involved with GAMP since 2001, including service as GAMP Americas Chair from 2002 to 2007, and GAMP Global Chair from 2013 to 2015. He was elected to the ISPE Board of Directors in 2005, and served through 2013, culminating in a term as Board Chair. Retired from Novartis since 2015, he currently teaches GAMP-based courses for ISPE. He has been an ISPE member since 2002.

CLINICAL TRIAL MANAGEMENT

Adaptation to ICH E6 (R2): Good Clinical Practice

Yumi Wakabayashi, Hitoshi Matsui, Masahiro Hayashi, Kohji Ikai, and Keiichi Yamamoto, PhD

This article presents an adaptation of clinical trial management to ICH E6 (R2). A case study assesses quality risks in a clinical data management system.

ICH has issued many guidelines to standardize technical documentation for medicinal product registration and reporting. ICH topics are categorized as quality (Q), safety (S), efficacy (E), and multidisciplinary (M). ICH E6 is an efficacy guideline on good clinical practice (GCP). It covers roles and expectations for all clinical trial participants.

In the past, regulatory authorities and the pharmaceutical industry monitored quality in clinical trials using GCP standards detailed in ICH E6(R1), which was first published in 1996. [1] The ICH E6 Expert Working Group E6(R1) began to revise E6(R1) in 2014, with a focus on risk-based monitoring and quality risk management. The revised guideline, ICH E6 (R2), published in November 2016, covers risk-based monitoring based on quality risk assessment and quality risk management (QRM). [2]

QRM IN CLINICAL TRIALS

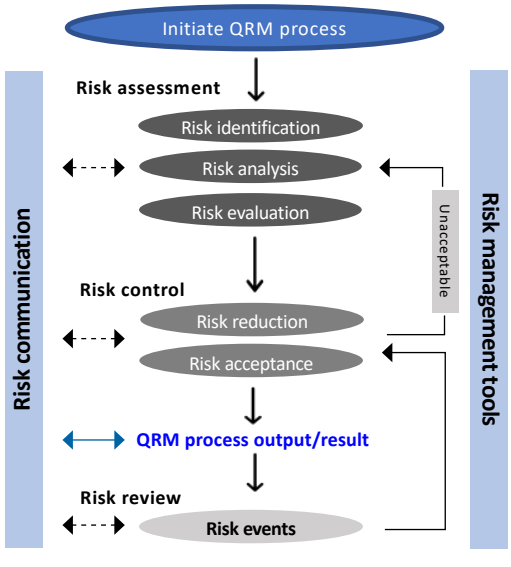
Complex global-scale clinical trials must be managed by prioritizing crucial tasks, which can be determined by assessing quality risks. Clinical research associates (CRAs) monitor investigator sites to ensure that management of a clinical trial by a site team is in compliance with the trial protocol and documented procedures such as patient site visit timeliness, drug accountabilities, compliance with protocols and SOPs, adverse events handling, etc.

As regulation of global clinical trials has increased, so have their development costs. They now include travel expenses, transportation costs, computerized systems implementation and operation, training and education, laboratory tests, and so on. Manpower costs include experts with therapeutic area knowledge, clinical trial design, medical writing, clinical data management, monitoring, statistical analysis, project management, communication, and negotiation.

We, the five members of the Special Interest Group No. 3 of the GAMP Community of Practice, ISPE Japan Affiliate, have adapted clinical trial management to ICH E6 (R2) by considering QRM in clinical systems implementation and operation. We conducted a case study to assess quality risks in clinical data management systems (Table A).

We assumed that clinical data management system operation has high risks related to human error such as data checking mistakes and wrong programming. Mitigation measures of these risks were mainly

Figure 1: General quality risk management process



Adapted from ICH "Quality Risk Management: Q9." 9 November 2005. Copyright ICH. Reprinted with permission.

to eliminate human error, e. g., training data managers, double programming, and program validation. Our results indicate that this could improve oversight and management of clinical trials, allocate time and resources more e ciently, improve patient safety, and protect subject anonymity.

RISK-BASED APPROACH CASE STUDY: QRM

Introduced in ICH Q9 in 2005, [3] QRM is a framework to identify quality risks and mitigate them by taking suitable risk reduction measures. The QRM framework originated from good manufacturing practice (GMP) and ts manufacturing processes well, [3–4] but it is also employed in nonclinical and clinical arenas. A European Medicines Agency re ection paper illustrated QRM processes in clinical trials in 2013, [5] with a framework almost the same as the Q9 approach: critical process and data identification, risk identi cation, risk evaluation, risk control, risk communication, risk review, and risk reporting. Risk-based clinical operation has also been discussed by the US Food and Drug Administration (FDA). [6–7] The agency recommended monitoring plan factors such as scope, frequency, method, target sites, etc.

In QRM, communication and a common understanding are essential for all participants. In a clinical trial operation, for example, one quality risk is that investigators and/or site members could fail to follow the trial protocol because of misunderstanding. In such cases, one risk reduction measure could be a site-initiation meeting prior to the start of the trial. The CRA in charge should explain the trial protocol, operating procedures, medicinal products handling, and adverse events reporting to all team members. Training and review of procedures for clinical team members are additional risk reduction measures. If sponsors delegate some of these tasks to a supplier, risks can be mitigated by con rming the supplier's quality management system (QMS) before the trial begins.

Risk mitigation programs must be monitored and reviewed to evaluate their e ectiveness and appropriateness. They should be revised, if necessary, to mitigate newly identi ed risks.

Clinical Systems

In many clinical trials, data is collected and managed through web-based clinical data management systems (CDMS) with electronic data capture (EDC). Clinical project management is conducted with the assistance of clinical trial management systems (CTMS). Both CDMS and CTMS are usually constructed using con gurable software—category 4 software as de ned in the GAMP® 5 Guide. [8] A clinical system user can perform a system validation as shown in the GAMP 5 guide. [8–9] Risks related to data integrity should also be considered. [10]

By leveraging information technologies such as EDC and cloud computing services, CRAs and data managers may conduct central monitoring and/or remote monitoring. CRAs should generate their monitoring plan prior to their rst site visit. If an investigator doesn't have enough experience in conducting a clinical trial, for example, the CRA would need to visit the site frequently. Monitoring frequency should be documented in the monitoring plan.

When a CRA goes through a trial database on data management system with EDC function, they can determine whether subjects are coming to the investigator sites on schedule or not. If no protocol violation is observed through the database checking, the CRA doesn't need to visit the site as frequently. If some protocol violations are observed, however, the CRA should go to the site, meet the site team members, and provide a comprehensive explanation of the protocol again in person.

SOPs

According to ICH E6(R2), sponsor standard operating procedures (SOPs) should include system setup, installation, use, validation, functionality testing, data collection and handling, maintenance, security measures, change control, data backup, recovery, contingency planning, and decommissioning. [2] Nowadays it is common for sponsors to delegate their clinical operation tasks to clinical research organizations, technical suppliers, and/or other third parties. [11–12] When a clinical system is set up as a cloud computing service or software as a service (SaaS), some technical activities can be performed by the SaaS supplier. We identified task allocation to sponsors and SaaS service suppliers in Table B. In these cases, some risks can be mitigated by confirming the supplier's QMS beforehand.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FUTURE CLINICAL TRIALS

To deal with the e ects of recent technology on clinical trial categorization, a January 2017 ICH re ection paper proposed an eventual renovation of ICH E6 and modernization of ICH E8. E8 was rst issued in 1997 to clarify general considerations for clinical trials, focus on clinical trial categorization and timing, [13] and serve as a guide to other ICH standards on clinical trials. [14] Citing the Declaration of Helsinki, E8 also emphasizes protection of trial subjects and scienti c approach in design and analysis. [15] One concern,

Table A: Case study of risk assessment: possible errors, risks, and mitigation measures in clinical data management processes

	Process	Steps	Possible error and risk	Mitigation measure(s)	Supplier*
1-1	Clinical database setup and trial preparation	Setup according to trial protocol; data definition	Poor data definition	Training and skill improvement of data manager	
1-2		Setup according to trial protocol; interface preparation and eCRF preparation	Data entry is difficult because of poorly organized eCRF	Training and skill improvement of data manager	
1-3		Setup according to trial protocol; edit checking (univariate)	Mistake on edit checking program	• Training and skill improvement of clinical programmer • Double programming	
1-4		Setup according to trial protocol; edit checking (multivariate)	Mistake on edit checking program	• Training and skill improvement of clinical programmer • Double programming	
1-5		General	Bugs with the software	Confirmation of supplier's QMS**	Software developer
1-6		Site-initiation meeting	Team members are reluctant to attend the meeting	• Meeting scheduling • Communication skill improvement of clinical leader	
2-1	Clinical data processing	Investigator input data to eCRF	Data entry error	• Annotated CRF • Training for investigator • Frequent monitoring	
2-2		Investigator input data to eCRF	Data entry by unauthorized access or identity spoofing	Training for investigator and co-worker(s)	
2-3		Investigator input data to eCRF	Data alteration by unauthorized access	Confirmation of supplier's QMS	Data center provider
2-4		Automatic edit checking during data entry via computer program	Computer programming error	Program validation	
2-5		Data transfer from eCRF database server to central server at Sponsor	Transfer failure because of computer programming error	Program validation	
2-6		Data checking by data manager with computer program	Checking mistake because of computer programming error	Program validation	
2-7		Data checking by data manager manually	Checking mistake by data manager	Skill improvement of data manager	
2-8		Source document verification by CRA	Discrepancy unsolved because of wrong procedures	• Skill improvement of CRA • Manager to supervise CRA's operation	
3-1	Data acquisition from central lab	Lab test results report delivered to investigator	Test results with mistake because of central lab system error	• Reporting system maintenance • Confirmation of supplier's QMS	Central lab
3-2		Investigator input comments of lab data to eCRF	Data entry error	• Annotated CRF • Source document verification by CRA	
3-3		Investigator input comments of lab data to eCRF	Data entry by unauthorized access or identity spoofing	Training for investigator and co-worker(s)	
3-4		Investigator input comments of lab data to eCRF	Data alteration by unauthorized access	High security	
3-5		Lab test results to be downloaded from lab server to sponsor server	Download failure because of computer programming error	Program validation	
3-6		Lab test results to be downloaded from lab server to sponsor server	Operation mistake	Training for operator	
4-1	Patient-related data acquisition via ePRO	Patients input relevant data electronically to ePRO device	Operation mistake	Training for patient	
4-2		Date transfer from ePRO device to third-party server	Transfer failure because of computer programming error	• Program validation • Confirmation of supplier's QMS	ePRO device provider

(Continued) Table A: Case study of risk assessment: possible errors, risks, and mitigation measures in clinical data management processes

	Process	Steps	Possible error and risk	Mitigation measure(s)	Supplier*
4-3		Date transfer from third-party server to sponsor server	Transfer failure because of computer programming error	• Program validation • Confirmation of supplier's QMS	Data center provider
5-1	Clinical data processed to clinical study report and M5 dossier	Dataset for statistical analysis generated by data manager with computer program	Dataset generation failure because of computer programming error	• Program validation • Training and skill improvement of clinical programmer	
5-2		Statistical analysis results, subjects list, tables, and figures to be generated by statistician with computer program	Statistical analysis failure because of computer programming error	• Program validation • Training and skill improvement of clinical programmer	
5-3		Clinical study report preparation	Documentation error	Double-checking	
5-4		M5 dossier preparation based on clinical study report	Publication error	Double-checking	
6-1	Technical maintenance	Data backup or server mirroring	Backup failure because of technical error	Confirmation of supplier's QMS	Data center provider

* Relevant supplier is indicated if applicable ** Supplier's QMS may be confirmed during supplier assessment
eCRF: electronic case report form QMS: quality management system CRA: clinical research associate PRO: patient reported outcome

for example, is that in the future investigators could use a database investigation to conduct a clinical "trial" and generate evidence without patients' consent or participation. [16–18]

Obviously it is important for researchers to utilize a well-organized and reliable medical database. The National Cancer Institute's SEER (Surveillance, Epidemiology, and End Results) program, for example, is a source for cancer statistics in the United States that has generated many successful studies. Database study with real-world data is quite new and likely to increase in the future.

The General Data Protection Regulation (GDPR) [19] focuses on patient information handling and anonymization in the EU. It became effective in May 2018, but anonymization rules have not yet been clearly defined nor agreed globally. Under GCP, subject identification codes are commonly used for anonymization in clinical trial operations, but it is unknown whether this is sufficient under the GDPR.

CONCLUSION

We discussed and investigated the adaptation of clinical trial management and system to the ICH E6 (R2) guideline. The ICH E6 (R2) guideline affects both clinical operation and clinical systems validation activities. We conducted a case study to assess quality risks of clinical data management system and its operation. Training for clinical team members and operation procedures review are important risk-reduction measures. A sponsor may delegate some tasks related to clinical system to a supplier, relevant risks can be mitigated via ensuring the supplier's QMS. The supplier's QMS should be confirmed through supplier assessment beforehand.

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Table B: Electronic data processing system and task allocation items to be included in sponsor SOPs

Item*	Task allocation	
	Cloud computing (SaaS)	**System on the premises**
System setup	Service supplier	Sponsor
System installation	Service supplier	Sponsor
System use	Sponsor	Sponsor
System validation	Sponsor	Sponsor
Functionality testing	Service supplier mainly Sponsor partially (only functions to be used in their business processes)	Sponsor
Data collection and handling	Sponsor	Sponsor
System maintenance	Service supplier	Sponsor
System security measures	Sponsor	Sponsor
Change control	Service supplier mainly	Sponsor
Data backup	Service supplier mainly	Sponsor
Recovery	Service supplier mainly	Sponsor
Contingency planning	Sponsor	Sponsor
Decommissioning	Service supplier mainly	Sponsor

* Items are cited from ICH E6(R2) [2]

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