PHARMACEUTICAL ENGINEERING®

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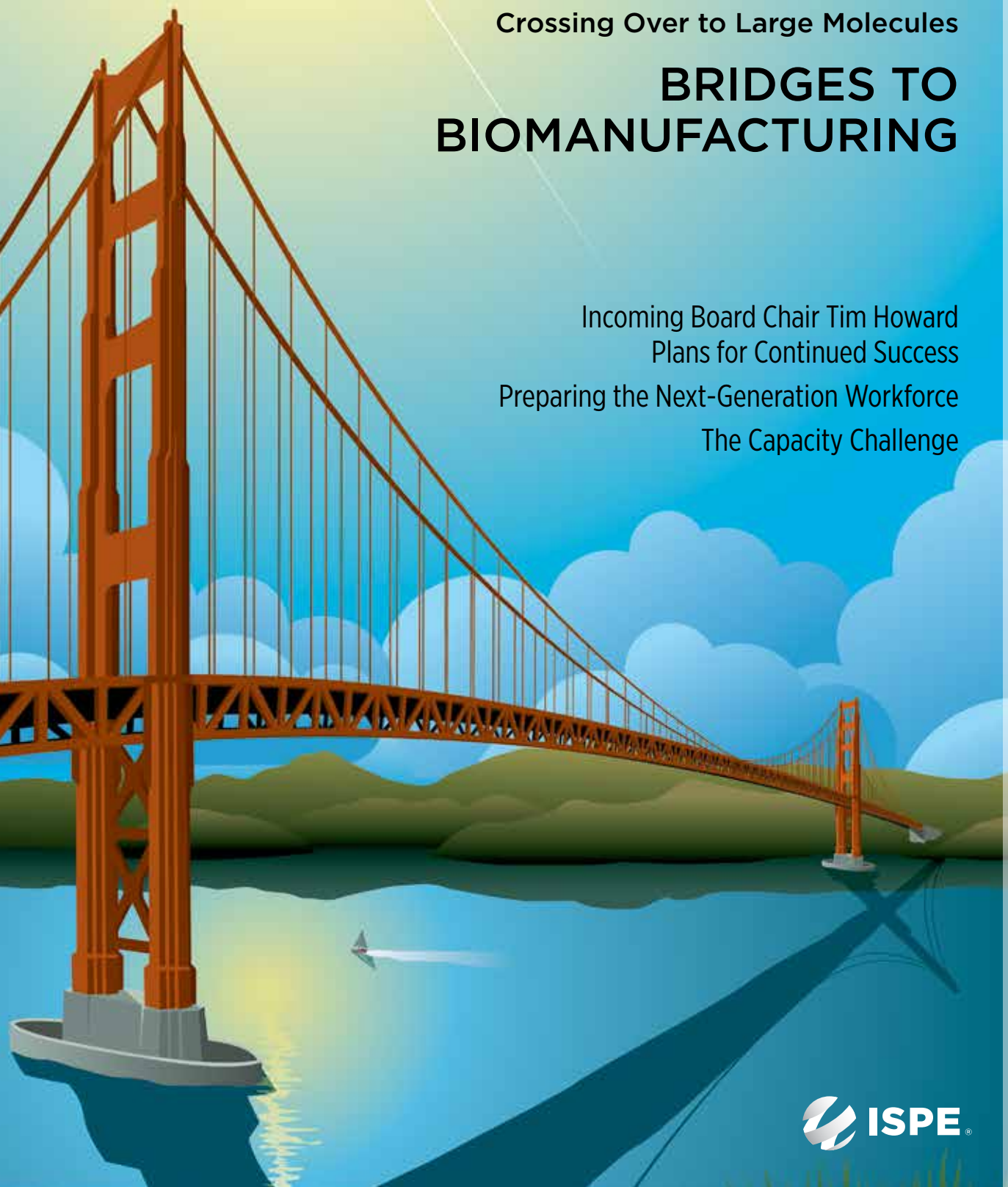
Crossing Over to Large Molecules

BRIDGES TO BIOMANUFACTURING

Incoming Board Chair Tim Howard Plans for Continued Success

Preparing the Next-Generation Workforce

The Capacity Challenge



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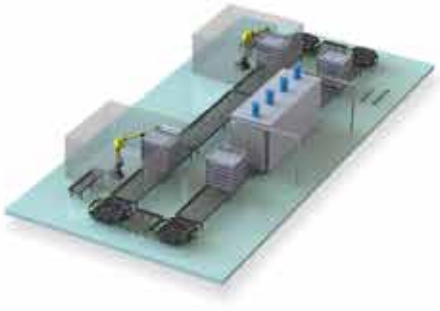

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TRANSITIONS

Ch-ch-ch-ch-changes
(Turn and face the strange)
—David Bowie, "Changes," 1972

Anna Maria di Giorgio
Editor in chief

The end of a year, the start of a new job, a groundbreaking scientific development: These are events that give us pause, moments that help us transition to a new mind-set, focus, or even a new career. Managing these moments is as important as being a part of them. In this issue, we look at transitions that our members—and the industry in which they operate—are experiencing.

We welcome Tim Howard, ISPE Board of Directors Chair for 2017–2018. His editorial provides insight into his plans for the next year and articulates his top priority: strengthening ties at the grassroots level with chapters and affiliates.

Our cover story by Rick Lawless, Director of Industry Programs at the Biomanufacturing Training and Education Center (BTEC) at North Carolina State University, addresses how engineers in traditional pharma can move to biopharma, discussing the skills that are transferable and those that require additional training. Kelly Scalva and Kerren Bergman, both of Hyde Engineering + Consulting, Inc., look at the subject of mentoring from the perspectives of a Gen Xer and a Millennial.

Nissan Cohen, industry consultant and member of the *Pharmaceutical Engineering* Committee, is guest editor of our Special Report on Data Integrity. We look at what we can learn from the Sarbanes-Oxley Act when implementing a data integrity strategy, how we must control privileged access to protect the integrity of database content, and how we can prepare suppliers for data integrity audits.

On the membership front, ISPE adviser John Berridge reports on an EMA workshop about shared facilities, GPMLF members Ferdinando Aspesi and Tony Moreira discuss a new workforce of the future initiative, we welcome a new affiliate to the fold, zoom in on two Guidance Documents, and highlight training and milestones in Thailand and Japan. We also provide a sneak peak of the environs in which the Europe Annual Conference will unfold next April in Rome.

In our technical articles, John Noble looks at capacity challenges in biopharmaceutical facility development; John Klostermyer, Bruno Aze, Alberto Garcia, and Don Eddington make the case for integrated VPHP systems; and Jeremy Lewis, Cuong Nguyen, Anh Lam, and Keith M. Forward discuss free-surface electrospinning of microemulsions to increase API solubility. Roger Zanon, Limin Shi, Kyle Johnson, and Jeff Hanson present a new statistical methodology for CU testing of CPV batches.

And to wrap it all up, Dr. Yoram Unguru, a physician at Children's Hospital at Sinai, Baltimore, Maryland, addresses the issue of ethics in pediatric oncology, where young patients face drug shortages, their parents endure an anguish we can't imagine, and hospitals must make decisions no health care facility should have to make.

Thanks for reading and I look forward to serving your needs in 2018! ‹›

ISPE

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Editorial Policy

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

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Letters to the editor
Pharmaceutical Engineering welcomes readers' comments. Letters must include the writer's full name, address, organization, and years of ISPE membership. If published, letters may be edited for length and clarity.

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FROM GRASSROOTS TO STRATEGY

New Board Chair Tim Howard Plans for Continued Success

Timothy P. Howard, CPIP, PE, and an ISPE member since 1993, is a Vice President at Commissioning Agents, Inc. (CAI), and President of Coactive, Inc., a wholly owned subsidiary of CAI.

I am very excited and equally humbled to serve as Chair of the 2017–2018 ISPE Board of Directors. During my six years on the Board, I have seen several critical shifts in the organization, with the three most significant changes being the addition of an office in Bethesda, the renewal of our positive engagement with regulators as a representative of industry, and the success we've had with initiatives around drug shortages and quality metrics. The level of engagement from industry volunteers with those two key initiatives, the quality of deliverables, and the volume of information made available to members as a member benefit have all been remarkable achievements for ISPE. These volunteers have served our membership, the industry, and ultimately, patients, with great distinction.

I would like to thank Mike Arnold for his leadership this past year. He has delivered in earnest on his four areas of focus. I'm most appreciative of his level of transparency, which I will carry forward to my objectives in the coming year.

In addition to maintaining the momentum created by Mike's initiatives, I plan to engage with and draw focus on our affiliates and chapters, make sure we establish a viable ISPE foundation, and continue to drive implementation of the 2016–2019 strategic plan.

AFFILIATES AND CHAPTERS: PRIORITY 1

Most people who interact with ISPE do so at the chapter level and along with almost every one of my board colleagues that is where I got started as an ISPE volunteer—by attending and networking at a local chapter event. A key focus for me this year will be to establish regional working groups to look for ways to make it easier for affiliates and chapters to better serve their members. These working groups will focus on "low hanging fruit," activities that facilitate better connectivity and partnering among our CoPs, operational committees, and ISPE staff. Something as simple as exchanging suggestions for speakers and topics that tie into the international body of knowledge will go a long way to strengthen ties at the grassroots level.

We have also seen great benefit from chapters working hand in hand with CoPs to produce local programming: A recent Great Lakes chapter event produced with the GAMP® group was a tremendous success. I will be assembling working groups in the coming weeks, and will share their composition and mandates in an upcoming column. Extension efforts with our affiliates and chapters is my number-one priority for the year.

EXTENSION EFFORTS WITH OUR AFFILIATES AND CHAPTERS IS MY NUMBER-ONE PRIORITY FOR THE YEAR

A NEW FOUNDATION: PRIORITY 2

The work that Tom Hartman and the Business Development Committee achieved developing the concept for an ISPE foundation is tremendous, culminating in the Board approving the establishment of a foundation. Getting the foundation up and running is my second priority for the year. The foundation will function as a support entity for ISPE, and the spectrum of ways it can add value is incredible. Initial activities will be easy to effect, such as sponsoring student travel to meetings, enabling fund-raising for the Women in Pharma initiative, and program scholarships for our conferences. The longer term requires greater consideration and we expect the complexity of the projects sponsored and the value delivered to industry and ISPE to be extensive.

STRATEGIC PLAN: PRIORITY 3

The 2016–2019 Strategic Plan provides a road map that guides the Board of Directors and CEO on allocation of resources in five key areas of focus. Along with the Board of Directors and our CEO, I will continue to operationalize the strategic plan, review the current plan, and make minor updates where warranted. In future columns, I will update you on our progress against this plan, focusing on one area per column.

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Sports fan, travel buff

What Tim Howard liked most about his last vacation was the pace. He was in Belize with his wife of 22 years, where he says, "nothing was hurried." A self-professed travel buff who enjoys scuba diving, golfing, and grilling a nice steak on the weekend, he also enjoys watching and attending sporting events. Howard, a former naval nuclear submarine officer, credits a fellow officer with his entry into pharmaceutical engineering and meeting Bob Chew, his current superior at Commissioning Agents.

"There is a sad element to the story, however," he confides. "My friend and colleague was a victim of the 9/11 attacks, while he was working reserve duty at the Pentagon. When I travel, I'll periodically look for his name on the flag of honor posted at airports. Ron was partly responsible for where I am professionally, and the life I enjoy today."

Today, Howard is a Vice President at Commissioning Agents, Inc. (CAI), and President of Coactive, Inc., the collaborative application development platform for technical teams to create, organize, and accelerate business solutions. He earned a bachelor of science degree in mechanical engineering from North Carolina State University, is a certified pharmaceutical industry professional, and a licensed professional engineer in North Carolina. ‹›

Tim Howard scuba diving with his family.

THE RESULTS ARE IN

The ISPE Board of Directors elections are a summer ritual, just like weddings, vacations, and graduations. Members once again voted for a slate of industry leaders that will govern and chart the society's strategic direction during their two-year terms. The new Directors will assume their positions at the 2017 ISPE Annual Meeting & Expo, 29 October–1 November in San Diego, California, US.

"I am looking forward to collaborating with the incoming International Board of Directors to further the organization and advance the Society mission and vision," said John Bournas, ISPE CEO and President. "The new leadership team will not only provide invaluable guidance with regard to our strategic direction and efforts to support the biopharmaceutical manufacturing industry, but will continue the organization's further globalization."

EXECUTIVES

The 2017–2018 ISPE Board Executives are:

Chair: Timothy P. Howard, CPIP, PE, Vice President, Commissioning Agents, Inc.

Vice Chair: James Breen Jr, PE, Lead, Biologics Expansion, Janssen Pharmaceuticals

Treasurer: Frances (Fran) M. Zipp, President & CEO, Lachman Consultant Services, Inc.

Secretary: Thomas Hartman, Vice President of GMP Operations, Biopharm CMC, GlaxoSmithKline

REELECTED DIRECTOR

Tony (Antonio) Crincoli, PE, Executive Director and Head of Global Engineering Services, Bristol-Myers Squibb, served from 2015 to 2017 and has been reelected to a second two-year term.

NEW DIRECTORS

Four new Directors have been elected to two-year terms:

Flemming Dahl, Senior Vice President, Novo Nordisk A/S

Kelly Keen, Project Portfolio Management, BPm, F. Hoffman-La Roche Ltd.

Alice Redmond, PhD, Vice President, European Operations, Commissioning Agents, Inc.

Michael Rutherford, Consultant–Laboratory and Quality Systems, Eli Lilly and Company

CONTINUING BOARD MEMBERS

In addition to those named above, the following Directors, elected in 2016 to two-year terms, will continue their service on the Board:

Joanne R. Barrick, RPh, Advisor in Global Validation Support, Eli Lilly and Company

Peter S. Carbone, Vice President, Quality Head Solids Americas & Special Technologies, Novartis

Christine M.V. Moore, PhD, Global Head and Executive Director, GRACS CMC - Policy, Merck

Fatma Taman, Chief Technical Officer, MS Pharma

Jörg Zimmermann, Vice President of Vetter Development Services, Vetter Pharma Fertigung GmbH&Co KG

The 2016–2017 Board Chair will continue service on the Board in 2017–2018 as Immediate Past Chair:

Michael A. Arnold, RPh, Business Process Owner Investigational Products and Senior Director of Strategic Partnerships, Pfizer's Global Clinical Supply Chain

Complete biographical information on all of ISPE's International Board can be found at the ISPE Board of Directors webpage: www.ispe.org/about/international-board-directors.

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ISPE Europe Pharma 4.0 Conference
23–24 November | Verona, Italy

ISPE Biopharmaceutical Leadership Forum
3 December | San Francisco, CA

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

2018 EVENTS

ISPE Facilities of the Future Conference
20–22 February | Bethesda, MD

ISPE Aseptic Conference
6–7 March | Reston, VA

ISPE Europe Annual Conference
19–21 March | Rome, Italy

ISPE Quality Manufacturing Conference
4–6 June | Arlington, VA

ISPE Continuous Manufacturing Conference
6–7 June | Arlington, VA

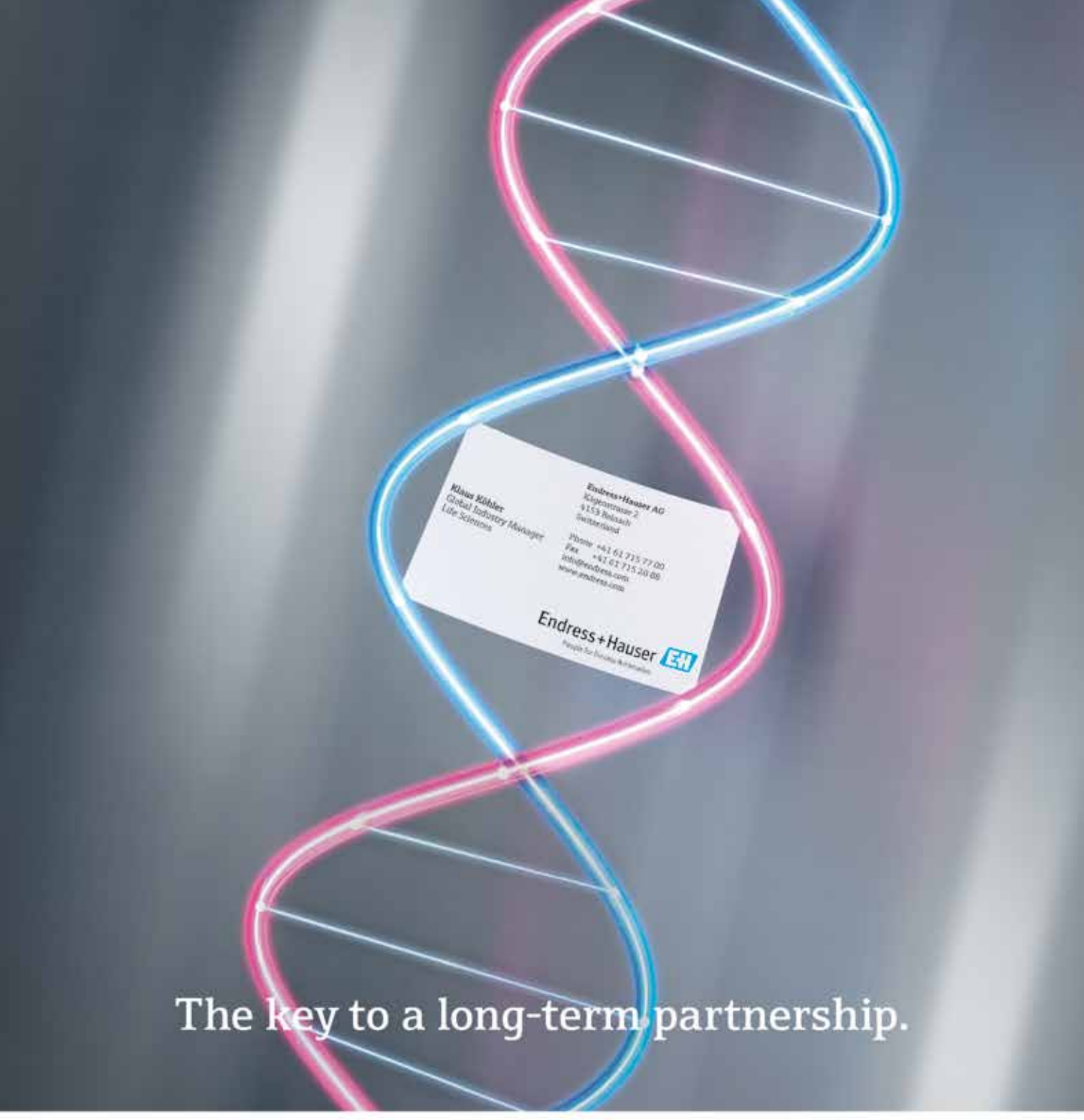
ISPE Annual Meeting & Expo
4–7 November | Philadelphia, PA

ISPE Biopharmaceutical Leadership Forum
2 December | San Francisco, CA

ISPE Biopharmaceutical Manufacturing Conference
3–5 December | San Francisco, CA

Watch our website for details on additional 2018 events!

www.ISPE.org/Conferences



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CROSSING OVER TO LARGE MOLECULES

Bridges to Biomanufacturing

Rick Lawless

Improvements in genetic engineering techniques have fueled the growth of well-characterized large molecules since the 1980s. Today, revenues from the sale of biopharmaceuticals in the United States exceed $100 billion annually.[1] Global sales are growing at a rate of more than 8%, double the rate of traditional pharmaceuticals.[2] To reduce business risk, big pharmaceutical companies have added biopharmaceuticals and vaccines—the so-called natural biological products—to their portfolios.

Engineers looking to enter the biomanufacturing workforce may feel unprepared without a background in cell culture or chromatography. There are, however, several positions that provide process support or technical assistance to production operations that require no direct experience with biological products. These can serve as effective bridges to the biomanufacturing space. Once there, it's easier to move to another position within biomanufacturing after a few years of on-the-job training and experience.

This article describes some of the processes and skills required to produce large molecules, several of which can help individuals bridge gaps in work experience. Closing some of those gaps through technical training is also discussed.

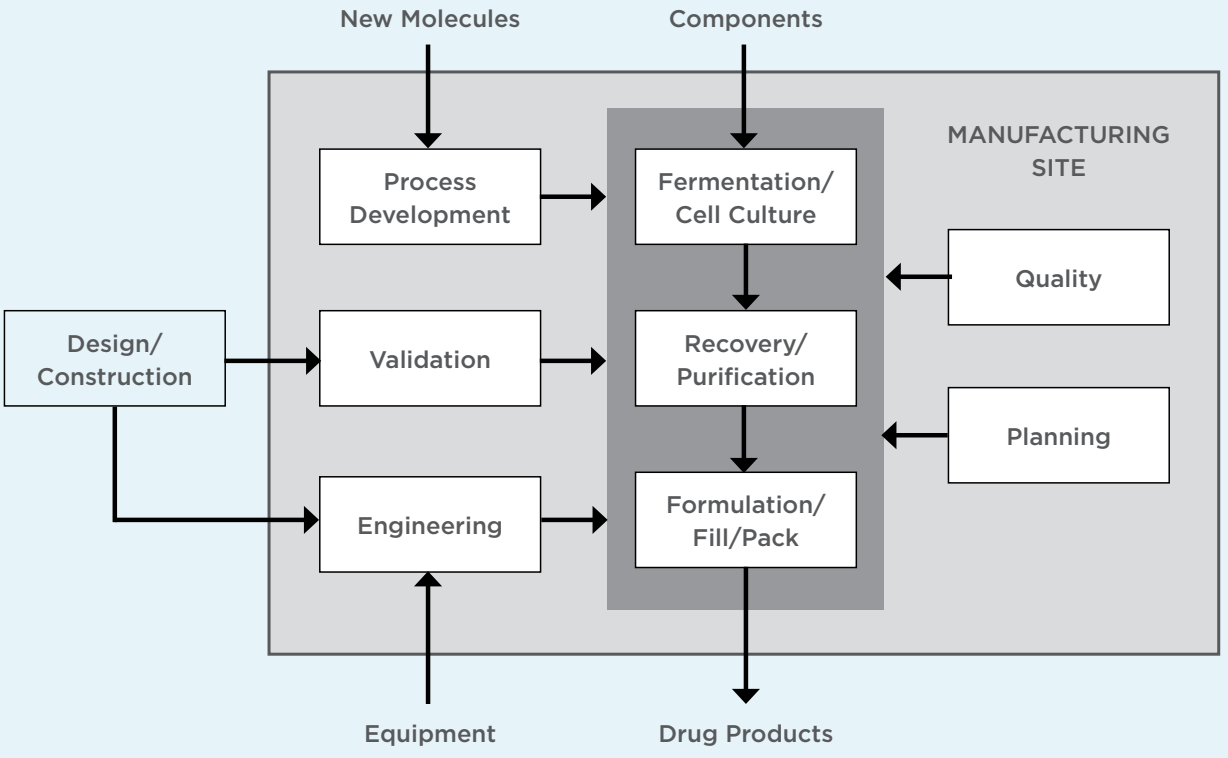
TRADITIONAL VS. BIOMANUFACTURING PHARMACEUTICAL PROCESSES

For this article, traditional pharmaceuticals are considered to be small-molecule active pharmaceutical ingredients (APIs) or dosage forms containing one or more APIs that are administered orally. These dosage forms are available from pharmacies via prescription or over the counter at retail outlets. The unit operations that produce APIs and liquid forms are quite similar to some of those used in biomanufacturing, but specialized equipment for blending, granulation, and compression is required for the production of oral solid dosage forms. In general, traditional pharmaceutical processes are fairly resistant to microbial contamination and active ingredients are stable during processing.

Biomanufacturing, on the other hand, yields biological products that contain whole cells or complex proteins. These biological systems must retain their structure or post-translational modifications, or both, to maintain functionality, so they can't be ingested and exposed to the harsh environment of the gastrointestinal tract. Instead, they are typically administered via injection or infusion, often in a clinical setting.

Critical attributes of any injectable drug product are sterility and stability. Manufacturing processes involve fermentation, mammalian cell culture, and recovery or purification operations such as centrifugation, microfiltration, column chromatography, and ultrafiltration. The requirement for drug products to be sterile and have low endotoxin levels leads to special processing to maintain low bioburden and a final aseptic filling process. Process failures can result in microbial contamination, unwanted byproducts, or both.

Figure 1: Functions and flows at a biomanufacturing site



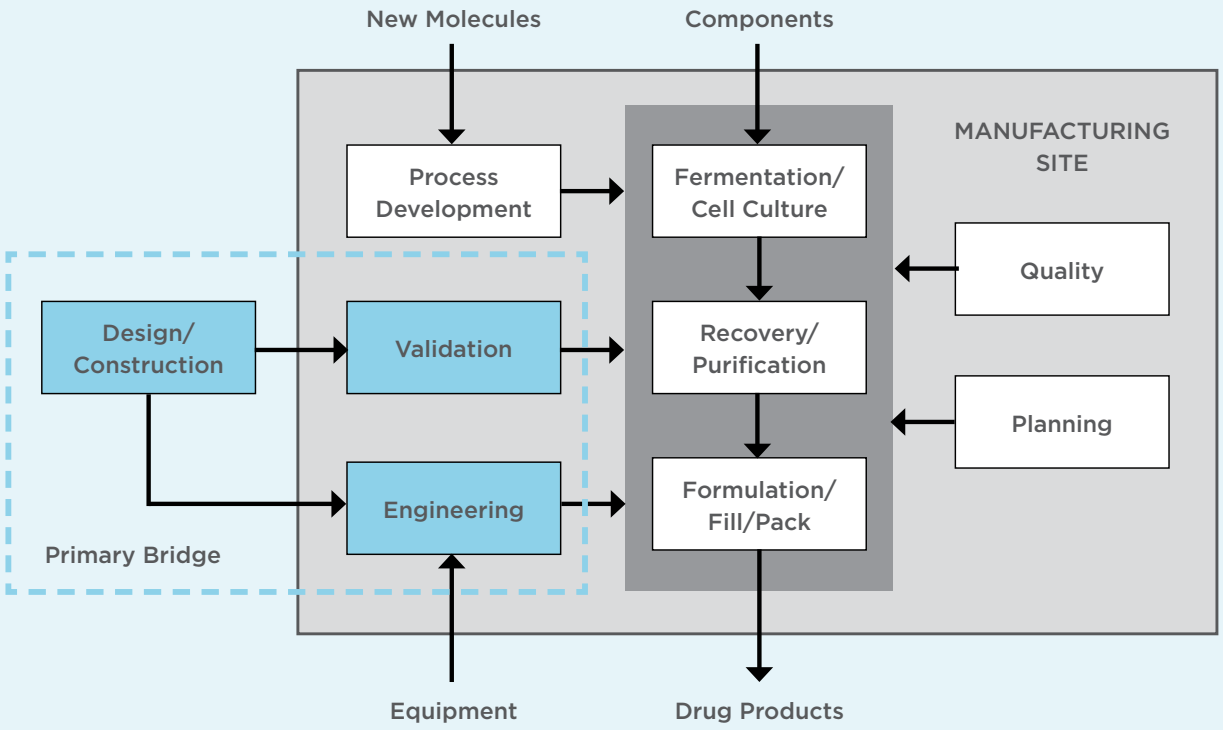
JOB SEEKERS CAN FIND PLENTY OF BRIDGES LEADING TO THE BIOMANUFACTURING SPACE

BRIDGES TO BIOMANUFACTURING

Bioprocessing operations used to produce biological products are shown in the central section of Figure 1. Microbial cells (fermentation) or mammalian cells (cell culture) grow in bioreactors and may be engineered to express complex proteins such as monoclonal antibodies. The protein or desired cells are recovered from the rest of the culture and processed to maximize purity. Finally, the protein is formulated and filled into the specified container. Since these unit operations are based on biological principles, the staff that execute production typically have extensive training in the principles of biology, microbiology, or biochemistry.

Outside the core bioprocessing operations, functional groups provide process support that is critical to the biomanufacturing operation, but is often independent of drug product or process type. Raw materials and other components, for example, must be stored and dispensed. Process safety and environmental issues are similar across the drug industry. Engineering professionals execute improvement projects and maintain facilities. In general, personnel in these roles don't require a background in biological sciences. Open positions in these groups, therefore, can be good bridges

Figure 2: Primary bridges to biomanufacturing



to biomanufacturing, especially if the job seeker has equivalent experience and a working knowledge of current good manufacturing practice (cGMP).

Groups that provide technical assistance to biomanufacturing operations are another source of bridges. Professionals in these groups have relevant technical or compliance skills, or both, but knowledge of biological principles and experience in bioprocessing are not required to meet the minimum requirements of the job. For example, the professionals may be subject-matter experts in technology transfer, validation, automation, engineering design, and quality. These talents are fully transferrable to biomanufacturing. The primary bridges are highlighted in blue in Figure 2.

REAL BRIDGE STORIES

To obtain first-hand testimonials from professionals who had made the switch from traditional pharmaceutical processes to biomanufacturing, we interviewed four biomanufacturing professionals, all based in North Carolina: Severin Butler, Lead Process Engineer, Novo Nordisk; Greg Cox, Quality Specialist, Merck; David Knorr, Senior Process Engineer, Jacobs; and Russell Teague, independent consultant. Table A identifies the bridges that helped them make the transition. While bridges involving process equipment and cGMP were expected, the biggest surprise was that all respondents mentioned process safety.

CLOSING THE TRAINING GAPS

Once a bridge or set of bridges to the biomanufacturing space has been crossed, it's time to start learning biological principles and bioprocessing techniques. Some manufacturers offer in-house training courses, but these usually address only procedural or quality topics. Professional meetings

Table A: Bridges to biomanufacturing

Interviewee	Function(s) performed prior to biomanufacturing	Bridges
Severin Butler	Oral solid dosage (OSD)	□ cGMP □ Change management □ Process control and automation □ Process safety □ Product changeovers
Greg Cox	Oral solid dosage (OSD)	□ cGMP □ Manufacturing □ Process safety
David Knorr	Active pharmaceutical ingredients (APIs)	□ cGMP □ Mixing and heat transfer □ Process safety □ Project management □ Technology transfer
Russell Teague	Petroleum, food, and enzymes	□ Fluid transfer and containment □ Mixing □ Process safety □ Reactors

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Table B: Training examples

Interviewee	Training
Severin Butler	□ Company-mandated training requirements □ External training/workshop sessions, like ISPE seminars □ On-the-job training □ Optional in-house training □ Talking with colleagues
Greg Cox	□ In-house training in quality □ On-the-job training
David Knorr	□ In-house training in aseptic processing and protein chemistry
Russell Teague	□ External training in bioprocessing □ In-house training on facilities and utilities

and external training courses offer quick learning, but these are typically expensive for individuals, and company reimbursement is reserved for more established employees. The fastest way to learn the business is to read trade journals, visit biotechnology websites, and recruit a subject matter expert as a mentor. Table B summarizes the responses on training.

FINAL THOUGHTS

The biomanufacturing industry is attracting college graduates looking for job security and good salaries, but positions are also available for seasoned professionals with experience in other types of drug manufacturing. Job seekers can find plenty of bridges leading to the biomanufacturing space, and skills and experience can be gained while providing process support or technical assistance. Finally, some training in biological sciences or bioprocessing will help with the transition but can also be completed after hire. ‹›

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About the author

Rick Lawless, CPIP, Director of Industry Programs, is a manager and instructor at the Golden LEAF Biomanufacturing Training and Education Center (BTEC) at North Carolina State University. As an independent consultant, he also provides GMP manufacturing expertise to start-up companies. Prior to joining BTEC in 2006, Rick accumulated more than 20 years of industry experience with companies such as Eastman Kodak, Johnson & Johnson, and Wyeth. He was involved in the start-up of four biomanufacturing facilities and has managed several GMP production units that manufactured commercial quantities of clinical diagnostic products and vaccines. He received a BSE in chemical engineering and a BS in microbiology from the University of Michigan, and an MBA from the State University of New York at Buffalo. He earned his Certified Pharmaceutical Industry Professional (CPIP) credential in 2013.

ISPE Japan Celebrates 15th Anniversary

Also in this section

EMA PUBLIC WORKSHOP

Shared Facilities

ISPE advisor John Berridge shares highlights from an EMA workshop on HBELs

ISPE representatives Bruce Naumann, Stephanie Wilkins, and I joined other trade and professional association delegates at a valuable European Medicines Agency (EMA) public workshop held 20–21 June 2017 in London. The meeting was intended to discuss the establishment and use of health-based exposure limits (HBELs) in quality risk management of cross-contamination in shared manufacturing facilities. Participants included industry toxicologists and quality experts, as well as members of the EMA GMP/GDP (good manufacturing practice/good distribution practice) Inspectors Working Group and the Safety Working Party, representing the workgroup supporting the development and implementation of regulatory guidance on shared facilities. The EMA summary of the workshop was recently published.[1]

DAY 1: HOW HBELS ARE ESTABLISHED

Much of the first day's discussion was prompted by a Q&A document[2] on cross-contamination and HBELs in shared facilities published for consultation in December 2016 by the EMA. We heard the background to the questions, especially regulators' desires to facilitate industry implementation of HBEL concepts in a proportionate way based on potency. Inspectors also shared findings related to HBELs and cross-contamination. Establishing the validity of an HBEL determination could be challenging, they noted. Even when HBELs are established, however, we heard that many companies fail to use them appropriately.

Industry presentations focused on the science of HBELs and their value in determining the hazard of a compound. Bruce Naumann's discussion of the life cycle approach to HBELs explained that appropriate toxicological expertise is required at all phases. Use of traditional 1/1,000 of the (lowest) clinical dose lacks scientific rigor and was universally opposed. Cleaning limits established using traditional approaches can help set priorities for those still working through their portfolio, but formal HBELs for all compounds being handled should be determined by a qualified toxicologist according to an appropriate standard operating procedure. The HBEL is then used in risk-identification processes.

European requirements are likely to be adopted by the Pharmaceutical Inspection Cooperation Scheme (PIC/S), whose GMP guidelines are aligned with those of the European Union (EU). PIC/S were also reported to be in the process of forming an Expert Circle on the control of cross-contamination. In addition, there was a useful discussion about what inspectors might look for, which could help them assess the validity of an HBEL determination.

A very welcome review of the draft Q&As enabled a shared understanding of industry and regulatory perspectives. While regulators were keen to facilitate simple establishment of HBELs by companies that lack toxicological expertise and handled only low-hazard compounds, industry participants felt that the "highly hazardous" categorization was a retrograde step that lacked scientific rigor.

Toxicological expertise would always be required to establish a robust classification, and relevant data should be readily available for legacy compounds. It was acknowledged that the 1/1,000 of the minimum clinical dose proved appropriately conservative in around 85% of cases, but sufficient exceptions exist such that a toxicology review is recommended to ensure that the categorization is scientifically valid. After such a review, the concept of a "hazard continuum" can be used. The newly revised *ISPE Baseline® Guide Volume 7: Risk-Based Manufacture of Pharmaceutical Products* (second edition)[3] describes this concept in more detail in its Chapter 5 on Risk Identification. Such a continuum could be helpful to regulators classifying operations at manufacturing sites.

Most companies have already completed their HBEL determinations, but we heard that there are a number of smaller companies with limited ranges of low-hazard products for which the regulators felt it was disproportionate to impose a full toxicological evaluation process. Many of these companies find it challenging to complete the evaluations, but inspectors are generally applying a light touch to enforcement at the present time.

Industry response to this difficulty was to restate concerns over the lack of scientific rigor in the proposed highly hazardous categorization and the dangers of oversimplification, but to support that there may be opportunities for some flexibility with well-established prod-

ucts where hazards are clearly low. It was evident that we all supported the need to protect patients from the risk of cross-contamination with a highly potent or highly hazardous agent. Further discussion among regulators will follow.

Cleaning limits were also a topic of discussion, including the possible misunderstanding that HBELs would become limits for cleaning validation, despite visual cleanliness requirements. Another misperception may have been that 1/1,000 or 10 parts per million represent standard regulatory acceptable limits. Perhaps what added confusion was the reference to additional safety factors that could be misinterpreted as requiring adjustments to factors used in calculating a permitted daily exposure.

Following that, it was clarified that the intention was to ensure that cleaning limits are set sufficiently below the HBEL limit to provide a suitable safety margin to accommodate variability. In many cases, traditional limits would provide this headspace (but this would need to be justified). All agreed that "visually clean" was a minimum requirement for cleaning, but it would need to be shown how the visually clean threshold aligned with an HBEL limit, since the latter could be higher or lower. There is a helpful discussion on these concepts in Chapter 6 of the newly revised Risk-MaPP guide.[3]

DAY 2: RISK ASSESSMENT AND USE OF HBELs

Three presentations from inspectors exemplified their rigorous approaches to evaluation of cross-contamination, although the focus was not so much on the determination or use of HBELs. It was somewhat surprising to hear that many of the problems encountered are related to poor application of basic GMP expectations for the control of cross-contamination and not to HBELs.

Three industry case study presentations followed. The first considered the challenges of handling veterinary products. The second, presented by Stephanie Wilkins on behalf of ISPE and drawn from Scenario 4 of the Application Examples within the Risk-MaPP guide, focused on the integration of cross-contamination controls within the overall quality system. In addition, Wilkins clearly answered the question of how to determine margins of safety and set alert, control, and acceptance limits for cleaning validation. The third case study considered a large portfolio of legacy and innovator products. We were reminded of the differences between small and large molecules, particularly with respect to cleaning, where the risk is considerably lessened due to degradation where this can be definitively established.

Conclusions

This extremely valuable workshop, with its science-based focus, concluded with a discussion on next steps. Industry asked for a better understanding of inspectors' expectations and how they could be met. Inspectors opined that they are unlikely to carry out a detailed examination of HBEL determinations at this time, although their understanding is always increasing so this may happen more in the future. This led to a discussion on training for both inspectors and industry.

ISPE offers training on Risk-MaPP, and the second edition of the Baseline Guide takes into account these latest regulatory developments. Both small and large companies could benefit from Risk-MaPP training, which can help even if HBEL determinations are being outsourced; Risk-MaPP training has also been welcomed by non-EU authorities. Other educational opportunities identified included the publication of case studies on HBEL determinations. ISPE's Risk-MaPP guide contains a selection of valuable case studies.

Some topics are still to be addressed. These include the chemical manufacture of active pharmaceutical ingredients, where the same approaches may be applicable, except that the impact of intermediates must be addressed. Advanced therapy medicinal products may also need consideration, although they are governed by separate GMP guidance. Further work is required to define so-called "highly sensitizing products" (e.g., beta-lactam antibiotics). Current GMP guidance requires dedicated facilities for these, yet this is becoming open to scientific discussion. It was also clear that more discussion on veterinary facilities would be helpful. Further consultation on these subjects is anticipated.

Finally, the question of whether the draft Q&A document should be withdrawn was considered. Since consultation had already occurred, it should be self-evident that the document does not provide the definitive regulatory position. Nevertheless, the EMA agreed that some might understand it to be a final position, and so will consider their next steps with some urgency. ‹›

—John Berridge, ISPE Advisor

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2018 EUROPEAN ANNUAL MEETING COMES TO ROME

Rome's Esposizione Universale Roma, or EUR district, has seen more than its fair share of history. Originally planned as the site of the 1942 World's Fair under Italy's prewar fascist regime, the uncompleted EUR suffered extensive damage during the Second World War and was not fully developed until the 1950s and 1960s. Now a thriving business and residential district, the EUR will host the ISPE 2018 Europe Annual Conference from 19 to 21 April 2018 at the Sheraton Roma Hotel and Conference Center.

"With its proximity to central Rome, wide boulevards, tree-lined streets, and cafés and *gelaterias* (shops selling Italian ice cream), the EUR district is a great destination for this year's conference," said Thomas Zimmer, ISPE Vice President of European Operations.

Among the EUR's buildings, the Palazzo della Civiltà Italiana is perhaps the most recognizable example of the city's prewar fascist architecture. Nicknamed the *Colosseo Quadratto* (Square Colosseum), the building was completed in 1943 and was intended to be the district's focal point. Today it serves as the headquarters of the luxury fashion house Fendi. The building also houses an

The Palazzo della Civiltà Italiana is perhaps the most recognizable example of the city's prewar fascist architecture.

intriguing scale model of imperial Rome that will be of interest to history buffs.

The *Palazzo dei Congressi*, designed originally as a modern version of the Pantheon, was the site of some events at the 1960 Olympics and is currently used to host conferences. It is but a short walk from this example of rationalist architecture to its modernist neighbor, the striking new convention center and hotel complex designed by the architectural firm Studio Fuksas.

The renowned Giolitti gelateria is also a short drive from the conference center, in a beautiful park surrounding a man-made lake.

A STRONG TRADITION OF MANUFACTURING AND R&D

"Italy's thriving domestic market is complemented by the country's production of medicines for other countries in the European Union (EU)," said Zimmer. "In addition to its strengths in pharmaceutical production, Italy has many excellent machine manufacturers and technical consultant companies."

Several multinational pharmaceutical companies have chosen to locate their European R&D and manufacturing in Italy because of this existing infrastructure and strong tradition. The sector is first among all manufacturing sectors in Italy in terms of investment and exports of foreign-owned companies. Exports have grown more than 50% since 2010, due largely to improved quality of medicines and vaccines that the country exports around the world.

"Many Italian pharmaceutical companies have struck production alliances in Europe with specialization of technologies in dedicated factories," said Zimmer.

Italy ranks second in the EU for pharmaceutical manufacturing, producing a quarter of medicines among the top five producers, and has experienced the fastest growth in pharmaceutical exports among the member states. Collaborations between companies, public-private partnerships, universities, and biotech startups round out a robust pharmaceutical manufacturing ecosystem that includes significant research and development.

"Italy has a great academic tradition, well-established universities feeding R&D sites with skilled people, and competitive labor costs," said Zimmer.

According to Farmindustria, an association of more than 200 pharmaceutical companies operating in Italy, investment in R&D has grown 20% in the past three years. The country's R&D efforts focus on biotechnology, which accounts for 71% of investment, vaccines, plasma products, advanced therapies, rare diseases, and rare diseases. The country has led the way in development of novel products, including the first stem-cell medicine, Holoclar.

Fully 40% of pharmaceutical firms are domestic, not unusual for the European pharmaceutical sector, according to Zimmer. "Many companies started from pharmacies or small chemical factories that are more than a century old. Italy's R&D strength comes out of this rich history as many companies are or were family owned and conducted their own research and development. When acquired, some international companies developed these R&D sites as a nucleus for their own efforts."

Farmindustria notes that women make up nearly half (44%) of the workforce in Italy's pharmaceutical sector.

"We at ISPE are pleased to see the role of women in our industry changing," Zimmer said. He points to such ISPE initiatives as Women in Pharma and notes that women already play a strong role in domains such as quality assurance, quality management, and drug regulatory affairs. "Even in production, which has been traditionally a male domain, we're seeing more and more women involved. Management is still predominantly male, but even here there is some progress for women.

"I'm looking forward to the Europe Annual Conference in March," said Zimmer. "It offers our members a chance to see a beautiful and historic part of Rome that is often overlooked by tourists." ‹›

—Scott Fotheringham, PhD

For more information, see "ISPE Italy: Poised for Leadership," *Pharmaceutical Engineering* 37, no. 3 (May-June 2017): 28–29.

PREPARING THE NEXT-GENERATION WORKFORCE


Ferdinando Aspesi, Senior Partner, Bridge Associates International LLC

"It's a large subject," admits Ferdinando Aspesi, when we ask him how the Global Pharmaceutical Manufacturing Leadership Forum (GPMLF) plans to address one of the hottest topics in the industry: the workforce of the future.

The GPMLF is represented by 65 thought

Dr. Antonio Moreira (right) hosting an international event at UMBC.

leaders who meet regularly to discuss such critical industry issues. Its Chair is Andy Skibo, Head of Global Biologics Operations and Global Engineering at MedImmune/AstraZeneca. "The GPMLF," says Skibo, "exists as a kind of neutral setting within which we address and progress areas of common interest. And we work with ISPE on mutually agreed upon initiatives that fit within its scope and strategy."

Workforce of the future is one such initiative, and Aspesi, Senior Partner at Bridge Associates International LLC, is chair of the task force tasked with bringing "something concrete" to the topic. "We formed a 16-member team within the GPMLF to develop an action plan that will see ISPE provide education to the next generation of professionals." says Aspesi. He says the team is looking at a five-year horizon.

GPMLF leaders Skibo and Past Chair Lou Schmukler, President, Global Manufacturing and Supply, Bristol-Myers Squibb, made it clear they wanted to focus on areas where the team could make an impact: active pharmaceutical ingredients (APIs) and drug products, biotechnology, combination products, and cold chain supply.

1. APIs AND DRUG PRODUCTS
   Assumption: Major part of the API and drug product manufacturing will occur in low-cost countries, except for continuous manufacturing, where the investment will go mainly into the United States and Europe
2. BIOTECH DRUG SUBSTANCE
   Assumption: Major part of the investment and manufacturing will occur in the United States and Europe
3. DELIVERY SYSTEMS AND COMBINATION PRODUCTS
   Assumption: Major part of the investment and manufacturing will be in the United States and Europe
4. COLD CHAIN DISTRIBUTION
   Assumption: Applies to any geographical area

There are not enough professionals truly skilled in these four areas, says Aspesi. "We would like this education and training initiative to begin as early as 2019. The question is how to educate, develop them, and close the current gap?"

OFFERING EXPERIENCE

Subcommittee member Antonio R. Moreira, PhD, Vice Provost for Academic Affairs, University of Maryland, Baltimore County, and current ISPE Board Director, believes it is important to reach out to students before they enter industry. "Industry wants students to acquire experience before they join," says Dr. Moreira, "so we want to target, at a minimum, students working toward a master's degree."

The first step was to identify the workforce requirements and related technical profiles. Next, the team will match the technical profiles with university programs around the world.

"In the last year, the team has developed 34 technical profiles," says Dr. Moreira. "We are now ready to identify the gaps that may exist between what we (industry) perceive as a need and what the universities currently offer," he adds.

The use of robotics and automation, for example, is emerging as a major trend in biopharmaceutical manufacturing. Robotic systems are also becoming central to aseptic processing and R&D productivity increases, and engineering automation and IT are critical partners to manufacturing, leading to the design and implementation of an integrated and robust manufacturing control strategy. Students will be best prepared for industry careers when they understand system architecture, functionality, and configuration at the operations level, and have a fundamental understanding of robotics and how it enables process redesign with a focus on the finished product.

The team intends to join forces with targeted universities in North America, Europe, and Asia, and deliver a series of pilot education and training programs related to the four areas of concern. "The first pilot will be held with North American universities," says Aspesi, "the second with European universities, and the third, most likely with a university in China."

While much of the upfront work will occur directly with academia, industry will play a large role once the curricula have been finalized and universities selected. In fact, Aspesi believes it has "the biggest piece" of this initiative: "We'll need contributions in the form of internships for the students, in factories or development labs, as well as industry representatives to organize seminars with academia and teach students topics specific to their area of industry expertise."

DEVELOPING SUPPORT

ISPE will work very closely with the team and has made a commitment to provide assistance with a dedicated website. Wendy Sturley, Vice President, Membership, Marketing and Communications will lead this project with Maria Robertson, Senior Director of Marketing and Communications. The website will launch in 2018.

"This GPMLF initiative dovetails nicely with our strategic objectives, both from training and diversity perspectives," says Sturley. "It will also promote ISPE's desire to reach out to potential members—students—with a concrete plan for education and training before they enter the workforce."

The GPMLF and ISPE are breaking new ground with this initiative, and making way for similar collaborations in the future. ‹›

COMING SOON: ISPE EURASIAN ECONOMIC UNION AFFILIATE

A delegation of pharmaceutical industry professionals and regulators from Russia met with ISPE leadership and staff on 20 July. The visit was arranged by the International Visitor Leadership Program (IVLP), a professional exchange program run by the Bureau of Educational and Cultural Affairs at the US Department of State. The IVLP's website states that its goal is "to provide firsthand knowledge about American society, culture, and politics, while cultivating lasting relationships."

Since 1940, more than 200,000 people have taken part in the IVLP. Participants are nominated by the staff at US embassies, and thematic topics are based on key foreign policy objectives.

Of the 12 attendees, seven were from the Russian Ministry of Industry and Trade, two from Unica Engineering Ltd., and three were translators. Representing ISPE were Board Chair Michael A. Arnold, RPh, Investigational Product Business Process Owner, Pfizer Global Clinical Supplies; ISPE CEO and President John E. Bournas; ISPE Director of Regulatory Operations Carol Winfield; ISPE Senior Director of Membership and Component Relations Ciara Durkan; Joseph C. Famulare, Vice President, Global Compliance, Genentech, and immediate past chair of ISPE's Board; George P. Millili, PhD, Senior Principal Technical Advisor, Genentech, and Co-Chair, ISPE Regulatory Quality Harmonization Committee; Roger Nosal, PhD, Vice President and Head of Global Chemistry, Manufacturing and Controls, Pfizer Inc., and Chair of the ISPE Regulatory Steering Committee and ISPE Pharmaceutical Engineering Committee.

GOOD NEWS FOR EAEU

The delegates requested a meeting with ISPE to learn about its role in building effective partnerships with regulators and agencies around the world, the Quality Metrics initiative, and to discuss the launch of a new ISPE affiliate. Delegates also want to foster cooperation with ISPE's Board of Directors and communities of practice, organize an annual conference, hold professional and technical seminars, and translate select guidance documents into Russian.

"We had a very productive meeting with the delegation from Russia," said John Bournas. "We have been working with them since April on the establishment of the ISPE Eurasian Economic Union (EAEU) Affiliate, and our goal is to have an official launch in Moscow this October. "The affiliate goal is well underway, with some 100 members already enlisted. Among the EAEU Affiliate's top priorities will be the harmonization of industry standards that promote the circulation of quality products throughout its territory.

The EAEU is an international organization for regional economic integration whose member states are the Republic of Armenia, the Republic of Belarus, the Republic of Kazakhstan, the Kyrgyz Republic, and the Russian Federation.

"This is an amazing opportunity that will allow us to bring all of ISPE's member benefits to professionals in the EAEU region," said Ciara Durkan, Senior Director, Membership and Component Relations. "Now companies can learn best practices to produce generic and innovative drugs, create new medical products, and train their staffs.

"Industry professionals will not only be able to access *Pharmaceutical Engineering* magazine, join compelling conversations via the CoPs, attend our conferences, and more, but they will also have an organized local network," she continued. "Personal connections are essential in an industry as important and complex as ours, and we're so excited for the people of the EAEU to have that."

The team took time out of the meeting to commemorate the visit

THE DELEGATION

Ministry of Industry and Trade
Russian State Institute of Medicines and Good Practices

- Nadezhda Valentinovna Arkhipova, Lead Specialist, Production Inspection, Department of Medicines
- Vyacheslav Viktorovich Goryachkin, Lead Researcher, Department of Inspection
- Mikhail Dmitrievich Morozov, Head, International Cooperation Department
- Vladimir Aleksandrovich Orlov, Deputy Chief, Department of Pharmaceutical Production Inspections
- Vladislav Nikolaevich Shestakov, Director
- Elena Sergeevna Zelenova, Administrative Assistant to the Director

Russian State Research Institute of Pharmaceuticals
Igor Vsevolodovich Falkovsky, Department Head, Proper Engineering Practices

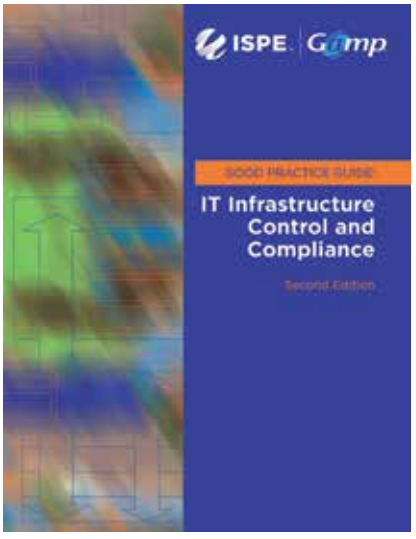
Unica Engineering Ltd., Moscow

- Vakhtang Giaevich Dzhanashvili, Managing Director
- Alla Anatolyevna Iurtaeva, Unit Leader, Unica Engineering Ltd.

Translators
Marina Moyer, Roman Borukhov, and Artem Mkrtchyan

New Guidance Documents Available

ISPE GAMP® GOOD PRACTICE GUIDE: IT Infrastructure Control and Compliance (Second Edition)



The *ISPE GAMP Good Practice Guide: IT Infrastructure Control and Compliance* (second edition) is intended to provide comprehensive guidance on meeting regulatory expectations for compliant IT (information technology) infrastructure platforms, both traditional and cloud-based. The increasing prevalence of new technology has presented regulated companies with significant technological advantages as well as a changed compliance model.

The validated status of GxP* applications that are dependent upon an underlying IT infrastructure can be compromised if the IT infrastructure is not maintained in a demonstrable state of control and regulatory compliance. Data integrity can also be affected by problems related to IT infrastructure, leading to increased risks that can in turn affect product quality or patient safety.

The *ISPE GAMP Good Practice Guide: IT Infrastructure Control and Compliance* (Second Edition) applies a structured approach, including risk management, to the qualification, management, and control of IT infrastructure platforms supporting GxP-regulated applications. The Guide provides a scalable qualification framework that can be applied to different platform types, across both the physical and virtualized space, in order to determine the extent and scope of qualification efforts. The Guide also provides an overview of industry best practices for the design, qualification, and operation of an IT infrastructure, with emphasis on the qualification requirements of the major components.

The revision expands the scope of the Guide to include guidance on the emergence of cloud and virtualized technologies. Information has been added to reflect significant changes in the technologies that make up IT infrastructure, including:

- The use of virtualization technologies that allow the sharing, combining, and maximization of resources
- The use of cloud computing, including cloud-based infrastructure and three cloud-based service models: infrastructure as a service (IaaS), platform as a service (PaaS), and software as a service (SaaS)
- The delivery of GxP applications "as a service"
- Outsourcing and the increased use of third-party data centers

For more information, or how to order the updated Guide, visit https://www.ispe.org/publications/guidance-documents/gamp-it-infrastructure-control-compliance. ‹›

* One or a combination of GCP (good clinical practice), GMP (good manufacturing practice), GLP (good laboratory practice), or GDP (good distribution practice)—where "x" refers to clinical, manufacturing, laboratory, or distribution; often used for everything of interest for regulatory bodies. Source: ISPE Glossary (www.ispe.org/glossary)

ISPE BASELINE® GUIDE: Risk-Based Manufacture of Pharmaceutical Products (Second Edition)

Manufacturing multiple products in a facility increases the risk of cross-contamination, potentially threatening product quality and patient safety. Many regulatory bodies require that companies operating multiproduct facilities have risk management processes in place to minimize the risk of cross-contamination.

"There's a need to support companies with multiproduct facilities in how to manage these risks," said Stephanie Wilkins, president of PharmaConsult US, which provides cross-contamination and containment consulting to the pharmaceutical industry. Wilkins has been a member of ISPE since 1993, is a member of the Guidance Documents Committee, and co-led the team that produced the updated Baseline Guide. "Many generic manufacturers and CMOs (contract manufacturing organizations) have additional risks due to the nature of their business, and this Guide is an excellent resource to help them manage those risks. We often see the highest risk of cross-contamination from failures to follow basic GMPs (good manufacturing practices)."

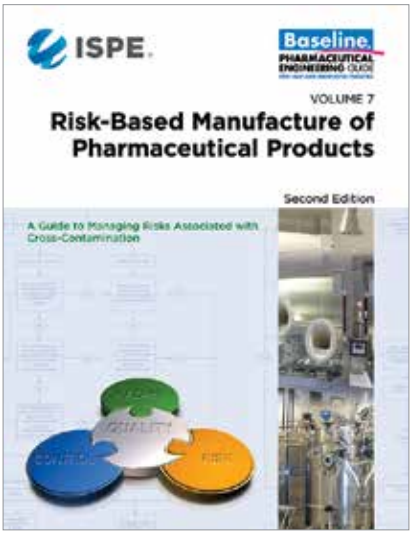
The second edition *ISPE Baseline® Guide: Risk-Based Manufacture of Pharmaceutical Products* incorporates the latest updates to European Union GMPs. Risk assessments and risk-management principles are now required to ensure the safe manufacture of products in a shared facility and to determine whether a particular product should be manufactured in a dedicated facility.

Risk-based manufacture of pharmaceutical products (Risk-MaPP) can help pharmaceutical companies develop and maintain risk-management plans to minimize the risk of cross-contamination. It also provides a scientific risk-

based approach, based in the ICH Q9 guideline "Quality Risk Management,"[1] to manage the risk of cross-contamination to achieve and maintain an appropriate balance between product quality and operator safety.

"Risk-MaPP gives companies a process for risk management and what they should focus on in terms of cross-contamination," said Wilkins. "Sometimes, if the operators don't understand the importance of a particular SOP (standard operating procedure), they may think a step is not important and they can bypass it. Risk-MaPP provides an outline on how to assess risks so that the importance of some SOPs can be better understood."

Wilkins uses the gowning regime as an example. "When you enter a GMP space, gowning serves to protect both the person and the product. When you leave the manufacturing space of one product, you take off the gown to prevent the spread of residue elsewhere in the facility—and especially in other production areas producing different products. There are many places we consult where this protocol is not understood, and workers will wear the same gown everywhere, all day. Studies have even found that residue has made it into office areas of facilities because of this."



Risk-MaPP adheres to the primary principle of ICH Q9 quality risk management that the evaluation of risk should be based on good science and risk-based approaches to determine the controls that are needed to make safe, high-quality products.

Individual chapters in the second edition of the Risk-MaPP Baseline Guide detail how to create a risk-management strategy that identifies, analyzes, evaluates, and controls the risk of cross-contamination. Risk-MaPP describes the health-based limit of exposure, referred to as the acceptable daily exposure (ADE)—a dose that is unlikely to cause an adverse effect if an individual is exposed, by any route, at or below this dose every day for a lifetime. The ADE is the starting point used in assessments to determine if there is a cross-contamination issue. The European Medicines Agency (EMA) considers the ADE synonymous with its health-based limit, called the permissible daily exposure.

The Risk-MaPP Baseline Guide outlines the four modes of cross-contamination—mix-up, retention, mechanical transfer, and airborne transfer—and has a logic diagram that can be used to assess whether the manufacture of a product requires the use of a dedicated facility.

"The EMA reviewed Risk-MaPP and agreed that it is in line with the agency's updated GMPs," said Wilkins. "I would expect the EMA to

point companies struggling with managing the risk of cross-contamination to [the] Risk-MaPP [Guide].

"There were a lot of companies that implemented the principles outlined in the first edition and, for the most part, had good experiences. The process has the added benefit of helping companies better understand their products, their facilities, and their processes."

The *ISPE Baseline Guide: Risk-Based Manufacture of Pharmaceutical Products* (second edition) is available for purchase on the ISPE website.[2] ‹›

—Scott Fotheringham, PhD

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2. International Society for Pharmaceutical Engineering. *ISPE Baseline® Guide: Risk-Based Manufacture of Pharmaceutical Products*, 2nd ed. https://www2.ispe.org/imis/ItemDetail?iProductCode=BGRMAPP2DLUS&CATEGORY=DOWNLOAD

San Francisco/Bay Area Chapter

SUPPORTING A PROSPEROUS INDUSTRY

With more than 600 biotech and pharmaceutical companies and 700 medical device and equipment companies, the pharmaceutical industry in the San Francisco Bay Area is flourishing. In 2016 alone, biotechnology and pharmaceutical investment in California, and the Bay Area in particular, resulted in 63 deals worth $2.2 billion.[1]

Like its home region, ISPE's San Francisco/Bay Area Chapter is equally robust and growing—engaging its membership with a series of events that both educate and provide much-need networking and social interaction.

Founded in 1991, the Chapter covers the greater San Francisco Bay Area, a populous, area in northern California that includes major cities such as San Jose, San Francisco, and Oakland as well as Silicon Valley. With more than 810 members, the chapter reflects the region's diverse business landscape, with representation from biotechnology, pharmaceutical and medical device manufacturers, architects, engineers, construction firms, government agencies, universities, and equipment manufacturers and suppliers.

FOSTERING ENGAGEMENT

To support such a large and diverse membership, the chapter's board maintains a high level of engagement through a series of educational, market-information, and social events, among others. "We try to cover everything our membership might be interested in," says Chapter President Patti Larson.

The chapter was the first to offer CEO nights, which are fast becoming popular among other ISPE Chapters and Affiliates. The dinner meeting—the chapter's first event of the year—features one or two senior executives from local firms who present an overview of their organizations and discuss challenges and opportunities.

The highly popular Vendor Night, held in March, is a major contributor to the chapter's annual revenues. "Two years ago, we moved the event to AT&T Park, home of the San Francisco Giants baseball team," says Kimberly Syre, Chapter Manager. "By moving to AT&T Park, located in downtown San Francisco, we increased our participation from both attendees and vendors."

The chapter's other major annual event, and its largest networking activity, is Fun Day, where attendees can either play golf at one of two adjacent courses or tour some of the region's famed wineries.

In addition to these large annual events, the chapter provides many opportunities for members to get together, among them the unique Commuter Conferences, which are members-only activities held about four times per year from midafternoon to early evening.

"We have been working hard on making content strong enough at our events, but things are complicated by extreme traffic," explains Larson. "The idea with the Commuter Conferences

QUICK FACTS

Founded: 1991
Region: San Francisco/Bay Area, California, US
Membership: 810+

CONTACTS

President
Patti Larson, XL Construction

Vice President
Ralf Elsaesser, Dome Construction Corp

Secretary
Brian Vaughn, CRB

Treasurer
Trevor Auer, CRB

Past President
Dr. Karl Wilks, WCS, Inc.

Directors
Arnold Asuncion, Total Validation Services Inc.
Tareq Barakzoy, ACCO Engineered Systems
Jason Beck, Alexandria Real Estate Equities
Germaine Bickel, Genentech
Logan Kelley, BioMarin

Membership Chair
Shawn Mazzeo, University of California-San Francisco

Young Professionals Chair
Heather Bennett, ACCO Engineered Systems

Student Affairs Chair
Heather Bennett, ACCO Engineered Systems

Chapter Manager
Kimberly Syre, Attention To Detail

is to get people to the meetings before traffic starts and let them out after it ends."

The event calendar in the region has been supplemented in the last two years by the ISPE Biopharmaceutical Manufacturing Conference, an annual event that launched in 2016.

NOURISHING THE ROOTS

Since 2006, the chapter has been involved in the Chocolate Factory Program, a community outreach initiative designed to spark an interest in science and engineering among fifth-grade students in the South San Francisco Unified School District. "Each month, a sponsor company brings in people to show the kids how to build a mock chocolate factory using craft supplies," says Syre. "They explain how the whole system works—using raw materials to produce an end product—which is somewhat similar to the pharmaceutical industry."

The chapter also has strong student chapters at local colleges, such as San Jose State University and the University of California, Berkeley, as well as an active Young Professionals (YP) Committee. "Students and YPs are a great resource for us as far as getting volunteers to help," says Larson. "They support the chapter in a big way."

ALL ABOUT THE VOLUNTEERS

Keeping the chapter running smoothly means relying heavily on the volunteer efforts of Board and Committee members. To ensure a tightly knit group, the chapter organizes a retreat for its Board as a team-building experience. "I think it really helps set the tone for the entire chapter as well as the events," says Larson. "We have a really strong group of people who genuinely like and respect each other."

The chapter also holds an annual volunteer appreciation day to say thank you to the many committee members. "We invite the committee members, the Advisory Council and the current Board of Directors," says Syre. "Just like the retreat does, the day helps us keep strong committees and strong working groups." ‹›

—Mike McGrath

References

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ISPE THAILAND COHOSTS CLEANROOM TESTING AND CERTIFICATION COURSE

ISPE Thailand cohosted "Cleanroom Testing and Certification," a joint meeting between the affiliate and the Thai Industrial Pharmacist Association on 2–3 May 2017 at the Ambassador Hotel Bangkok.

The meeting drew 250 attendees—including 30 from the Thai Food and Drug Administration—as well as 18 exhibitors. It was accredited by the National Environmental Balancing Bureau (NEBB), a feature that attracted many NEBB delegates from abroad. ISPE Singapore also sent its event director to help in ISPE Booth—a wonderful sign of collaboration among ISPE members in this region.

ISPE Thailand President Totsapon Santitewagun, Managing Director, Global Tech Co., Ltd., opened the meeting by introducing the course instructor, cleanroom expert Dan C Milholland, Managing Partner of Milholland and Associates and an ISPE member since 1991. Milholland presented the in-depth content over the next two days, with topics that covered:

- Basic cleanroom design
- Cleanroom standards, past and present
- Primary and secondary cleanroom tests
- Cleanroom testing and certification

"I am sure after this event," said Santitewagun, "we will see a significant increase in membership."

To reciprocate the collaboration they enjoyed at their cleanroom event, 10 ISPE Thailand members traveled to Japan from 16–21 May to celebrate that affiliate's fifteenth anniversary and network with ISPE colleagues (see page 26). "It seems that we will have interactive activities throughout the whole year," said Santitewagun. ‹›

ISPE JAPAN CELEBRATES 15TH ANNIVERSARY

ISPE Japan's Annual Meeting, always the leading event in the affiliate's calendar, was especially festive this year as the group celebrated its fifteenth anniversary. Held 18 and 19 May at the Toyama International Conference Center in the mountainous Chūbu region on central Honshū, the event was titled "A Brave New World of Innovation: What Does It Hold for Us?"

With Asia-Pacific emerging as a major pharmaceutical market, ISPE Japan has enjoyed vigorous growth since its establishment in 2001. Membership is now well over 800, a remarkable increase from the below-100 level of the pre-inauguration days, and most of the affiliate's activities are performed by its 16 communities of practice.

The meeting, which celebrated the affiliate's history while looking forward to future industry trends, hosted 567 attendees, with an international cast of invited speakers, full program of sessions, table-top exhibitions, and events that included the popular networking party. Participants came from the pharmaceutical industry, academia, and regulatory authorities. Simultaneous translation between Japanese and English was provided during the first day of meeting sessions.

Keynote speakers were:

- Norikazu Eiki, former Chairman of Bayer Japan and a member of the ISPE Global Pharmaceutical Manufacturing Leadership Forum
- Siôn Wyn, Director, Conformity Ltd.
- Harry Rothenfluh, PIC/S Assistant Secretary Manufacturing Quality Branch, Therapeutic Goods Administration Department of Health
- Shingo Sakurai, PMDA Office of Manufacturing/Quality and Compliance, Office Director

Concurrent with the Japan Annual Meeting, the affiliate also hosted the Asia Pacific Affiliate Council annual face-to-face meeting, with excellent attendance from both council members and ISPE staff. ‹›

USING SOCIAL MEDIA IN YOUR JOB SEARCH

Hi David: You seem to be very active on social media. Do you have any best practices for job seekers?

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

Most companies leverage social media as part of their recruiting strategy, so if you don't use it in your job search you put yourself at a huge disadvantage.

First, determine your brand: How do you want others to see you? Who do you want to find you? What qualities set you apart as professional? Having a clear vision about your social media identity will help the right people want to get to know you.

BUILD YOUR PROFILE

Social media platforms—including LinkedIn, the most important one for job seekers—require that you establish a profile. Doing this properly will make it easy for recruiters and hiring managers to find you and determine you value as a candidate. Here are some tips:

Picture: Dress appropriately, and smile! This will encourage people to connect with you. A professional photographer can help create the right image, so take advantage of hiring events that offer free head shots. Use the same profile picture for all your social accounts.

Headline: This is the first thing people see when they view your profile. A successful headline should be pithy, communicate your expertise, and describe the value you can bring to an employer. By default, LinkedIn populates your headline with your current job title and employer, but it's probably better to create your own. Which sounds better: "Project Engineer with XYZ Company" or "PMP-certified professional engineer, leader of successful multimillion-dollar projects in the US and EU"?

Contact information: Make it easy for people to reach you. Add a phone number and email address that you plan to monitor. Match your voicemail greeting and email address to the image you are trying to project.

Experience: On platforms such as LinkedIn that allow you to highlight work history, sync your content to your resume. Include key words and industry-appropriate terms that are likely to appear in recruiter searches. (Note: The rules for social media content are similar to those for your resume, so look through some of my previous columns for additional tips.)

Profile: Make sure your profile is complete, with all fields populated. Attach your resume, include other documents to support your value proposition, and embed website links. When creating a "handle" or username, choose one that is professional and consistent with your brand.

Separate work from personal: Finally, review your security settings to ensure that your profile is open to your intended audience. Establish separate personal and professional accounts to align your professional interactions with your professional brand, and engage privately with family and friends.

ENGAGE

Armed with a solid profile, how should you engage?

Join, follow, like: Group memberships and the pages you like communicate your interests, so be selective. Following thought leaders can help you gather information about industry trends and new opportunities.

To post or not to post: Before you share anything, make sure it aligns with your brand. If you are employed, review and comply with your company's social media policy. Once you post, consider it permanent and searchable.

While authenticity is good, not everything should be shared. Ask yourself if the post will help you reach your target audience. Pay attention to grammar and spelling. If you're sharing content, read the article first—don't just rely on the headline.

After you share, review the post. If you catch an error, edit or delete it. If you have been using social media for a while, review your posting history. Google yourself to find and delete anything that doesn't represent you well.

Contribute: Commenting on other posts is another way to get noticed, show yourself as resourceful, competent, and helpful, and encourage others to include you in their networks. You don't have to avoid controversial topics, especially if you are an expert and can offer a perspective that shows your knowledge well, but choose your battles wisely. Before engaging, ask yourself if the subject fits with your brand. If you wouldn't want your boss, a hiring manager, or your mom to see it, then don't post.

Find and apply for jobs: Company pages often list open positions and offer alerts when new jobs are posted. Recruiters and hiring managers also highlight positions for their followers. When applying for jobs via your social media profile, however, exercise caution. Although it's easy to do, it's also difficult to know what and how data is transmitted. To avoid this, find the position on the company website and apply directly.

Thank you for your question, and I wish you the best of luck expanding your social network. If you would like to connect, you can find me on LinkedIn at https://www.linkedin.com/in/davidglennsmith and on twitter at @DavidGSmithNC. ‹›

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

GEN X, MILLENNIAL

The Mentoring Relationship, Step by Step

Kerren Bergman and Kelly Scalva

Mentoring is a hot topic these days. Do a quick Google search of the word "mentoring" and you'll get some 95 million results. A narrower search, "mentoring an engineer," will get you about 11 million results, or 12% of the first search. For even more targeted results, try searching "mentoring a woman engineer," which returns 438,000 results—about 0.5% of the results for mentoring. And how many of those 438,000 results are relevant? Every article offers similar messages: It's important to mentor the younger generation; young engineers need mentoring to succeed. How does this mentorship play out? And how does one become a mentor or mentee?

What follows is a case study of a mentoring relationship between Gen Xer Kerren Bergman and Millennial* Kelly Scalva. The study includes examples of reading materials, topics of guidance, lessons learned, and the joint successes both the mentor and mentee have seen in both their personal and professional lives.*

Kerren Bergman

Kelly Scalva

Gen X Steps, Kerren Bergman

I have noticed that as I age, I get more set in my ways. If you're like me, in your late 40s with 25 years or so of work history, you probably find it easier to do things as you've been trained to do. You rely on knowledge gained from years of experience.

But experience can cage us in. Young people hold a key that can set us free, and mentoring them is a great way to obtain that key. For those of you who think mentoring is a burden, I can guarantee that you will receive far more than you give.

STEP 1: MAKING A CHOICE

We Gen Xers are proud to recall how things were "back then":

- We started working before the internet, email, cell phones, or Google existed.
- Our mail was physically delivered to us daily in interoffice envelopes.
- Our tools were typewriters, transcription machines, *Encyclopedia Britannica*, and card catalogues.
- Hard-copy calendars and day planners captured meetings, notes, and to do lists, and we carried them with us everywhere.

Think of how much technology has changed throughout our careers!

Beyond their ability to embrace new technologies, young people today have open minds, unending curiosity, and desire for information. They want to contribute, and will carry you forward with their spirit.

Millennial Steps, Kelly Scalva

I am an engineer. Holding that title in society has allowed me to find a niche for myself and comfortably fit in. I've always been drawn to the crisp, clean knowledge of numbers, where there are only ever two options for an answer: right or wrong, yes or no. So, when I was struggling with a manager, I figured there were only two options: be miserable forever, or find a new job.

It had never occurred to me there might be another option, until my father suggested I find a respected colleague, someone with an impeccable reputation, whom I could ask to be my mentor. I took his advice, and it changed my life and my career.

STEP 1: MAKING A CHOICE

Spoiler alert: Mentoring changed my life and my career. You may think you can do this on your own, and I bet you could get through 80% of it without any help. But it's the last 20% that's the most valuable part of the experience. If you'd rather go straight to the end, read ahead! For the rest of you, let's go back to the beginning.

How would a mentor help me address the issues I had with my manager? I wasn't sure. "Run away," the engineer in me said. "The problem has no solution. Time to move on to the next assignment." But I was torn. I loved the company, so perhaps asking someone to be my mentor would be a good idea. But the terror of having to actually ask made me want to procrastinate.

* The Harvard Center defines Generation X as people born between 1965 and 1984, and Millennials as those born between 1985 and 2004.

You have a choice: You can be a rock in the river and let all this change flow around you, or you can let go and experience an amazing new world. Your mentee will accompany you—and it's so much more fun navigating together.

STEP 2: WHERE TO BEGIN?

If you're asked to be a mentor, and if you think there's a connection between you and that person, say yes! If you're not asked, but have a desire to mentor, identify a high-potential performer in your organization with whom you may have a connection, and make the commitment.

Why would you venture down this path? Because it will inspire your own personal and professional growth. Your mentee will keep you aware of the fabulous tools that just keep on coming. You will make a deep connection with another human being that may last a lifetime. You will strengthen your organization, improve communication, and increase employee retention.

The professional environment continues to evolve. There are still basic ingredients like people, products, and deadlines, but now there are endless variations of communication and potential outcomes. To navigate this landscape, the wisdom of knowing how to interact professionally is essential. Long years of experience teach you the wisdom of knowing an email can be misinterpreted, depending on tone and context, or the wisdom of knowing how to listen to an alternative perspective and collaborating to find a solution. Mentoring will give you the opportunity to pass on that knowledge.

I began by defining my choices:

- Love job + communication issues with manager = must quit job.
- Find mentor + love job + communication issues with manager = stay at job?
- Find mentor = identify a person, ask person ...

Courage was what I needed. Google helped. I quickly searched "How to ask someone to be my mentor," and, like a video game code hacker, I searched until I found the courage and knowledge I needed to try to get to the next level in this real-world video game. I wasn't going to let this be my "game over."

When I finally asked Kerren to be my mentor, it was no big deal. One text-message meeting time, one 20-minute phone call, and the problem was solved. The last three years have been one easy conversation after another, with solution-based feedback that has led to one of my most significant work relationships.

STEP 2: NOW WHAT?

So, you've made the leap off the wooden wharf and onto the ferry to escape from oncoming Ringwraith; you've asked someone to be your mentor—or someone has asked you to mentor them. Well done! Now, where will this take you? Gandalf isn't around to lead the two of you through Middle Earth!

There is more online information about *The Lord of the Rings* than there are search results for "questions to ask your mentor or mentee." In fact, the

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STEP 3: THE MENTORING PROCESS EXAMINED

When you begin the mentoring relationship you will drive the format of your meetings, timing, and content. Given how many people are working remotely these days, you may have to mentor virtually: over the phone, by webinar, Skype, etc. If you have the luxury of working together in the same office (as Kelly and I did), it's much easier to coordinate meetings, and anything occurring face-to-face is more powerful.

Kelly did not have expectations regarding process, but I decided we should meet biweekly, off-site, to avoid usual office interruptions. I chose one of my favorite restaurants for us to meet, but you could meet at a coffee shop, a library—anywhere that is comfortable for both of you and relatively private. There were many occasions where frustrations were aired and lots of emotions were shared, so it helped to have a quiet space where we could interact.

Our biweekly appointment was "sacred" on my calendar. I realized that if I moved it frequently, I would be sending a message that my meeting with Kelly was not a high priority, when in fact, I cherish our hour together.

I asked Kelly to keep a notebook and told her there would be homework. I also committed to doing homework myself. I'm a "lead by example" manager and never ask anyone who supports me to do something I would not do myself. Kelly took this directive very seriously, and by the time we decided to write this article, she had several notebooks to which we referred. I would assign her homework based on a concept, book, or article we'd read, and she would keep notes and details of her progress. She is a true engineer: methodical, diligent, and dedicated. Her level of commitment is directly reflected in the strides she has made.

Although we met off-site biweekly, our mentoring activity seeped into our daily work life. Kelly would come into my office and excitedly tell me about a success she'd had, based on our recent exercises. Or she would send me an email chain and ask for feedback on her response. There were days she would text me in dismay over an argument, or suggest a walk around the block to process a team meeting. The beauty of this work is that it seeps into your daily moments, whether at work or at home. The growth that you experience is not limited to the work environment. This is why mentoring fundamentally encourages human growth.

results make it sound like you're about to go on a very awkward date. I don't know about the rest of you, fellow engineers, but I've been on enough awkward dates. I bet most mentors are as excited about meeting their mentee for the first time as I was—which is to say, not excited but extremely nervous.

STEP 3: THE MENTORING PROCESS EXAMINED

When I showed up for our first meeting, I was nervous, sweating, and wondering about my decision to dress up. I mean, it wasn't an interview, was it?

Kerren had arranged to meet at a local restaurant for breakfast, just after the start of the workday. I showed up 15 minutes early, and wasn't sure if I should hang out in my car or get a table. When I finally walked through the door, I saw it was a friendly place: open at 6 a.m. for the older crowd (seriously, there must be a senior center next door) and closed well after the professionals at the bar had no excuse not to be home with their families. After four cups of coffee, I realized fifteen minutes alone at a restaurant awkwardly waiting for someone can feel like forever.

Normally a subtle person, Kerren began by asking me three questions point-blank: "Where do you see yourself in a year? Are you working at the same company? What are you doing every day?"

My heart, aflutter with too much caffeine, almost slammed to a halt. I stammered out long-forgotten answers, including, "Above all, staying at our current company." She held my gaze, assessing my responses, sipped her tea, and nodded. "All right then," she said. "We start today. Bring a notebook and pen next time. You'll want to take notes, and I'll be giving you homework."

I can't say what I was expecting for the first meeting, but I was not expecting homework, or the requirement to keep a notebook. So, I think my first notes were scribbled on the back of an old receipt I found in my wallet, using a pen lent to me by the waiter. As I was new to the whole process and really wasn't sure if there might be some sort of exam at the end, I wrote down every detail.

I began taking notes at every meeting, mentoring or otherwise, jotting down favorite phrases and documenting odd moments I might want to look over later. The process of note-taking over the years has made me a "Jedi Master" at talking, typing, and running a meeting at the same time. My notes have kept me honest and accountable for attempting to improve every day.

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STEP 4: TOOLS FOR GEN XERS AND MILLENNIALS

This is our list of our top 10 tools, but we didn't run mentoring like a book-club. These books were inspiration for our learning and growth. We should also mention the fun we had having a "no complaints" day, when we weren't allowed to grumble (I'd recommend trying it—your eyes will open to just how much negativity people use in the work place). Or the week we experimented with observing and then copying other people's body language to determine the changes in interactions based only on the variable of body signals. Or the kick-boxing classes we attended together during the company wellness challenge. When you start punching bags together, there's no going back!

We began this journey with a tool to guide our process: the book *StrengthsFinder 2.0* and the associated internet-based Clifton StrengthsFinder assessment test. Please note the word "we." Both the mentor and mentee started this process with an assessment of strengths and then moved on to the following reads and exercises:[1]

1. *StrengthsFinder 2.0*, by Tom Rath (Gallup Press, 2007)
2. *How to Win Friends & Influence People in the Digital Age*, by Dale Carnegie (Simon & Schuster Paperbacks, 2012)
3. *The 7 Habits of Highly Effective People*, by Stephen R. Covey (Simon & Schuster, 1989)
4. *Difficult Conversations: How to Discuss What Matters Most*, by Douglas Stone, Bruce Patton and Sheila Heen (Viking Penguin, 1999)
5. *The Four Agreements: A Practical Guide to Personal Freedom*, by Don Miguel Ruiz (Amber-Allen Publishing, 1997)
6. *Lean In: Women, Work, and the Will to Lead*, by Sheryl Sandberg (Alfred A. Knopf, 2013)
7. *Smart Women Finish Rich: 9 Steps to Achieving Financial Security and Funding Your Dreams*, by David Bach (Broadway Books, 1999)
8. *The Life-Changing Magic of Tidying Up: The Japanese Art of Decluttering and Organizing*, by Marie Kondo (Ten Speed Press, 2014)
9. *Callings: Finding and Following an Authentic Life*, by Gregg Levoy (Harmony Books, 1997)
10. *The One Minute Manager*, by Kenneth Blanchard and Spencer Johnson (William Morrow and Company, Inc., 1982)

1 Reference information for the works listed refers to original publisher and year of publication.

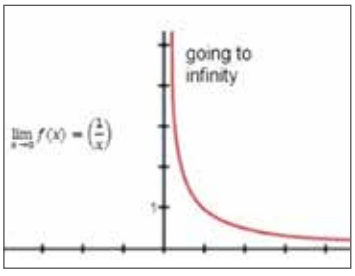
STEP 5: PS

The differences among generations can be illustrated by this section's header. How many young people today know that "PS" stands for "PostScript?" Does it matter if they don't? How much do we keep of the "old" and adopt of the "new"? How do you even define either of those categories anymore? In what time frame?

As Kelly states, there is no ending to the growth in a person's career or personal life. Whether you're at the beginning of your career, at the mid-career stage, or close to retirement, there is no end to our growth process. We can always learn more, gain new skills and perspectives, face fears, and take risks.

If we choose to cultivate the worth and potential in all generations at work today through mentoring, there is no limit to the benefits for our organizations or for ourselves. ❮❯

STEP 5: THE END?



At this point, you may want to know, "Where does this mentoring relationship end?" I think it can best be answered utilizing the limit of a rational function in which x approaches zero. Using the formula shown in the chart, when x becomes smaller and smaller, the value of f(x) becomes larger and larger, approaching a value larger than any we can imagine. Our problems at work get smaller, while our value continues to grow. Thus, the limit does not exist, and there is no ending. ❮❯

About the authors

Kerren Bergman, MEd, SHRM-SCP, an ISPE member since 2011, is Senior Director of Human Resources + Internal Systems at Hyde Engineering. She has over 25 years of training and development experience, and holds a master's degree from the University of California, Los Angeles. Bergman is President of the International Society for Pharmaceutical Engineering Rocky Mountain Chapter, as well as a member of the Society for Human Resource Management (SHRM).

Kelly Scalva, BS, an ISPE member since 2010, is a Proposal Manager at Hyde Engineering + Consulting, Ltd., where she uses her engineering capabilities to ensure the technical accuracy, cost estimation, scheduling, and compilation of proposals from each of Hyde's domestic and international regions. She holds a bachelor's degree in chemical and biological engineering from Colorado State University.

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SPECIAL REPORT

COMPLIANCE TRANSPARENCY CONTROL

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DATA INTEGRITY AND BIOPHARMACEUTICAL MANUFACTURING

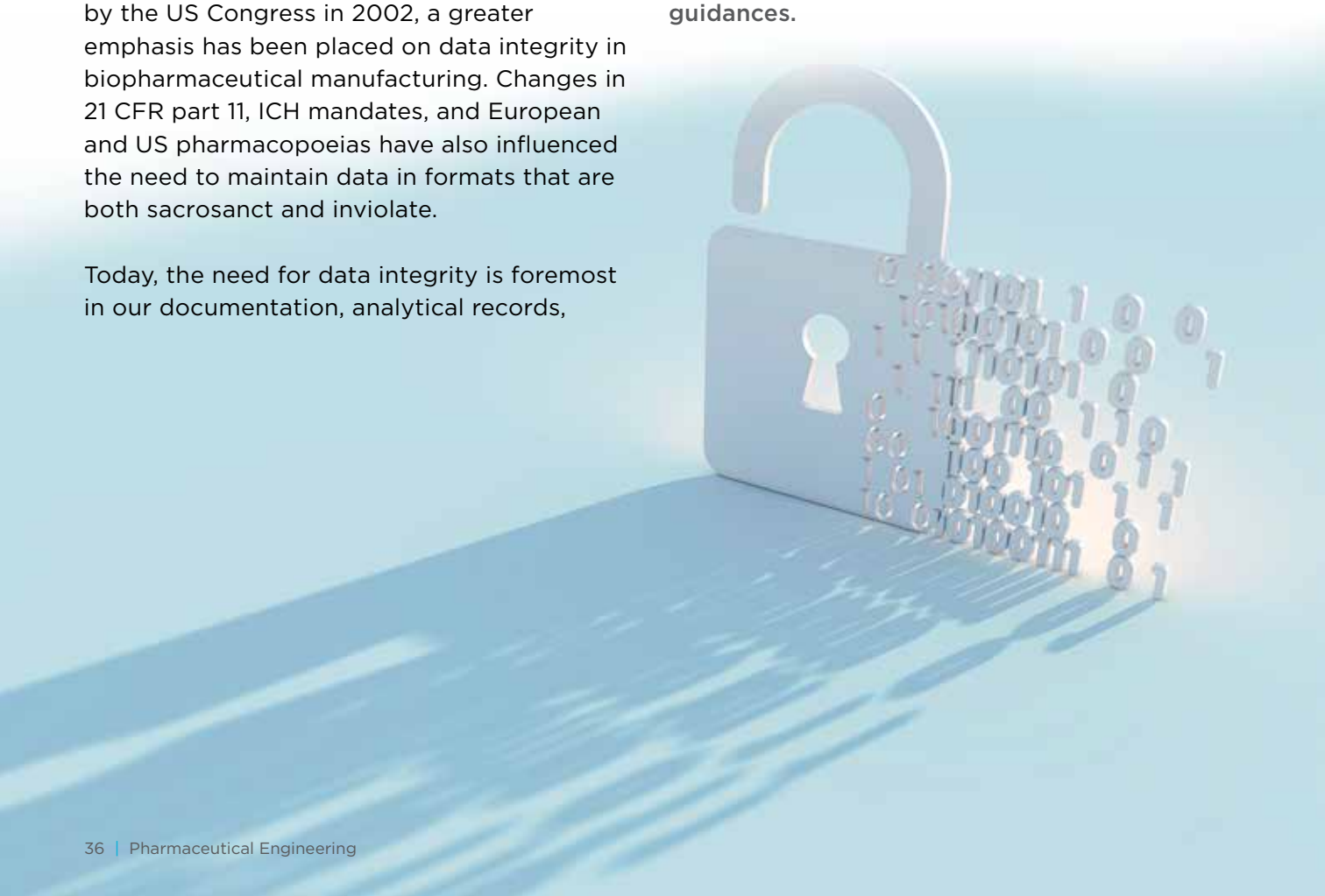
Nissan Cohen

Before the advent of integrated computer systems, LIMs, HMI interfaces, comprehensive software, CGMP, BAS, process control systems, PAT, and the use of statistics, manual record keeping was fraught with errors—most of them unintentional. This led to citations for missing data, signatures, and date and time entries, to say nothing of the risks posed to patient safety.

Since the Sarbanes-Oxley Act was passed by the US Congress in 2002, a greater emphasis has been placed on data integrity in biopharmaceutical manufacturing. Changes in 21 CFR part 11, ICH mandates, and European and US pharmacopoeias have also influenced the need to maintain data in formats that are both sacrosanct and inviolate.

Today, the need for data integrity is foremost in our documentation, analytical records, measurements, and requirements. Data integrity demonstrates that processes operate within proscribed limits, and ensures that we can archive, retrieve, and show the data for any state of the process at any given moment in time.

This Special Report provides insights into how we manage, use, and incorporate data to protect the integrity of all values, measurements, and processes—as well as comply with regulatory mandates and **guidances.**



A MATTER OF TRUST

Lessons Learned from the Sarbanes-Oxley Act

James Canterbury and Chris Jacobson

IN THE WORLD OF SOX, REPORTS ARE EVERYWHERE

Fifteen years ago, corporations embarked on a journey toward SOX compliance; along the way they have learned a tremendous amount about data integrity as it relates to financial systems. Those lessons learned are directly applicable to many of the data-integrity challenges facing the pharmaceutical industry today.

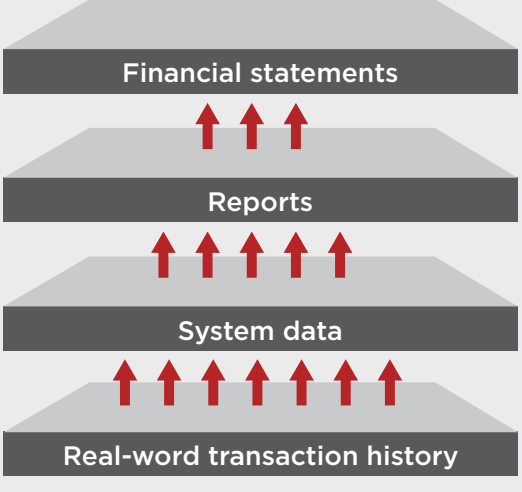
In 2002, the US Congress passed the Sarbanes-Oxley Act (SOX) act to protect investors, creditors, and employees from harm due to fraudulent financial reporting and accounting activities by public corporations. The law was a reaction to front-page news of the direct impact of financial reporting scandals and the accompanying overall decline of trust in financial reports and the institutions that produced them.

SOX focused on four key areas: auditor oversight and independence, restrictions and ethical expectations of analysts, executive responsibility for financial reporting, and internal control reporting (section 404), which outlined requirements for information technology (IT) departments regarding electronic records and the need to establish internal controls regarding the completeness and accuracy of information.

The bipartisan SOX legislation, enacted in July 2002, included the creation of the Public Company Accounting Oversigh t Board (PCAOB) to regulate the auditors of public companies, a profession that previously had been self-regulated. Since then thousands of companies of different sizes across diverse industries have journeyed through SOX compliance, each working to apply the related regulations to their unique situations and implement a system of internal controls that met the requirements. Supporting technology has evolved and companies have been able to optimize their control environments, allowing them to more efficiently and effectively know that their financial data is materially accurate.

When we reflect on data integrity as it relates to GxP (e.g., good manufacturing practice or good laboratory practice), the same issue of trust applies. In the GxP scenario, however, the US Food and Drug Administration (FDA) replaces the PCAOB, and plays the roles of both auditor and regulator. By not requiring that an independent third-party attest to the completeness and accuracy of the reports, the onus of data integrity for GxP is placed squarely on the shoulders of the owning organization.

Hierarchy of SOX data



There is also a fundamental element common to the control of GxP processes and financial processes: reports. Financial statements are reports that represent a formalized, consolidated view of real-world transactions that the public relies on (and that the US Securities and Exchange Commission [SEC] regulates). This is similar to how batch release approval is

obtained through reports, which are consolidated views of individual test results and raw data: The principles of data integrity must be embedded throughout the process in order to elicit confidence that the final statements are true.

HOW DID COMPANIES START THEIR SOX JOURNEYS?

Asking "What can go wrong?" is where most SOX programs began. Given the objective to prove that a business is creating accurate financial reports, four types of risks are typically identified in any given process:

1. Process and/or supporting system is not designed correctly
2. Systems do not function as intended
3. Human error—accidental (some people make mistakes)
4. Human error—not accidental (some people cheat)

Companies identified business processes, the risks associated with them, and controls to address those risks. Controls could be designed to prevent an error or to detect and correct one in a timely manner. Some companies seized the opportunity to challenge and enhance their processes, while others sought solutions that complied with the law and avoided foundational change. In time, industries and service providers began to join together through professional organizations to develop standards governing what a control framework should include and how it should work.

One of the most recognized of these organizations is the Committee of Sponsoring Organizations of the Treadway Commission (COSO), a joint initiative whose mission is to provide thought leadership through the development of comprehensive frameworks and guidance on enterprise risk management, internal control, and fraud deterrence designed to improve organizational performance and governance and to reduce the extent of fraud in organizations.[1] COSO issued its initial "Internal Control—Integrated Framework" in 1992, and the framework and its subsequent updates became the main standard that companies follow to assess internal controls.

The PCAOB's initial Auditing Standard No. 2 was widely criticized for being unwieldy and prescriptive.[2] In 2007, the SEC unanimously repealed Auditing Standard No. 2 and replaced it with the much shorter Auditing Standard No. 5, which was intended to make standards principles-based, flexible, and scalable. Companies shifted their focus to a smaller set of "key" controls, and much of the SOX testing effort was put into making sure these were designed and operating effectively.

Organizations put a lot of thought into specific testing approaches for these controls, requiring them to be tested by people who were both competent and objective, and where possible implementing automated controls to prevent issues from happening. A classic example is a three-way match between a vendor invoice, a purchase order, and goods receipt before payment is distributed—most enterprise resource planning (ERP) systems now handle this as core functionality. As awareness of controls increased, companies put pressure on software vendors to bake controls (and configurations for controls) into their systems. This has led to more software-driven compliance and systems that are designed with controls in mind.

Out of this grew a new breed of software for governance of risks and controls (GRC). These software programs were geared initially toward managing an entity's risk and controls framework while automating or at least better organizing much of the routine testing of controls. They have expanded into software administration platforms that help manage access, design role-based security and monitor changes to the environment. The prevalence of GRC and its ability to drive business value beyond compliance suggests that it is an approach that might have a positive impact on data integrity initiatives within GxP environments as well.

The main lesson learned with determining key controls is: Pick your controls carefully. There needs to be a balance between preventing and detecting, and not every control needs to be tested. Understanding the risk that the control addresses is a critical aspect of picking the right controls. It is also helpful to ask "What must go right?" when establishing a controls framework. If SOX is any indicator of the direction that GxP software vendors might take in response to increased scrutiny on data integrity, we could find an increased level of configurable security controls and audit trails within standard software packages.

RELIANCE ON REPORTS

In the world of SOX, reports are everywhere and are intended to instill confidence in a public company's overall consolidated financial reports. To achieve that goal, a company must rely on hundreds of individual reports and sources of data. Many controls are considered IT-dependent manual (ITDM) controls, meaning that a system generates some data in the form of a report or data extract but a person is responsible for reviewing that report to execute the control. The control is only as good as the quality of the data in the report. The reliance on system output in ITDM controls is similar to how pharmaceutical companies rely on reports within GxP processes. It is in these reports that we can glean many of the lessons learned about data integrity.

The testing approach for ITDM controls provides a good parallel to efforts currently underway in many data integrity initiatives. Understanding the source, of which there are usually four categories, is a good starting point:

1. Standard system report (comes with system functionality; can't be configured)
2. Custom system report (developed for a specific need; configurable)
3. Data extracts/queries (user-defined parameters)
4. Spreadsheets

After understanding the source, we focus on the logic. Each report performs the following sequence:

Input→ Transform/Aggregate → Output

Let's look at these in reverse order:

Output: When dealing with reports, completeness and accuracy are two sides of the same coin. It is no coincidence that completeness and accuracy are two components of ALCOA+.* "Completeness" means that a given report represents everything that it was designed to represent and meets the criteria (filters) specified in the report. In other words, the data was not cherry-picked to tell a particular story. "Accuracy" means that the data is true. The majority of the data-integrity issues that life sciences companies face today fall under the context of accuracy. Verifying accuracy can be a

* The FDA introduced the acronym "ALCOA" (attributable, legible, contemporaneous, original, accurate) to provide attributes of integrity; the term "ALCOA+" adds four additional attributes: complete, consistent, enduring, available. Source: http://blog.ispe.org/data-quality-and-data-integrity-what-is-the-difference

REGULATORY TENSION STILL EXISTS, AND REQUIREMENTS OFTEN CHANGE UNDER THE GUISE OF "CONTINUOUS IMPROVEMENT"

much more difficult task than verifying completeness.

It is worth noting that inaccurate or false data is not necessarily aberrant. Performing tests that focus on identifying outliers (control limits, standard deviations, etc.) may help identify human error or data generated by a system acting abnormally, but it is not sufficient in detecting false data that is fraudulent—most of the time that data appears to be legitimate and requires more sophisticated testing to detect.

Transform/Aggregate: This is the processing logic of the report, a combination of the configuration and the computer code that applies programmed functions under given conditions. Processing may be as simple as displaying raw data that meets certain conditions or providing simple sums of defined data sets. Or it may be very complex, requiring statistical calculations, time series, or even advanced processing such as artificial intelligence. And if the report includes a graphical interface (e.g., a dashboard), then the charts and graphs in that dashboard may also perform some calculations.

The transform functions of a report should be treated the same way as a system; in most cases, in fact, they are systems. For SOX, we might require a review of the source code, an understanding of how the report was tested during development, a parallel calculation, or evidence that the report logic has not changed since the last time a full review was performed. In GxP, this could fall under the computer system validation approach.

Input: This is the source data for the report. Data sources can come in many different shapes and forms, with some reports having multiple data sources. For companies that are required to be SOX-compliant, that source is typically an ERP system used to support their financial processes. Identifying and understanding underlying systems are critical components of SOX scoping and testing, because a company needs to determine if it can rely on these systems throughout the time period under review to produce complete and accurate reports.

RELIANCE ON SYSTEMS

Developing confidence in the systems that generate the reports or enforce other SOX-related controls at a business-process level has been, and still is, a focus of many SOX programs. It can be quite difficult to get comfortable with a process output if one does not have confidence in the systems that support it. To address this, companies perform IT general controls (ITGC) testing, which is designed to confirm that the system has been operating as intended over a specified period of time. ITGC testing covers three general areas:

Access controls

Who has access to the system, and what can they do? Most systems today have some sort of role-based access control (RBAC) that limits what system users are able to do based on their role in the organization. RBAC design typically incorporates organizational functions, training requirements, and segregation of duties (such as designing permissions to prevent a single individual from having too much control over a process, similar to checks and balances in government).

Along with enforcing sufficient password parameters, access controls also need to account for "super users" and system administrators (who might have the ability to grant themselves permissions and erase audit trails). By following the principle of least-required-access and by checking the level of access enjoyed by active employees, companies are often able to identify a large number of employees and contractors who have far more access in the system than they need to perform their jobs, or uncover access that could allow someone to circumvent an internal control (e.g., by logging in using a terminated employee's ID.)

Change control

How the system is modified and kept in accordance with approved design requirements is more than just good development practice. The change control process has become the cornerstone of trust that a system continues to work as intended over time. In the absence of continuous monitoring or evidence that no changes have been made, change control must be effective.

IT operations

Backup/data retention, processing of scheduled jobs, interfaces, reliability and incident management, and physical and network security: these some-

Service organization control reports

SOX placed the onus on management to demonstrate controls over their entire organization, including any third parties to whom processes may have been outsourced (e.g., payroll or IT services). And it didn't make sense to have a service organization supporting several customers get their controls evaluated by each customer and their auditors separately.

The American Institute of Certified Public Accountants (AICPA) and its international counterparts developed what are known as "SOC 1" reports that create a framework for an organization to publish a report on their controls relevant to financial reporting and the results of independent testing. SOC 2 and SOC 3 reports also exist that may cover areas of internal control broader than financial reporting, such as security, privacy, confidentiality, availability, and processing integrity. The explosive growth of cloud-based services has made SOC 1, 2 and 3 reporting increasingly common. The reports also set expectations regarding the controls a company using a service organization should have in place (a company outsourcing its payroll, for example, must provide accurate timesheet records to its payroll firm).

While there is no industry standard (yet) that guides an attestation approach for GxP services and systems provided by third parties for pharma companies, many service providers (specifically those that offer cloud-based services) do provide guidance on how to apply their services within a corporate environment. This guidance often references the service provider's IT controls documented in its available SOC reports (Amazon Web Services is an example). As the overlap between the data integrity controls from a finance and GxP perspective become more obvious, we expect that third-party pharma service providers (contract research organizations, contract manufacturing organizations, etc.) may take an approach similar to SOC reporting to provide evidence of consistent data integrity controls across their customer base.

times-underappreciated factors are foundational to the overall IT control environment. A company must have confidence that data flows as intended between systems, that data is backed up and recoverable in a timely matter in the event of an IT event, and that the IT environment has protection and an ability to recover from cyberattacks.

It's important to note here that because an application, operating system, or database layer can affect controls and access to underlying data, the concepts described above need to be applied to all three of these elements (which comprise the "application stack," a set of applications typically required by an organization).

LESSONS LEARNED

From the start, it was apparent—following passage of Sarbanes-Oxley—that programs would need to stabilize and evolve to become more efficient. Industry expected this to happen fairly quickly; it didn't quite work out that way. SOX programs have become more efficient, and audit findings have been the impetus for process and IT change that drive value. Yet many organizations still see SOX as an onerous process and adopt a "just get it over with" mentality with regard to audit and controls testing. Temporary solutions are preferred over investment in robust process improvements. And an overall lack of dialogue between departments or entities within an organization leads to redundancy in controls and inconsistent processes.

Lesson 1: SOX costs

The cost of SOX compliance was expected to drop drastically in the first few years and then continue to modestly decline as programs matured. In most cases, there has been a drop from the Year 1 stand-up costs, but year-over-year SOX compliance costs have been sustained.

Lesson 2: Spreadsheets still rule

It seemed that the role of GRC technology and the integration of controls into standard ERP software would drive continuous automated testing, and control logs would provide all the evidence auditors would need. While GRC and analytics have come a long way in improving audit techniques, there are still a lot of Excel spreadsheets in use and manual controls testing being performed.

Lesson 3: Control deficiencies persist

Fifteen years after the enactment of Sarbanes-Oxley, control environments should be mature, there should be a very low volume of errors, and the few false positives detected should be used for training in audit programs. As it turns out, there are still many persistent control deficiencies. Instead of fixing root issues, companies are spending energy to prove that deficiencies do not result in any significant errors or trying to argue that the control is inconsequential.

Lesson 4: Each company is unique

"SOX in a box" was touted as a canned suite of standard controls and leading practices that could be implemented in nearly any company as it became public. But most companies still struggle significantly (and spend accordingly) with their first year of SOX compliance; every company is unique.

Lesson 5: Continuous improvement needed

It was thought that the regulatory environment would stabilize and attention would turn to improving specific areas, and encourage leading practice behavior. Yet regulatory tension still exists, and requirements often change under the guise of "continuous improvement." The PCAOB continues to see significant findings when reviewing an auditor's work, which in turn drives changes to the audit approach.

Lesson 6: Outsourcing not necessarily the answer

The industry envisioned a world where remote testing would be performed continuously using offshore resources and then summarized in annual audit reports. This has proven to be difficult to achieve. Many of the audits are being performed onshore by auditors who understand the organization and have long-standing relationships with process owners.

CONCLUSION

There is much to be learned from the SOX journey that is directly applicable to data integrity within a GxP environment. An organization that does not consult with its internal audit team when designing a data integrity program is potentially missing a wealth of knowledge and may be setting itself up to repeat mistakes. ‹›

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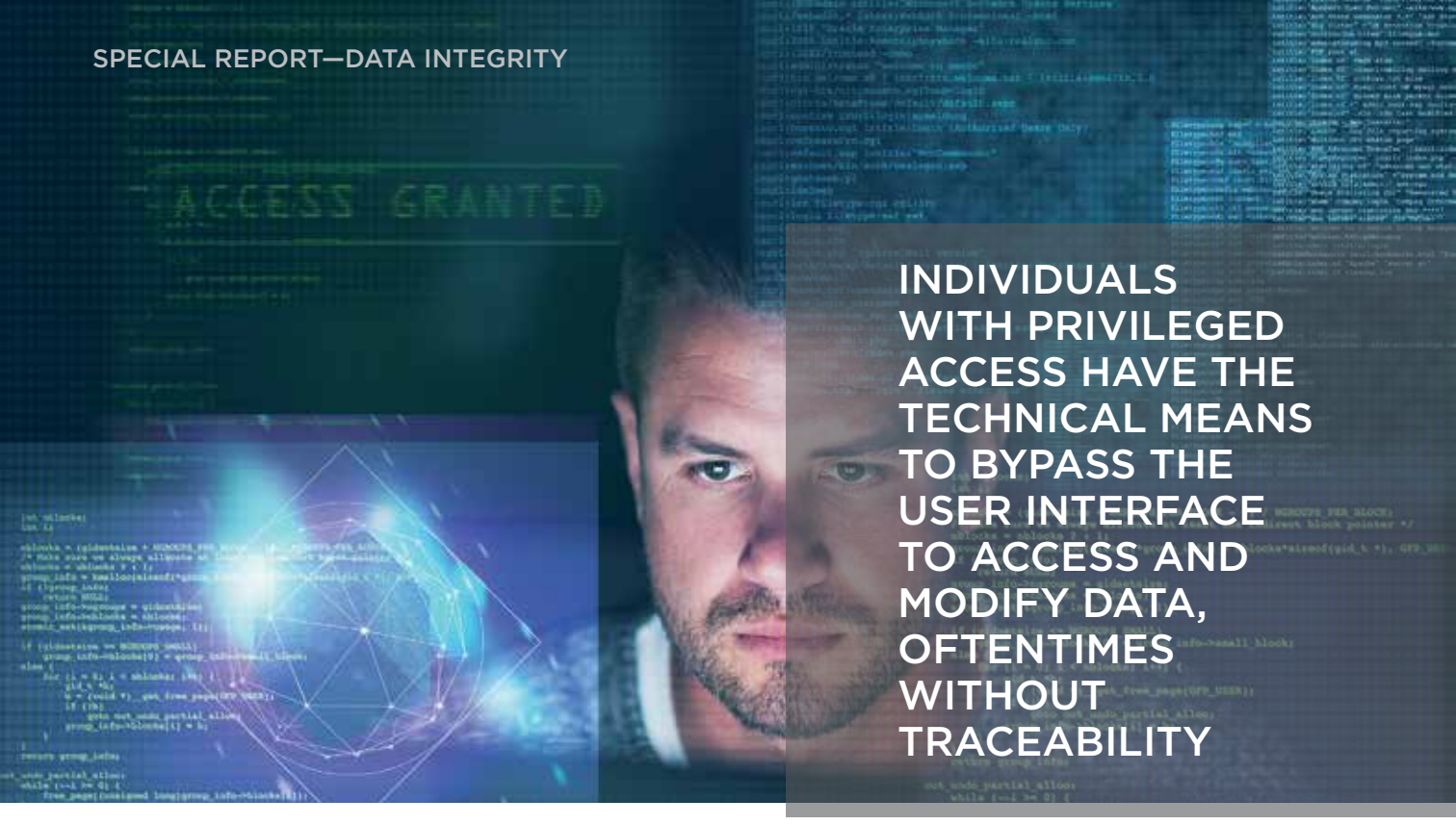


INDIVIDUALS WITH PRIVILEGED ACCESS HAVE THE TECHNICAL MEANS TO BYPASS THE USER INTERFACE TO ACCESS AND MODIFY DATA, OFTENTIMES WITHOUT TRACEABILITY

CONSIDERATIONS FOR DATABASE PRIVILEGED ACCESS

George Evgrafov, Sam Andrews, Sophie Ding, Nichola Stevens, Steven Valeri, and Michelle Vuolo

Computerized systems used in the GxP world (e.g., good manufacturing practice or good laboratory practice), call for strict controls to maintain data reliability and integrity that protect product quality and patient safety. While these controls come in various forms—such as technical controls and checks, procedural controls, and audit trail reviews—organizations often overlook the back door: individuals with privileged access to the database.

"Privileged access" is enhanced permission granted to perform administrative tasks that require additional system or application visibility, such as issue resolution and system modifications or development. The term also applies to legitimate transactional data corrections under appropriate approvals and change documentation.

Individuals with privileged access have the technical means to bypass the user interface to access and modify data, oftentimes without traceability. It is advisable, therefore, to place additional controls and safeguards around privileged access. Modern database engines offer granular access controls and database-level audit trail functionality, both of which can extend data integrity controls to the database layer.

It is imperative that those with privileged access are trained to realize that controlled access is related directly to patient safety; they should also understand the risks they assume if they participate in illicit activities or knowingly allow them to occur.

This article discusses considerations for privileged access—data categorization and levels of control that should be implemented to protect the integrity of the data that resides in the database.

DATA CLASSIFICATION

To protect your data, you must protect your database. Whether traditional, back-end, or cloud-based, databases are central locations that store data and metadata; this makes them prime targets for attacks. With the "big data" explosion and proliferation of data from legacy or emerging technologies (such as the Internet of Things), some of the biggest challenges organizations face today include the need for:

- An inventory of data and information asset owners
- An understanding of the data and its value
- A framework that mandates different levels of protection and control implementation based on a structured and well-defined approach

The good news is that a well-defined data-classification process and framework will provide solutions for these challenges.

Data classification is the process of assigning an economic value or rating to data. Examples include identifying and rating sensitive databases, tables, or columns, and identifying restricted or confidential information in database storage. Data classification determines how organizations understand and manage business processes at the most elementary level. It is a fundamental

element in data protection and in both enterprise data management and data governance.

As the first step toward data protection, data classification includes:

- Classifying a database data segment to allow tiered protection schemes and handling
- Encouraging proper labeling and handling of sensitive data
- Preventing unauthorized access to sensitive information
- Compliance with laws and regulations

The goal is simple: to create a classification framework that enables an organization to identity, label, and protect sensitive data in different databases. The framework consists of several components, including:

- Classification policies: Define scope, responsibilities, and other governance requirements
- Classification scheme: Determines tiers of data and associated levels of protection (Today, three- or four-tier schemes are common; five-tier schemes are usually found in industries that produce intellectual property.)
- Labeling guidelines: Instructions for labeling that enable automated protection tools
- Handling guidelines for different data classification levels
- Classification mapping to link data types or data sets to classification levels

There is no one-size-fits-all approach to building a data classification framework, however. It should be based on the types of organization and overall data-protection strategy. At a minimum, a high-level policy that specifies the protocol for protecting sensitive data should be in place and link to the data-classification policy. Classification guidelines (i.e., labeling and handling guidelines) and compensating controls must be linked to each classification level. Data classification processes should be defined for consistent and repeatable execution. More importantly, because data and its value change over time, its sensitivity and need for protection also change. Data or database owners must keep classification guidance up-to-date.

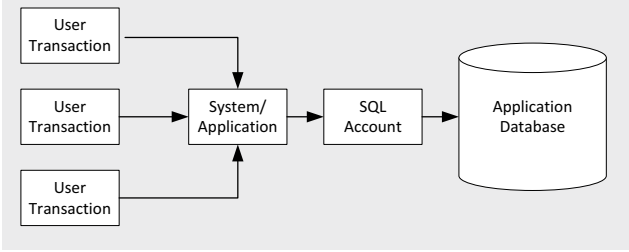
CONTROLS

Computerized systems need risk-based network- and account-level security controls to limit access to the database. These controls include:

- Tiered system design
- Database connection restrictions for service account(s)
- Separate administrative accounts (which differ from user accounts for day-to-day work)
- Database connection restriction for database connection restriction for doing-business-as accounts
- Database connection (in transit) encryption
- Database encryption at rest

System access controls should be strictly managed, documented, and authorized, including enforcement of unique usernames and passwords that expire in accordance with the US Code of Federal Regulations (CFR) Title 21, Part 11[1] and other regulations. Where applications are hosted, individual user log ins may be imposed. However, the application uses a generic account to access and store the data within the database/server (Figure 1). This is acceptable if the user who undertook the activity is traceable and each transaction is attributable.

Figure 1



Remote server access should be controlled in the same manner as in the system or application account, but additional controls should be established to record who needs access, the rationale for it, and the duration necessary.

SEGREGATION OF DUTIES

In the world of pharmaceutical products, we would never have the same person manufacture a product and release it to market. Regulations require checks and balances, known as segregation of duties (SOD), to separate tasks and assign responsibilities to different people. In manufacturing, there are roles for people who create data (i.e., the manufacturing operators) and roles for those who approve or release data (i.e., the quality specialists). The SOD is clear: Different functional groups are responsible for the creation and the approval of data or records.

The same holds true when a computerized system automates a business process. We apply SOD at the operating system, application, and/or database levels. As previously mentioned, those with privileged access are able to change the way the system works, turn off the audit trail, or even change data that was created in the system—often without traceability. For these reasons, controls require another distinct person to perform these activities. This person should not have any responsibility, accountability, or direct interest in the data and/or records that are created and maintained in the computer system and should be detached from the business process.

While SOD can be costly and/or inefficient, these controls should be applied according to a documented risk-based approach.

ACCESS CONTROL AND REVIEW

Access to computerized systems should be granted only to individuals who have been trained to perform the activity and have a legitimate business reason to access the system; a record of the request for access (or additional access) should also be documented in accordance with onboarding standards of practice (SOPs). Access for employees who leave the company should be revoked in accordance with SOPs, with no residual access available (i.e., the application access has been removed but the user-account related metadata remains to ensure the accuracy of the data and audit trail).

Privileged database account access should be minimal, in keeping with what Jerome Saltzer has described as "the principle of least privilege."[2] If the database administrator account will be used by multiple individuals, a password storage database (password vault) should be established. This lets individuals use their own passwords (presuming they have sufficient permission) to log in to the system and prevents the administrator password from being revealed. Each access is recorded in the audit log.

In smaller organizations, procedural risk-based controls should be in place so that access requests are recorded and approved before being granted. The password is changed after each use and stored in a secure location, whether physically sealed in an envelope or kept electronically in a password-management tool.

Review of the controls placed on privileged access is almost as important as the controls themselves. Privileged access may be temporary or permanent, depending on the nature and complexity of the access needed. It is essential that privileged access be revoked as soon as an individual no longer requires it: The system could otherwise be left vulnerable to unauthorized modification. Periodic review of user account and access privileges is essential so that only proper access is permitted. Supplementing this with automated monitoring is even more effective.

DATABASE AUDITING

For critical databases containing sensitive data, database auditing confirms that the company's security policy supports data integrity. The most common database-level security issues are external attacks, unsanctioned activities by authorized users, and mistakes. Developing a risk-based audit strategy will confirm that appropriate security measures are in place, identify necessary improvements, and facilitate forensic analysis when an incident does occur. The strategy should audit the following:

- Privileged user access, to determine who has accessed the database, when access was obtained, how it was obtained (i.e., where it originated), and what data was accessed.
- Failed access attempts, which may indicate efforts to gain unauthorized access.

CONTROLLED ACCESS IS RELATED DIRECTLY TO PATIENT SAFETY

- Activities performed when access is gained; this audit may be performed at the statement, privilege, or object level, or it may be a fine-grain audit, particularly when a data integrity violation is suspected or identified.
- Suspicious activity, to identify any unusual or abnormal access to sensitive data
- Account creation, to ensure that all accounts with database-level access were created through correct processes and have correct permissions.
- Changes and deviations from the database policy and configuration. To be effective, the auditing process must be methodical and repetitive; it should be reviewed periodically to determine that it remains sufficient to protect data integrity.

CONCLUSION

Computerized systems in a GxP environment require strict controls, management, and documented processes to protect and maintain data integrity. Areas of concern include classifying systems and data; controlling access at user, administrator, and supplier levels; segregating duties between individuals and functions; and historical and ongoing auditing.

Systems and databases contain a large array of data, including confidential patient, employee, and customer information, as well as manufacturing traceability; therefore, organizations should classify their systems and the data contained within them.

Organizations should have defined, accountable data owners who understand the value of data and the level of protection required, and have a clear framework to apply controls. While each individual organization will have a different framework, data owners must understand that both the data value and the framework design change over time.

While it is essential that organizations manage system-level access with appropriate controls and processes, privileged access should be treated with the same—if not greater—rigor and thoroughness. Privileged access should be kept to a minimum and reviewed regularly to prevent data deletion or unauthorized, malicious modification. SOD between interested parties in relation to data owners—ensuring that there is no conflict of interest, for example—is also important.

Privileged access is a key component of overall database security, which should include controls on both physical and remote access, access audit reviewing, and controls on user application access, such as those described in CFR 21, Part 11.

Organizations should also implement an appropriate audit strategy to monitor, among other things, the use of privileged access accounts and internal and external failed access attempts, as well as activities undertaken upon gaining entry and their traceability to suspicious activities such as out-of-hours access requests. This audit strategy should be repeatable and reviewed periodically so that it remains viable and effective. ‹›

PREPARE FOR REGULATORY AUDITS WITH YOUR SUPPLIER

Heather Longden

Data integrity continues to be a very hot topic for both regulators and the pharmaceutical industry. With the increased observations about data integrity in laboratories, could it be that analysts have changed how they do science in the laboratory? Are analysts working differently today? Have they suddenly started disregarding the importance of the data they generate? Can regulators no longer trust laboratory results?

Experienced lab managers are unlikely to observe any significant change in analysts' behavior, which could account for the increase in the number of US Food and Drug Administration (FDA) Form 483 observations and warning letters1 published each month. No one believes that the majority of analysts are falsifying results, intentionally or otherwise. But it is clear regulators do not have the same level of trust in scientists' motivations and behavior.

While based on the actions of only a few laboratories, this lack of trust seems justified. In a small number of cases, products or studies that should have been rejected based on scientific evidence have had that evidence hidden or manipulated to "push the data through" and deceive the quality unit into allowing it to pass. In a larger number of cases, it has become normal practice to polish results that almost pass to avoid the tedious work of either providing official scientific justification for the invalidation of out-of-specification (OOS) results or of instigating a full OOS investigation into failed products or studies.

In significantly many more cases, however, lax habits, insufficient care, poor understanding, or lack of knowledge have meant that laboratories, in particular, were not subject to rigorous oversight by quality units as they created data during the analytical process, provided the outgoing paper reports gave the appearance of being in compliance.

Why is it that in the last three years regulators are finding issues in electronic data, specifically chromatography data? Something has changed. To better understand analytic electronic data, regulatory agencies including the FDA began hiring experienced and knowledgeable scientists and trained them on how electronic systems were designed, how the technical controls work, and what records and metadata might be found in electronic data capture (EDC) systems in laboratories. Chromatography data systems (CDS) are the most common.

Inspectors are now more aware of how a computerized laboratory system works and are able look for evidence of:

- Missing technical controls that are explicitly defined in the regulations
- Insufficient quality oversight in cases where scientists must make scientific decisions that affect data accuracy
- Deliberate falsification of data
- Obscuring OOS results in nonreported orphan data

If not familiar with a given system, inspectors will expect that laboratory staff can help them understand how EDC systems work. Laboratory reviewers should be using these same tools to look for potential data integrity gaps or issues.

In an article published earlier this year, Barbara Unger writes, "How quickly can the audit trails be provided to an auditor? When it takes four staff members a half hour to locate them, it suggests the audit trails are not routinely evaluated."[2] So how can a lab manager be sure that his or her staff knows the application at least as well as the auditor?

Is your vendor knowledgeable about electronic records regulations and regulatory compliance?

The scope of expected technical controls has been defined for almost 20 years. Vendors serious about serving regulated companies will have equipped their customers with tools to help meet electronic record compliance rules. According to guidance provided by the UK Medicines & Healthcare products Regulatory Agency (MHRA), regulated companies still using software without audit trails have until the end of 2017 to address this issue.[3]

Vendors must have expertise in what the rules mean, how technical controls can help meet them, and how laboratories ought to leverage the tools to help manage or monitor users' behavior. Furthermore, the companies can advise when scientists should be trusted to be scientists, and when quality reviewers need to perform quality reviews.

Vendors also have general insight into how companies similar to yours

have addressed data integrity. While nobody expects vendors to divulge competitors' secrets, they will have had opportunity to experience many different approaches to meet compliance needs, and will know which are successful and practical.

Yet how often are the laboratory and quality unit staff able to leverage that expertise? Did the company try to save money by instigating "train-the-trainer" programs, whereby a handful of people were trained "a long time ago," by the vendor, but everyone else was trained "on the job"? Unfortunately, many regulated companies are conservative and resistant to change. The software version deployed in 2002 is often still in use, unchanged and un-updated as "it seems to do the job well enough."

Vendors should always be consulted for additional training and updated knowledge. The worst time to call a vendor for advice, however, is in the middle of an audit or inspection. There are a large number of caveats to consider before you pick up the phone:

- Does the laboratory run a standard version of software that your vendor can easily answer questions about?
- Is there anything customized or unique in how the software is configured and used?
- Are there procedures (documented, validated, and in use) to manage the data and secure user access in a manner that the vendor might describe as "normal use"?
- Does the vendor have any special knowledge about your company or your use of the software?
- Are the vendor's representatives trained in your SOPs and audit processes?
- Is there any chance that your vendor representative might just make matters worse, despite good intentions?
- Given that you may not know how many of the answers are "No," is it risk-free to ask vendors to interact live with your auditor?

What about talking to the war room and providing documentation during or after the audit?

In this instance, you should consider your understanding of your electronic systems and the timeliness of your answers.

If you really do not know the answer to a question and can't respond in a timely manner, it is likely that this aspect of the system is little known and therefore little used. For some questions, this may be acceptable. If it is a task you do relatively infrequently, and only a handful of people know the content of that particular standard of practice, not having an immediate response may be considered understandable. But not knowing if you have audit trails enabled, or where to find them, is a more serious issue.

Deferring an answer until after the inspection or audit, and then promising a "letter from the vendor on company letterhead," is equally full of risk:

- It indicates lack of knowledge in your organization.
- You are now relying on the vendor to help complete your regulatory response.
- Your vendor may not be able to respond in the timely manner that is required.
- Any such response may require detailed knowledge of your use of the application and possibly user actions related to a specific "event."
- The response may provide additional evidence that continues to uphold the auditor's view that you are not in control of your data.

HOW TO AVOID URGENT CALLS TO YOUR VENDOR

SUPPLIER ASSESSMENT When your computer-system validation (CSV) will depend largely on vendor testing, it is essential to perform a detailed supplier assessment, ideally long before any order is placed. During this process you can assess how knowledgeable your vendor is with your regulations, how detailed their own software development life cycle and verification is, and how responsive they can be to answer or escalate any questions. This is also the time to include an evaluation about other professional services they may offer: training, consultancy, and regulatory good practice advice.

DEPLOYMENT PLANS Most laboratory vendors understand that deployment cost and time should be kept to a minimum. Yet when it comes to deployment plans, a realistic projection for all its phases probably is based on dozens, if not hundreds, of similar cases. Insisting on shortcutting deployment plan proposals, whether to meet urgent deadlines or to save money, will introduce compromises, which may put your laboratory at risk. Unless you have expert users of these systems already in your

laboratory, it makes good sense to accept offers of help that will help you make the most of any new computerized system.

A company may have its own project managers or preferred third-party project managers to drive deployment plans. If the vendor offers such services (at least for the initial rollout), however, consider them to gain access to the vendor's solution-specific experience.

QUALIFICATION AND VALIDATION SERVICES As noted in the MHRA's March 2015 guidance document, "acceptance of vendor-supplied validation data in isolation of system configuration and intended use is not acceptable … vendor testing is likely to be limited to functional verification only."[4] The guidance highlights the issue, stating, "Computerised systems should comply with regulatory requirements and associated guidances, and be validated for their intended purpose. This requires an understanding of the computerised system's function within a process."[4]

How can a laboratory adopt and validate a new computerized system when they may not have full understanding of how this system will eventually be used? This conundrum is why vendor assistance in the qualification and validation of new systems is critical. Vendors (or knowledgeable third parties) should be able to offer learning experiences as they assist any regulated laboratory with CSV exercises.

Understanding how much documented verification is completed at the vendor site before release is a critical part of supplier assessment, and will connect directly with appropriate qualification and validation testing. If the vendor can provide documentation or a summary of testing either during or after assessment, the documentation or summary might guide a risk-based validation effort.

It is very common to leverage installation qualification and operational qualification services from vendors. As they can vary in detail and scope, make sure to understand what is offered, how long it might take to execute, and how much of your own verification testing it might cover. Additionally, if you intend to cover these topics in user acceptance tests, be sure to find this out in advance.

During the validation consulting process, a laboratory is very likely to design exactly how it will use any system or software application. Defining, documenting, and exercising standard operating procedures (SOPs) are critical pieces of the validation process and are unlikely to be included in the services the vendor can provide.

TRAINING AND CONSULTANCY Will training come before validation, during that process, or afterward? Learning is continuous during the deployment of any new computerized system, yet many laboratories treat training as an optional extra—something that can be skipped to minimize deployment costs or added on as a last-minute exercise. Keep in mind that part of validation is the transfer of the knowledge of the product from the vendor to the company.

With today's focus on a wide variety of data systems, and with auditors and inspectors gaining experience with these systems, it is essential that all staff (including IT support staff, department managers, and your quality unit) be knowledgeable in your deployed applications.

Review of paper records is no longer acceptable as a review of "complete data." All of the recently published guidance discusses the risks of relying on review of either paper or PDF records (static data) alone. Ensuring quality personnel are comfortable reviewing electronic data comprehensively is a major step from examining printouts.

Training a large number of expert users in a company is often seen as the best approach when introducing a brand-new computerized system. Subsequent user training can then be a combination of product training and laboratory-specific SOP training. But note that after that initial phase, relying on internal training alone has risks.

As use of the system changes, it is important to ask the vendor's advice about how to best approach those changes. These simply may be new users with new requirements, a new software version, or it might be a shift in how the software is used, i.e., from using chromatography software as an electronic peak integrator (with all further calculations being performed in a laboratory information management system, an electronic lab notebook or Excel), to automating those calculations in the chromatography software application. By simply continuing to use the software in the same way, you may be missing opportunities for further automation and for the elimination of risky manual steps. Asking the vendor's advice to help design new ways of working and devise new training material for expert teams can only improve efficiency and reduce errors in the long run.

KEEPING UP TO DATE

SOFTWARE PLATFORMS It is very common for regulated laboratories or manufacturing plants to invest significant time installing and validating a computerized system and then be ultraconservative regarding updates—or even service releases and hotfixes.

Designing validation protocols to permit regular updates "when they make business sense" will prevent a company from relying on software that inevitably is missing new features and may contain uncorrected (but now known) defects. Vendors are keen to improve functionality and address defects, yet the very users who report the defect or suggest the enhancement are often denied access to the new versions by management's reluctance or IT's inability to implement the new software.

Being aware of all changes and enhanced functionality included in new software releases is key if business units are to evaluate the effectiveness of any potential update. Too often, upgrades are not "permitted" unless some wider global IT or platform change requires it. The users' effectiveness or compliance appears to be subservient to the IT department's schedule. Vendors should be able to help you fully understand the productivity enhancements as well as the concerns that running severely out-of-date software can bring.

One of these concerns is the vendor's ability to support the users and quality unit in case of an audit. Release notes for each software version are normally widely available and may be read by the various regulatory agencies as well as by the quality units of other pharmaceutical companies that might wish to audit you. Ensuring that staff and support channels are aware of which service releases and patches you have deployed, and which you have chosen not to deploy, is critical when addressing technical questions.

INDUSTRY TRENDS Regulators are increasingly aware of the vulnerabilities of specific systems and vendors are well positioned to help companies fix or address these issues. Any reputable vendor will be watching the regulatory news and assessing the latest guidance, changes, and public regulatory findings, just as your own quality units will be doing. When anything new occurs or is cited as a concern, your vendor should be able to help you understand the root cause of that citation, the true concern of the regulator, and how it might affect use of similar software in your company.

This is an opportunity to tap into your vendor's knowledge about data integrity and prepare your teams for the next inspection. Software vendors have a major interest in your continued success and should be able to review how you intend to keep ahead of these industry trends.

SUMMARY

Vendors are often asked, "Do you provide training to the health authorities to help them identify issues within regulated companies?" No vendor wants to see their customers get into deep water with any agency or sponsor company that may be looking for confirmation of data integrity. Users or quality assurance teams are often tasked with "training the investigator" on software during the stressful time of an audit. This is especially difficult when the visitor's experience of that kind of system is limited.

Training provided to regulators directly from the vendor, outside of an audit situation, should ease the audit process rather than make it more uncomfortable. On the other hand, being prepared to clearly and confidently explain the software capabilities—and how your company leverages the functionality and tools to ensure data integrity in your operation—will enhance the auditor's impression of your understanding and control of the data supporting your quality products or research. ‹›

DATA INTEGRITY AND BIOPHARMACEUTICAL MANUFACTURING

About the author

Nissan Cohen, an ISPE member since 1994, is a worldwide expert in total organic carbon, high purity, ultrapure, reclaim-and recycle water systems, with profound expertise in instrumentation, automation, and organic contamination oxidation systems using ozone, UV, ion exchange, and catalysts. A member of the Pharmaceutical Engineering Committee, Chair of ISPE's Water and Steam Forum, and Founder and Chair of ISPE's Discussion Forums. He earned a BS in agriculture and genetics at the University of Wisconsin and Ruppin Institute, and an MS in agricultural water systems from Hebrew University.

A MATTER OF TRUST

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PREPARE FOR REGULATORY AUDITS WITH YOUR SUPPLIER

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THE CAPACITY CHALLENGE

Shifting paradigms in biopharmaceutical facility development: Point of view

John Noble, PhD

If you have been following the biopharmaceutical industry over the past 20 to 30 years, you were no stranger to discussions about its then-projected rise. In fact, in the mid-1990s and early 2000s, we saw promising growth waves. There was a surge of interest in 2007 and 2008 that ended with the Great Recession; at that time, many in the industry wondered if we would ever see additional large capital investments in biopharma facilities. Cell culture titers were rising, increasing the capacity of existing plants, and interest was shifting to more personalized medicine focused on smaller, single-use strategies.

That has all changed: A new wave of high-volume oncology- and Alzheimer-related therapies, along with the commercialization of low-volume products—including gene and cell therapy—is reinvigorating the industry.

It goes without saying these are very exciting times for life sciences, with a laser focus on "Facilities of the Future" for biopharmaceutical development and manufacturing. These include traditional stainless steel large-scale biomanufacturing facilities and small-volume highly flexible facilities built around single-use technology.

At the 2016 ISPE Biopharmaceutical Manufacturing Conference in San Francisco, California, US, former ISPE Board Chair and Global Pharmaceutical Manufacturing Leadership Forum Chair Andrew Skibo, Head of Global Biologics Operations and Engineering for MedImmune/AstraZeneca, highlighted 10 to 15 megaprojects (those in excess of $350 million) that are in various stages of development, design, and construction. We were very involved with companies, including Regeneron, Bristol-Myers Squibb, and Biogen, as they invested in this new phase of development, for both large- and small-scale manufacturing plants.

We then saw a second wave of investment start last year for both conventional stainless steel and single-use facilities. At that time, a third wave of similar facilities was anticipated, and while the focus has shifted somewhat from large-capital stainless steel projects to large- or mid-capital single-use facilities, 2018's pipeline still looks strong.

TRACK PROGRESS USING KEY PERFORMANCE INDICATORS, THEN WATCH AND TRUST THE NUMBERS

Below I outline some of the experiences we've had on these projects, in particular how the post–Great Recession market has shifted our paradigms and influenced our goals and execution strategies.

In 2014, the market was alive again but many of the old paradigms were gone—as were key human capital and supply chain elements. We saw a step change in demand, with the potential to stretch engineering, procurement, construction, and qualification capacity across the board. Additionally, there was a renewed focus on delivery from clients, particularly with regard to schedule and return on investment.

Edward Merrow, Founder and President of Independent Project Analysis, Inc., and author of *Industrial Megaprojects: Concepts, Strategies, and Practices for Success*, issued a fascinating study concluding that for a range of reasons—many of them regarding front-end planning in project definition—approximately 65% of all megaprojects fail to meet business objectives. This is an unacceptable outcome in today's life sciences industry. Even if processes and capacities are not well defined, we've learned and adapted during the past two decades and now have the ability to calculate how to deliver projects to stricter cost and schedule targets in today's overheated market. We've deployed a new initiative to

address these challenges identifying some of the warning signs, and how to respond.

Along with the focus on delivery, end users want to optimize their life cycle costs and minimize time to market. Here are the key themes we see:

- Minimize deployment time: We got used to fast-track projects in the mid-2000s; now we have to talk about "flash-track" or hypercompressed schedules. Our execution strategies must be nimble, and we must manage risk dynamically.
- Simplify the whole design and equipment cycle: replication and standardization are critical.
- Pick the best team: Know your vendors and contractors, and don't be afraid to collaborate. Depending on geography, a one-stop shop may not be the best answer.
- Know your key players: At the end of the day people make this all happen; secure your team early, because if you don't, someone else will.

Let's take each of these in turn:

FLASH-TRACK SCHEDULES

Our internal database shows that before the recent wave of work, the average cycle time for conventional large-scale stainless steel projects was 42 months; now, we are looking to reduce that by 6 to 12 months. How?

- Eliminate the classic critical path: Bioreactors used to be the key, but now if you clone them they can be there as soon as the building is ready. The next step is vendor data; again, if we clone and standardize, we already have that, so the issued-for-construction design can drive forward. Finally: automation, clone, and standardize.
- Embrace hypercompression: We have an extensive overlap in all phases that can be pushed even further by leveraging off-site fabrication for structural modules and super skids. We can also look at using existing buildings to make things go even faster.
- Manage the risk: All this compression pushes our current systems and procedures to the maximum. If we have a robust resource-loaded level-three schedule, we can manage risk and understand "what-if" scenarios. The critical path may not be what we think and may change rapidly. Also, this compression, along with earlier required dates for on-site equipment delivery, drives cash flow forward, so the *de facto* sanction now occurs at the end-of-concept and not at the front-end design stage—by then you have committed to most of the big stuff.

SIMPLIFYING THE DESIGN

How do we use cloning and replication to simplify design?

- Don't let "good" be the enemy of "good enough." Design the plant to be operable, then make improvements as production ramps up.
- We spend so much time chasing our tails in design, trying to keep up with development, when the big lesson is we never really get there. Let's accept that and find a way to get it done rather than make it perfect.
- Maximize replication, use standard off-the-shelf designs for bespoke equipment, and keep decision-makers to a minimum.
- Understand where the design risks are. They're usually downstream, so fence that in and don't let it derail the balance of the project.
- Minimize change. Draw a line in the sand at the end of the basis of design process and don't allow change unless you have a safety or compliance issue or the design simply doesn't work.

REMAIN DISCIPLINED, FOCUSED, ALIGNED, AND PRAGMATIC

- Bring vendors and contractors in early to streamline design and optimize the packages.
- Track progress using key performance indicators (KPIs), then watch and trust the numbers. If KPIs are off track and design is not going to plan, cost and schedule control will be lost quickly. A classic example is piping and instrumentation diagram changes made after the issued-for-design phase: If the changes are increasing, you are not cloning!

CAPACITY AND RESOURCES

Capacity and resources are the final piece to this puzzle.

- Don't wait until the project kicks off to align and tie in your key suppliers. There simply isn't room in the flash-track schedule. Bring them in early and allow procurement to do their important work, then drive forward.
- Assemble the best team possible and set the project vision, goals, and accountability metrics. Partnerships and integration are critical, especially in certain geographical locations.
- Remember the people. Many great talents have retired or left the industry, and those that remain are being pushed as hard as possible to work faster. Create a vision and a mission for the project, monitor your organizational health (turnover, burnout, and overtime) and take action to continuously improve. Recognize the staff challenge and try to work smarter.

So where does this leave us? If we remember the following, we are up for the task:

- Set a clear vision.
- Remain disciplined, focused, aligned, and pragmatic.
- Minimize change.
- Take care of your people and celebrate the wins.

Never forget: In the end, it's about making people's lives better, and creating a greater tomorrow, which makes it all worth the challenge before us. ‹›

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INTEGRATED VPHP DECONTAMINATION SYSTEMS: THE EMERGING UTILITY

John Klostermyer, Bruno Aze, Alberto Garcia, and Don Eddington

Integrated VPHP systems offer a versatile, automated, sporicidal process for cleanroom suites, isolators, RABS, chambers, and pass-throughs.

The first portable vapor-phase hydrogen peroxide (VPHP) generators developed in the early 1990s were designed to dry, decontaminate, and aerate target enclosures efficiently while controlling pressure. Today, these generators, which typically use a closed-loop airflow pattern, are used predominantly on isolators, small rooms, and material air locks.[1] As users sought to enhance process automation, increase cleanroom suite sizes, shorten cycle times, and standardize data capture, integrated VPHP generators were developed. These could be tied in with the heating, ventilation, and air-conditioning (HVAC) system and controlled and monitored by the building management system (BMS).

Integrated generators are designed to flash-vaporize hydrogen peroxide precisely and consistently, and deliver predefined quantities of VPHP to the target enclosure. Unlike portable VPHP generators, integrated units work with an array of external air-handling components that deliver, distribute, and purge VPHP from the target enclosure. Collectively, this is called an integrated VPHP system. In some facilities, use of an integrated VPHP system is as common as other utilities, such as compressed air.

Integrated VPHP installations provide the well-known benefits of hydrogen peroxide vapor decontamination while enhancing process repeatability and decreasing labor and total costs. Other key benefits include:

- Sporicidal surface decontamination
- No residues
- Excellent material compatibility
- Lower toxicity than other gaseous treatments
- Highly automated, high-output, consistent, and continuous operation
- Very low operating cost: no manual labor, setup, or fans
- System is installed and maintained outside the clean area
- No cross-contamination via equipment or personnel moving between target enclosures
- Single unit can be configured via a manifold to decontaminate multiple enclosures.

BACKGROUND

Initial VPHP applications were focused predominantly on pharmaceutical sterility test and aseptic production applications by pairing isolators with portable VPHP generators. Although this configuration is still common for smaller sterility test and research isolators, many large production isolators now utilize integrated generators that work in concert with their air-handling systems to distribute and purge hydrogen peroxide, resulting in short, effective decontamination cycles. Once an isolator is cleaned and dried, hydrogen peroxide vapor is applied for biodecontamination and to achieve sterility on all exposed hard surfaces.

Since the early 1990s, vaporized hydrogen peroxide use has expanded from barrier isolators to cleanroom suites. With the goal of achieving 4- to 6-log bioburden reductions, users have either purchased portable VPHP generators or contracted with specialized service providers that deploy multiple networked portable units, power cords, and fans to treat areas that can exceed 3,000 cubic meters (m^3). Gaseous biodecontamination can be obtained more cost-effectively when VPHP is deployed via an integrated system that is seamlessly incorporated into the HVAC system of classified production areas.

For successful integrated VPHP installation and optimal process performance, specialized user requirements may require a high level of cross-functional collaboration, with input from process engineers, automation programmers, quality, validation, and environmental health and safety personnel. Hundreds of integrated VPHP systems have been installed, primarily in Europe and Asia,[2] providing clear evidence that this improved automated technology has gained industry acceptance.

PLANNING CRITERIA

The decision to implement a VPHP process begins with selecting either a portable or integrated system. The choice often depends on existing or planned infrastructure, technical resources, intended frequency/ease of use, and a favorable cost-of-ownership projection. A comparison is shown in Table A.

Safety

Safety should always be a primary focus, even in the preliminary design phase. VPHP systems typically use concentrated liquid hydrogen peroxide in a range of 35%–59%; storage and handling of these containers should comply with health and safety rules. Preventing and detecting VPHP leaks from delivery piping or an enclosure should also be a primary concern. Hydrogen peroxide breaks down into oxygen and water, so exhausting the VPHP is usually not an environmental concern. A risk assessment should be conducted to determine if workers or pedestrians near the exhaust outlet could be exposed to VPHP. If necessary, catalytic converters can be installed to degrade VPHP in the exhaust to eliminate this risk.

Table A: Comparison of portable and integrated VPHP systems

Decision parameter	Decontamination system	
	Portable	Integrated
Frequency of use	Low to moderate	High: Pass-throughs, chambers, RABS, isolators
Initial Planning	Moderate	Detailed: Automation is integrated with other HVAC components
Initial Cost	Moderate: VPHP equipment, fans, and validation	High: VPHP equipment, distribution piping, valves, installation and programming, validation
Operating Cost	High: Manual labor to deploy generator and fan setup, HVAC operation	Low: BMS operation, no setup
Process Validation	Moderate: Human variability in deployment; BIs used for validation	High: Fully automated process; BIs used for validation
Versatility	High: Units can be transported between buildings or added to decontaminate large spaces	Moderate: Enclosures must be defined at time of installation; manifolds increase versatility
Cycle Time	Moderate: Longer cycle time due to setup and equipment handling; equipment in the target room is accessible only after aeration.	Rapid: Units have high output and no setup results in shortest cycles, particularly for larger spaces
Scale	Moderate: Room sizes up to 400 m^3	Large: Room sizes up to 1,100 m^3

Decontamination

The intended decontamination frequency should also be considered during the preliminary design phase. Doors can be a source of VPHP egress from the target zone. For large spaces, carefully controlling differential pressures between rooms and off-hours treatment is the preferred means of VPHP containment. For infrequent use, target zones adjacent to occupied areas can be locked and sealed with painter's tape. Doors with pneumatic seals are much preferred for frequently used applications, such as decontamination airlocks.

Process monitoring

Process monitoring should also be considered during the design phase. Low-level electrochemical sensors programmed to alarm at 1.0 or 0.5 parts per million (ppm) are usually installed in areas where VPHP leakage could pose a risk to personnel. Process validation is usually performed using biological indicators (BIs). For applications that are used often, high-level electrochemical VPHP sensors may be installed to measure and record concentrations. Standard relative humidity (RH) probes will read more accurately when exposed to VPHP when equipped with the addition of catalytic caps.

Exposed surfaces

VPHP is a surface decontaminant; it will not kill microbes protected by a covering. These occluded surfaces should be minimized. A standard operating procedure (SOP) that specifies item positioning or loading can make the decontamination process reliable and repeatable. Periodic cleaning procedures should also be incorporated in the SOP.

Design

Design factors to be considered are:

1. Integrated VPHP generators lack integrated dehumidification, catalyst control, and pressure control because they are designed to work with other HVAC system components. Most pharmaceutical production integrations are controlled by a master programmable logic control in coordination with the building management system (BMS).
2. Delivering VPHP from the generator to the target enclosure normally requires a single-pass dehumidified airflow of 60–200 cubic meters per hour (m^3/hr) using an insulated, dedicated piping system made of a suitable polymer, such as chlorinated polyvinyl chloride or polypropylene. Noncondensing temperatures and unrestricted flow determine pipe length and diameter. Target zones are selected and decontaminated using a supply manifold. When required, balancing dampers establish proper airflows to discrete target zones. Sequential decontamination is typical for multiple target zones, with one set of rooms being decontaminated while the prior set undergoes the dwell or aeration phase.
3. Well-conceived systems require no prepping, sealing, or portable fans for effective VPHP distribution. Airflows are balanced to eliminate or minimize

the need for the pretreatment sealing. Airflows are also designed to supply, distribute, and eliminate hydrogen peroxide efficiently.

Retrofit or new construction

The most efficient VPHP system integrations can be realized with new construction. Here a modern BMS optimizes and integrates airflows, valves, dampers, piping, and controls.

Despite this, most integrated decontamination systems are retrofitted into existing facilities. Retrofitting a facility with a recirculating HVAC system and an integrated VPHP unit is easier than installing a multiroom system in a facility with single-pass air. A recirculating HVAC system needs a single injection port to serve the entire zone, while a single-pass HVAC needs at least one port per room. In some cases, the main trunk exhaust air of a single-pass HVAC system can be redirected to the main supply trunk to create a recirculating system that is used only during decontamination. As with the recirculating system, a single point of injection can be used to decontaminate the entire zone.

HEPA filters

High-efficiency particulate air (HEPA) filter selection for applications in which they are exposed to the VPHP/airflow is another consideration. Cellulosic materials absorb hydrogen peroxide, so HEPA filters with metal housings and pleat separators are preferable.

Ductwork

Many older facilities have ductwork leakage. Ducts with positive pressure during operation may leak hydrogen peroxide vapor into the mechanical area; this may require the addition of an exhaust fan to prevent concentrations that exceed the permissible exposure level from developing in the mechanical area. Ductwork maintenance should locate and seal points of leakage. The use of handheld or permanently installed low-concentration hydrogen peroxide monitors to determine leakage or concentrations during reentry are an essential part of every application. In most countries, the hydrogen peroxide vapor exposure limit for an 8-hour time-weighted average is 1.0 ppm.

HVAC schematics

Figure 1 shows a typical cleanroom HVAC with a recirculating configuration, an integrated VPHP generator, and a continuous desiccant system. VPHP is injected into the central supply duct and distributed throughout the target zone. Cooling coils are deactivated and their drains are sealed. To avoid condensation they should be allowed to warm and dry before exposing them to VPHP. Hydrogen peroxide condensate can be especially damaging to copper cooling coils with solder joints because of galvanic corrosion. Airflow is balanced to accommodate the VPHP airstream. Once the decontamination phase is complete, VPHP injection is terminated, and fresh air intake and exhaust are maximized to facilitate aeration.

A single-pass HVAC system with an integrated VPHP system is shown in Figure 2. During decontamination the main airflow is shut off while VPHP is injected through well-positioned ports. The air balance and room pressure is maintained with proportional exhaust flow. An additional recirculation duct can be added to distribute the VPHP during the decontamination phase. Normal airflow resumes after the decontamination phase, purging VPHP from the enclosure.

Manifolds

The versatility of a single integrated VPHP generator can be greatly enhanced by pairing it with one or more manifolds: a supply pipe with two or more branches, each equipped with an on/off valve to direct the vapor to the target zone. Manifolds may be layered in succession or can lead to branches equipped with balancing dampers, where injection is directed though multiple ports.

CYCLE PHASES FOR LARGE SPACES

A dehumidification phase is usually conducted prior to VPHP injection. While this phase was historically used to dry and warm isolators and other small enclosures, it also allows higher VPHP concentrations during the decontamination phase. Integrated VPHP systems need a dehumidified airstream to deliver vapor to the target zone. The duration of the dehumidification phase has little to do with reducing the target room RH to a desirable range of 49%–65%. Target enclosure RH and temperature are established by the HVAC system prior to starting the decontamination sequence. The generator's dehumidification phase should be long enough to warm up the distribution piping to avoid condensation when the VPHP injection begins. The subsequent decontamination phase introduces and distributes hydrogen peroxide vapor to the target zone (without producing condensation in the ductwork). An initial subphase called "conditioning" typically uses a higher liquid hydrogen peroxide injection rate to ramp up VPHP concentration.

Once the desired exposure level (time and concentration) has been achieved, the aeration phase is initiated. During aeration, the generator purges VPHP from the distribution pipework while the HVAC system maximizes the percentage of fresh air purging VPHP from the target enclosure.

Figure 1: Recirculating HVAC system with integrated VPHP system

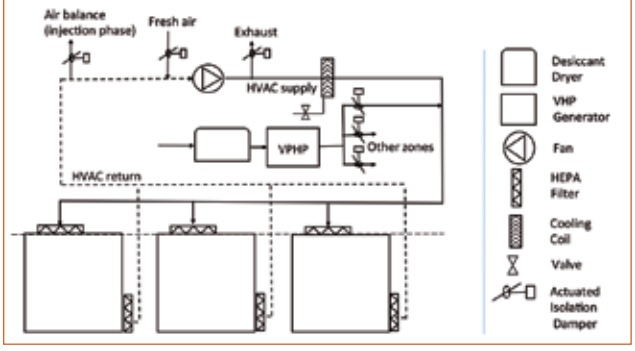

Figure 2: Single-pass HVAC system with optional decontaminationduct—dashed line

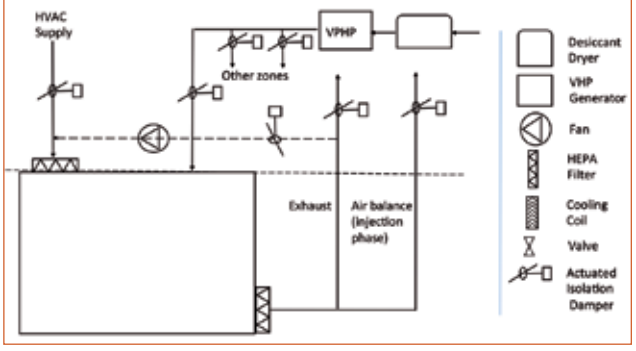

Figure 3: VPHP manifold with four outlets and spares for future use

Figure 4: VPHP integrated generator with a continuous desiccant and bulk source or hydrogen peroxide solution

The aeration process can take overnight on a retrofit application when the HVAC system is designed to use a low percentage of fresh air.

FACTORS FOR SUCCESSFUL CYCLES

Three key factors are critical for achieving the desired kill or bioburden-reduction levels with any VPHP system: saturation, distribution, and time.

Saturation

Since hydrogen peroxide is supplied as an aqueous solution, flash vaporization causes a simultaneous rise in both the water and the hydrogen peroxide vapor content of the target enclosure. Maximizing the atmospheric saturation of a peroxide/water vapor mixture at a given enclosure temperature achieves the shortest, most efficacious cycle[3] for large-volume applications. Introducing and dispersing VPHP into an enclosure while remaining below the dew point remains a key factor in the development of consistent, robust cycles. Preventing condensation greatly enhances distribution and efficacy, maximizes concentration, expedites VPHP passage through HEPA filters, and shortens cycle time. Well-developed noncondensing cycles also prevent potential material compatibility issues and prolonged aeration times.

Distribution

Standard recirculating HVAC configurations typically do an excellent job of distributing hydrogen peroxide vapor to all target enclosure surfaces. For rooms that use single-pass air, efficient vapor distribution is achieved by injecting at flow rates that create turbulence and mixing through well-positioned ports. This eliminates the need for mixing fans, as are commonly used with portable decontamination systems. Decontamination of large suites with integrated VPHP systems have been successfully validated without the use of fans in the rooms.

Time

Most installations are validated using the "overkill" approach; this determines the exposure time required to inactivate biological indicators (typically 10e6). These are placed in a geometric pattern throughout the enclosure, with emphasis on placement in those areas determined to be least exposed using chemical indicators. Once the injection time is determined to just achieve a 6-log reduction, a factor is used to increase injection time

Table B: Integrated VPHP decontamination examples

Application	Airlock: 15 m³			Fermentation suite: 900 m³		
Cycle parameters	Time, min.	Airflow m³/hour	Inj. rate, g/min.	Time, min.	Airflow m³/hour	Inj. rate, g/min.
Dehumidification	5	75	N/A	30	200	N/A
Conditioning	5	75	12	30	200	90
Decontamination	15	75	7	90	200	30
VPHP generator aeration	5	75	N/A	10	200	N/A
HVAC aeration	15 min. at 300 air exchanges/hour			3:20 h/min, 40 fresh air exchanges/hour		
Total time (h:min.)	0:45			6:00		

to achieve overkill. For example, a factor of 1.3 times the initial decontamination phase may be used for overkill. This will compensate for potential environmental variability in future runs.

RABS, CHAMBERS, AND PASS-THROUGHS

In addition to their use in cleanrooms and suites, integrated VPHP systems can decontaminate a variety of other enclosures, including restricted access barrier systems (RABS), decontamination chambers, and pass-throughs, using specially designed manifolds. Using integrated VPHP to decontaminate a room containing a RABS allows the system to be decontaminated with the doors shut and all filling components in place, just as in an isolator. The RABS air-handling system draws VPHP from the room either directly (active RABS) or via the room's ceiling-mounted HEPA filters (passive RABS) and exhausts it back into the room. All interior surfaces are decontaminated while the doors remain closed. In a single-pass configuration, VPHP is piped directly into isolators and then exhausted. Despite the similarities, the current minimum classification of the background environment is ISO Class 7 for RABS vs. ISO Class 8 for isolators.

Gaseous decontamination chambers and pass-throughs are a common fixture in many production areas. Integrated VPHP systems are often used during regular production hours to serve pass-throughs or chambers and are dedicated to the decontamination of clean-room suites during nightly or weekend shutdowns. Chambers and pass-throughs can be designed to have highly efficient cycles. One of the most rapid total cycle times is about 12 minutes.[4]

Examples

The time required to decontaminate an enclosure depends largely on the total volume and the fresh air exchange rate during aeration. Two examples of validated applications are shown in Table B.

CONCLUSION

Integrated VPHP systems are becoming more common, particularly in Europe and Asia—most often for ISO Class 7 and higher environments—indicating that this technology has gained industry acceptance. HVAC systems are typically used for one or more of the process steps, including VPHP supply, distribution, and aeration. The initiative for an integrated VPHP system may come from the consulting engineer or from the end user organization. Implementation involves cross-functional teams with a thorough knowledge of production processes. Although new construction allows the greatest flexibility for integration, most integrated VPHP systems are placed in existing facilities. The versatility of integrated installations can be greatly enhanced with the use of manifolds operated by the BMS to direct hydrogen peroxide vapor to any number of enclosures and HVAC systems, including cleanroom suites, rooms containing RABS, pass-throughs, decontamination chambers, and isolators. ‹›

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IMPROVED SOLUBILITY OF VITAMIN E BY MEANS OF FREE-SURFACE MICROEMULSION ELECTROSPINNING

Jeremy Lewis, Cuong Nguyen, Anh Lam, and Keith M. Forward

Free-surface electrospinning of microemulsions increases API solubility and may offer an alternative to batch powder processes.

The findings in this paper are research oriented. They are not intended to provide a method for immediate application.

According to the US Food and Drug Administration Biopharmaceutics Classification System, 90% of active pharmaceutical ingredients (APIs) are partially or totally insoluble in water due to their hydrophobic characteristics.[1] As a result, a majority of APIs pass through the gastrointestinal tract without being absorbed into the bloodstream.[2] While proven approaches exist to combat this, drug manufacturers are sometimes forced to introduce large doses of an API into the pharmaceutical to compensate for its low solubility.

There are other challenges as well: Most API powders are packed into tablets using a batch fill-and-pack process.[3] These powders exhibit variable flow and packing properties depending on their densities and coatings, which adds uncertainty to the final product composition.[4] Moreover, when these granular materials undergo friction they can become electrically charged by a process called "triboelectric charging." This can have unwanted effects.[5–6]

To address the challenge of API solubility, new strategies are being explored:

- **Salt formation** has proven successful in converting acidic and basic APIs into ionic salts, increasing solubility in polar solvents such as water.[7]
- **Micronization** decreases API domain size; this increases contact surface area and results in more surface interaction.[8]
- **Adding a surfactant** to an API has been found to increase solubility in both polar and nonpolar solvents. Surfactants contain both aqueous- and organic-soluble components, which increase intermolecular interaction between poorly soluble APIs and the surrounding environment.[9]

A combination of these methods is expected to be more effective than any single method alone.

ELECTROSPINNING

Electrospinning is a novel process that combines surfactants, a decreased domain size, and an amorphous microstructurea combination of the methods mentioned above. Traditional API electrospinning has involved needle-based electrospinning, a process in which a charged solution containing API, solvents, and a polymer is injected through a needle to form an electrohydrodynamic jet. A Taylor cone forms in the presence of applied voltage, and the jet travels down field towards a grounded plate. Before the jet reaches the plate, solvents evaporate, forming an amorphous API entangled in a nanofibrous polymer-based mat.[10]

Numerous studies have investigated the solubility of electrospun mats containing API. Nagy showed that the nanofibrous mats are 40% more soluble than the API alone.[11] Yu and Taepaiboon had similar results using APIs such as ibuprofen, sodium salicylate, diclofenac sodium, naproxen, and indomethacin.[12–13]

Although needle-based electrospinning has proven an effective technique to improve API solubility, the process has limited productivity. To achieve significant amounts of electrospun material, the process must be operated for several hours, as the injection rate from the needle is usually less than 30 milliliters per hour (mL/h), or 1 fluid ounce per hour (fl oz/h).[14–16] To increase productivity, researchers have used multiple-needle configurations,[17–18] which have shown higher productivity compared to single-needle electrospinning. This process, however, has produced inconsistent fiber diameters and less uniformity within the mat.

A method that has been introduced but not widely studied is free-surface electrospinning, sometimes called needle-less electrospinning. Like needle electrospinning, free-surface electrospinning uses the applied potential between a polymer solution and a ground-

ELECTROSPINNING IS A NOVEL PROCESS THAT COMBINES SURFACTANTS, A DECREASED DOMAIN SIZE, AND AN AMORPHOUS MICROSTRUCTURE

ed plate to produce Taylor cone jets. In free-surface electrospinning, however, electrohydrodynamic jets are produced in a greater density than in needle-based electrospinning and are created from a free liquid surface.

In this study, we consider a wired electrode rotating in a bath that holds the polymer solution. Droplets of solution form on the wires and then jet toward the grounded plate. This method increases productivity because multiple drops are able to form and jet from any exposed wire surface.[19] In addition, because the jets come from a homogenous solution, the fibers that form on the plate have the same composition. This eliminates variability that may occur in multiple-needle electrospinning, and maintains higher productivity than using a single needle.

Although API electrospinning has been done before in an effort to decrease domain size and shift the API to an amorphous phase,[10–14] limited studies have been performed on free-surface electrospinning of API with the addition of a surfactant. The surfactant decreases the API domain size by emulsification. The polymer serves as the excipient of the microemulsion and produces an amorphous microstructure matrix. In addition, Lin et. al. have shown that including a surfactant in the electrospinning solution produces a uniform mat composition by reducing the undesired beads-on-a-string morphology, which occurs when solvents become entangled in the nanofibers.[20]

In this paper, we consider free-surface electrospinning of a microemulsion—a poorly soluble API (vitamin E) and surfactant (Kolliphor EL)—to yield mats that exhibit high solubility and uniformity. Free-surface electrospinning creates a fibrous product at a higher rate compared to needle electrospinning. Furthermore, the process is continuous and liquid phase, offering an alternative to batch powder packing methods and a new tool to manage insoluble APIs.

MATERIALS AND METHODS

Chemicals

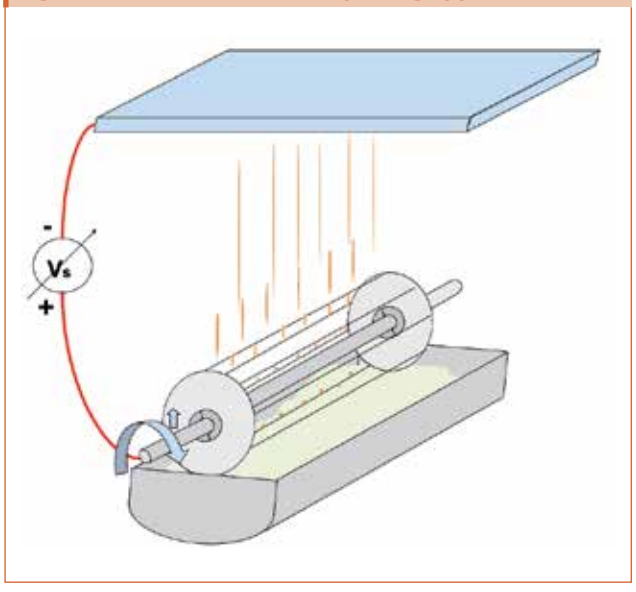
Chemicals were: vitamin E, EL-35, ethyl butyrate, reagent-grade ethanol, polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), high-performance liquid chromatography (HPLC)–grade methanol, acetonitrile, glacial acetic acid, sodium acetate, and polysorbate 80. Deionized (DI) water was dispensed at a conductivity of 18.02 megaohms per centimeter (cm) (1.150×10^7 parts per million total dissolved solids) from a water-purification system. Molecular weights of the PVP and PEG were 1,300,000 and 35,000 daltons, respectively.

Microemulsion preparation

Vitamin E, EL-35, ethyl butyrate, ethanol, and water were mixed at 3%, 10.8%, 3%, 76%, and 7.2% by weight, as previously done by Feng[21] in a 7-cm-/2.8-inch (in.)-diameter jar. With a 1-cm (0.39-in.) diameter and 2.54-cm (1-in.) long stirring rod, the solution was mixed using a magnetic stirring plate at 350 revolutions per minute (rpm) for varying amounts of time. The solution was then sonicated* for varying amounts of time at a maximum amplitude of 30%. Immediately after sonication, PEG and PVP were added in varying weight percentages (wt%) relative to the aqueous phase, and mixed on the stirrer for several hours until a homogenous solution was produced.

* Sonication uses sound waves to break the microemulsion into small drop sizes.

Figure 1: Free-surface electrospinning apparatus



Turbidity

Turbidity of the prepared emulsions were measured after both stirring and sonicating using a turbidimeter. Samples were prepared by diluting 0.10 mL (0.0034 fl oz) of microemulsion in 14 mL (0.47 fl oz) of DI water.

Setup and procedure

The microemulsion solutions were electrospun as per the free-surface electrospinning apparatus described by Forward.[19] An American wire gauge 36-gauge stainless steel wire was wrapped around two Teflon disks of a 10-cm- (3.9-in.)-long spinneret six times and held submerged in a fluid bath by two bolts. One end of the spinneret was attached to a drive belt powered by a direct current (DC) motor. Two power supplies were attached to the apparatus. One provided voltage to the DC motor and was held constant at 9.6 volts (V). The other power supply was connected to the solution bath and collection plate to maintain a 56-kilovolt potential between them. The collection plate consisted of aluminum foil wrapped around a square piece of plexiglass. The working distance was held constant at 40 cm (16 in.) above the solution bath by a ring stand and clamp insulated with polyvinyl chloride pipe and styrofoam tubing. The entire apparatus was enclosed in a plexiglass box and fed with dry air to maintain a relative humidity less than 10% and temperature of 21 °C (70 °F). Solutions were spun for times ranging from 5 minutes to 1 hour. A simple schematic of the apparatus is shown in Figure 1.

SEM procedure

The morphology of the electrospun mats was investigated using scanning electron microscopy (SEM). Small samples of the mats were coated with 20 nanometers (nm) (7.9×10^{-7} in.) of gold and analyzed using a scanning electron microscope.

Vitamin E release rate and HPLC analysis

One hundred milligrams (mg) (0.0035274 oz) of electrospun mats were dissolved in 50 mL (1.7 fl oz) of acetate buffer solution at 21 °C (70°F). The buffer

Figure 2: Turbidity of microemulsion as a function of stir time

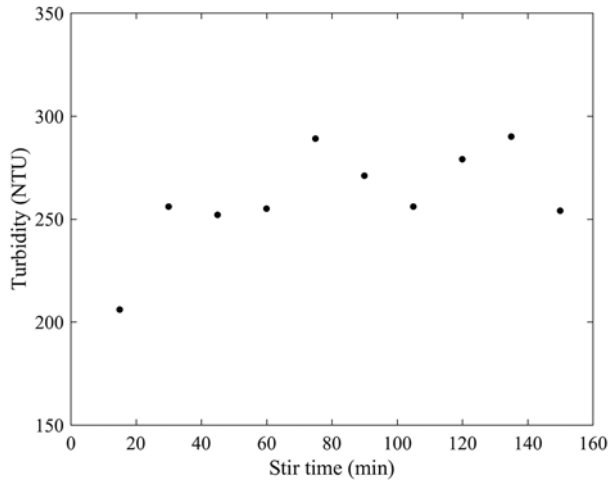
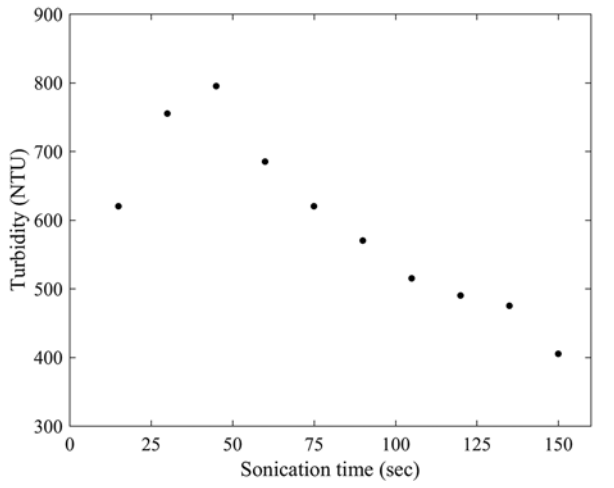


Figure 3: Emulsion turbidity as a function of sonication time. The highest turbidity occurred at 45 seconds, indicating the smallest possible drop size



contained 13% sodium acetate and 1.3% glacial acetic acid by weight in DI water. For comparison, 100 mg of electrospun mats were also dissolved in a buffer solution according to Taepaiboon[22] containing 13% sodium acetate, 1.3% glacial acetic acid, 0.5% polysorbate 80, and DI water by weight. Polysorbate 80 is a surfactant that improves vitamin E solubility in the buffer solution.

The mats were placed on an orbital plate at rate of 100 rpm. Over a period of 36 hours, 0.5 mL (0.017 fl oz) of test solution was removed at selected times and replaced with 0.5 mL of buffer to maintain a constant volume.

An HPLC instrument with a 5-micrometer particle size and 150 × 4.6 mm column was utilized to determine the concentration of the collected samples. The mobile phase was composed of 48:48:4 parts by volume of acetonitrile/ methanol/ DI water. The elution rate was set to 1 mL/minute (0.034 fl oz/ minute). Injection volume was set at 100 microliters (3.38×10^{-5} fl oz), with an ultraviolet light absorption at a wavelength of 295 nm. Peaks were shown at approximately 27 minutes. Calibration curves for the buffer solution with and without polysorbate 80 accounted for concentrations between 0 and 3.2 grams/mL (between 0 and 0.21 pounds/fl oz) of vitamin E, and were used to determine the concentration of vitamin E dissolved in solution.

Measuring productivity

To measure productivity, the collection plate was weighed before and after electrospinning at different spin times with constant parameters and a constant electrode length of 10 cm (3.9 in.). The mass difference was divided by the spin time and the electrode length to obtain productivity defined as mass per time per centimeter of electrode.

RESULTS AND DISCUSSION

Stir and sonication time

To obtain a stable microemulsion, solutions were mixed to obtain a similar Weber number of 1400, as defined by equation 1:

$$We = \frac{\rho v^2 L}{\sigma} \quad (1)$$

In this equation, ρ is the solution density, v is the speed of the stir bar, L is the stir bar length, and σ is the surface tension between the organic and aqueous phases. This unitless number was held constant throughout this paper; it would be an important parameter if the process is up scaled-up in the future.

Reddy and Fogler have proposed that a microemulsion is stable when the turbidity of that solution remains constant.[23] Figure 2 shows the turbidity stabilized at 60 minutes of stirring, indicating a stable microemulsion. After 60 minutes, the turbidity indicated periods of instability, likely a result of coalescence and separation among drops.

Because the solution concentration remained constant, turbidity served as a relative measure of drop size. To find the smallest possible drop size, which is thought to result in maximum dissolution, the microemulsion was sonicated for varying amounts of time. Figure 3 depicts a peak in turbidity at 45 seconds of sonication, indicating that the solution was stable and had the smallest drop size possible at that point. These conditions suggest high dissolution and uniformity in the final product.

Polymer concentration

Water, ethanol, and ethyl butyrate were used as solvents. They evaporate from the microemulsion during electrospinning, leaving the polymers, EL-35, and vitamin E to form a fibrous mat that can be rolled into a pill,[24] dissolved in fluid, or processed into a finished dosage form by thin-film techniques.[25] In this paper, the mat was simply removed from the foil and

FREE-SURFACE ELECTROSPINNING OF A MICROEMULSION YIELDS MATS THAT EXHIBIT HIGH SOLUBILITY AND UNIFORMITY

Figure 4: (a) Macroscopic view of desired mat (6% PVP, 9% PEG). All of the mat showed a thick layer of fiber formation. (b) SEM of desired mat (6% PVP, 9% PEG). (c)Macroscopic view of undesired mat example. Much of the mat showed areas of no fiber formation.

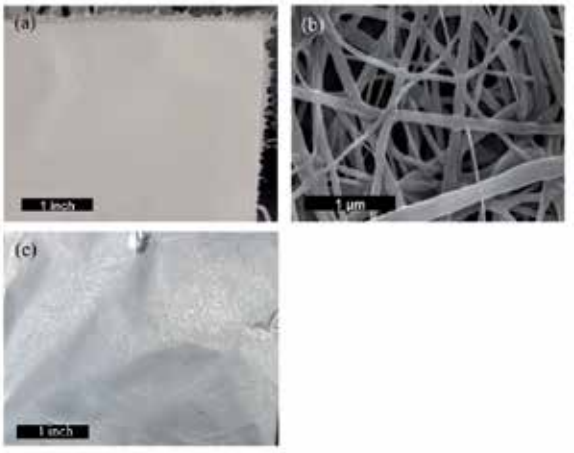
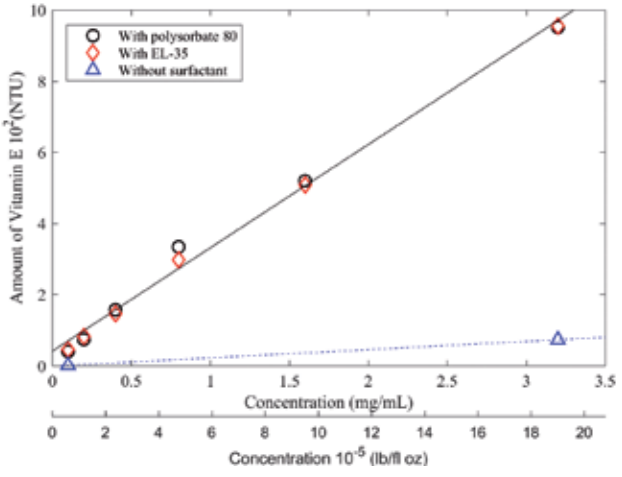


Figure 5: HPLC calibration curve for vitamin E dissolved in three different buffers



THE MORPHOLOGY OF THE ELECTROSPUN MATS WAS INVESTIGATED USING SEM

treated as a thin film without further processing.

Electrospun microemulsions with effective polymer concentrations of 6 wt% PVP and 9 wt% PEG relative to the aqueous phase produced high-quality mats (Figure 4A). An SEM image of these mats confirmed uniform fiber thickness and desired amorphous structure (Figure 4B).

Higher polymer concentrations yielded highly viscous solutions; these produced relatively large Taylor cone drops that were unable to jet. Lower PVP and PEG concentrations produced low viscosities that yielded minimal drop formation on the wired electrodes. When compared to the solution at effective polymer concentration, solutions with both high and low viscosities resulted in (Figure 4C) solvent splattering and thin mats that failed to maintain mechanical integrity.

HPLC calibration

HPLC calibration was used to quantify the vitamin E concentration in three different acetate buffers at 21°C (70°F). When vitamin E was introduced into the buffer solution without surfactant polysorbate 80 and allowed to mix for a substantial amount of time, vitamin E was almost undetectable in the sample solution. When vitamin E was introduced into a buffer containing either EL-35 or polysorbate 80, substantial amounts of vitamin E were detected. This identifies the importance of a surfactant in the dissolution process.

The HPLC calibration curve indicated the quantity of vitamin E in the mats (Figure 5). Release (dissolution) rates were based on the assumption that the mats contained only vitamin E, EL-35, and polymers at 10.5/38/51.5 wt%. These percentages were determined from the microemulsion composition without ethyl butyrate, ethanol, and water, which are expected to have evaporated during electrospinning. The mat was dissolved in buffers, both with and without polysorbate 80. The buffer with polysorbate 80 serves as a control, since it is known that vitamin E in the mat will dissolve completely in the presence of a surfactant.

The mats showed similar release characteristics in both solutions, reaching 100% dissolution within 16 minutes. This indicates that EL-35 was successfully incorporated into the mats and increased dissolution of vitamin E without the need for an additional surfactant.

These results were compared to cast-film microemulsion—in which the polymeric solution is left to dry into a film without being electrospun—and pure vitamin E, both of which were dissolved in the buffer without added polysorbate 80. The electrospun fibers showed much higher release rates than either the cast film or the pure vitamin E, indicating that electrospinning successfully increased the solubility of vitamin E (Figure 6).

Fickian diffusion

Fickian diffusion is a common mechanism used to describe the release characteristics of drugs in polymer carriers. The Higuchi equation is a simple but accepted way of verifying diffusion. The simplified Higuchi model is shown in equation 2:

$$\frac{M_t}{M_\infty} = K\sqrt{t} \qquad (2)$$

where M∞ is the cumulative absolute amount of drug released at infinite time, Mt is the cumulative absolute amount of drug released at time t, and K is a constant relating the system concentration and diffusivity.[26] Plotting release percentage versus the square root of time should yield a linear line with a slope of K.

The electrospun mat dissolved in a buffer with added polysorbate

Figure 6: Cumulative release of the nanofibrous mats in a buffer containing polysorbate 80, a buffer containing no added surfactants and cast film

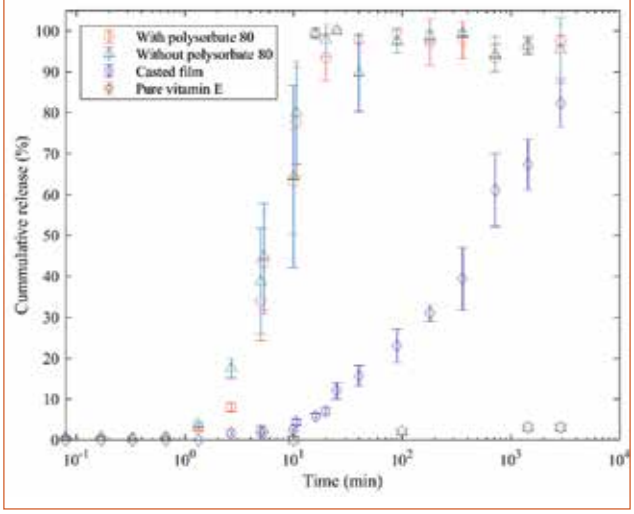


Figure 7: Fickian diffusion region for mat dissolution in buffers with polysorbate 80, without polysorbate 80, and cast-film emulsions

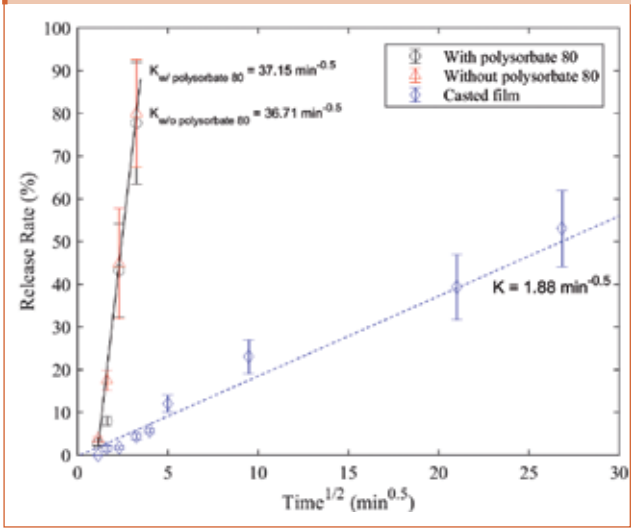
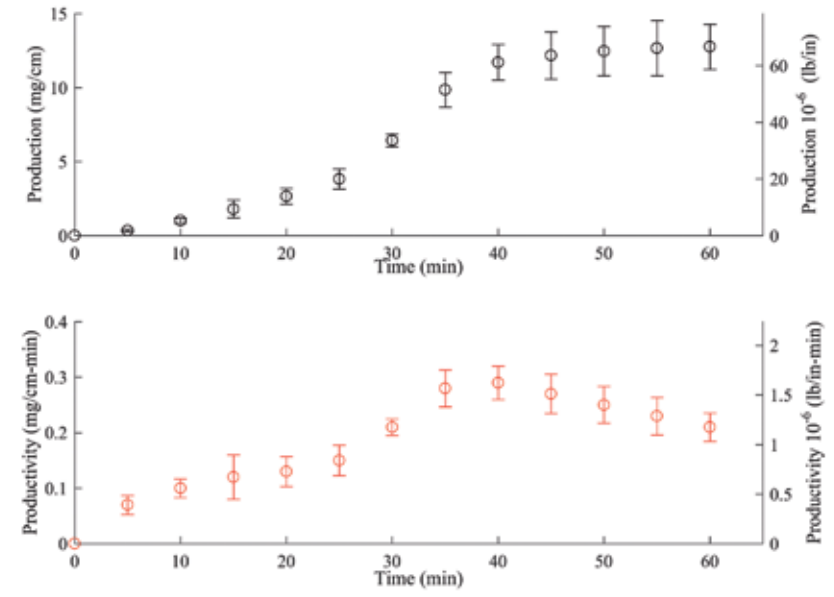


Figure 8: Production per length of electrode



THIS INDICATES FREE-SURFACE ELECTROSPINNING OF MICROEMULSIONS CONTAINING API AND A SURFACTANT IS AN EFFECTIVE METHOD TO INCREASE API SOLUBILITY

80 had a K value of 37.15 $min^{-0.5}$; the mat dissolved in the buffer without polysorbate 80 had a K value of 36.71 $min^{-0.5}$. The cast film had a K value of 1.88 $min^{-0.5}$. This verified that EL-35 improved the vitamin E release rate.

Productivity

Figure 8 shows the production per length of electrode and productivity of free-surface electrospinning defined by equation 3, where:

$$Q = \frac{m}{t\,l} \qquad (3)$$

and m is the mass of the mat produced after time t per electrode length l. Maximum productivity of 0.29 mg/cm-min (1.6×10^{-6} lb/in.-min) occurred at 40 minutes of electrospinning.

After 40 minutes, the solution became highly viscous as the solvents evaporated from the exposed free surface—a phenomenon called "solution aging."[19] When the solution aged, large drops formed on the wired electrodes but were unable to jet due to an increase in viscous forces. The productivity of 0.29 mg/cm-min (1.6×10^{-6} lb/in.-min), however, was significantly higher than needle-based electrospinning, which typically produces this quantity of fibers on a scale of hours.

CONCLUSION

An effective concentration of polymer mixture was determined based on macroscopic and microscopic characteristics of the nanofibrous

electrospun mats that were produced. In addition, EL-35 was successfully incorporated into the mats and effectively increased the dissolution of vitamin E. The electrospun mats showed higher release characteristics compared to cast-film emulsions, and productivity was found to be higher than needle-based electrospinning. This indicates free-surface electrospinning of microemulsions containing API and a surfactant is an effective method to increase API solubility. ‹›

ACKNOWLEDGMENTS

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A STATISTICAL APPROACH FOR CU TESTING OF CPV BATCHES AND COMPARISON WITH USP <905> UDU

Roger Zanon, Limin Shi, Kyle Johnson, and Jeff Hanson

The USP <905> UDU test, widely used for batch release since 2007, is no longer supported by FDA. We propose a two-sided tolerance interval method to alleviate this deficiency. The approach provides 50% confidence and 95% probability that future samples from the batch will conform to USP <905> criteria. In addition, this new statistical assessment provides the same practical look and feel as USP <905>.

A compendial test used routinely in pharmaceutical manufacturing, the US Pharmacopeia (USP) <905> uniformity of dosage unit (UDU) test is familiar across the industry. The test is a market benchmark, and its procedure and acceptance criteria have been widely used for batch release since its introduction in 2007, due to its convenient results reporting and ease of determining conformance to acceptance criteria.[1] Although used for batch release, the procedures and acceptance criteria in USP <905> do not represent a statistical sampling plan. As such, results derived from these procedures should not be extrapolated to a larger population —such as an entire product batch—due to a lack of statistical assurance that it would meet appropriate specifications and statistical quality control criteria.

As of 2013, the US Food and Drug Administration (FDA) withdrew its support for USP <905> procedures and acceptance criteria for batch release,[2] followed by the USP in 2014.[3] During continued process verification (CPV), however, there is a need for a statistical batch release testing method to provide reasonable assurance that a released batch will comply with USP <905>.[4] Alternative statistical approaches have been published in the literature,[6] suggesting 50% confidence and 95% probability with respect to USP <905>.[5–7] No such comparison has been presented for a two-sided tolerance interval option that provides 50% confidence and 95% probability of passing USP <905>. This paper presents such an approach.

BACKGROUND

The USP <905> content uniformity (CU) test methodology for batch release includes testing of individual doses of finished pharmaceuticals to ensure that the product meets quality specifications.[8] Testing starts during manufacturing, when at least 30 dosage units are sampled, usually as a random composite from the batch, and includes up to two stages of analytical testing to determine conformance to USP <905>.

Stage 1 begins with the assay of 10 individual dosage units to determine the amount of active ingredient in each as a percentage of the label claim (%LC). An acceptance value (AV) is then calculated, and if not more than (NMT) 15.0, the batch passes the content uniformity requirement. If the value is greater than 15.0, the testing progresses to Stage 2.

In Stage 2, another 20 units are assayed. Acceptance criteria are an AV of NMT 15.0, and all individual dosage units within determined limits. If results meet the criteria for either stage of testing, the batch passes the USP <905> requirements and is deemed to have demonstrated CU acceptable for release.

STAGE 1

1. Assay 10 dosage units.
2. Calculate the AV.

$AV = |M - \bar{X}| + 2.4s$

M	For $98.5 \le \bar{X} \le 101.5$, $M = \bar{X}$ For $\bar{X} < 98.5$, $M = 98.5$ For $\bar{X} > 101.5$, $M = 101.5$
$\bar{X}$	Average of the 10 assay values
s	Sample standard deviation of the 10 assay values

3. If AV is NMT 15.0, the USP <905> testing criteria are met.

STAGE 2

1. Assay 20 additional dosage units.
2. Calculate the AV.

$AV = |M - \bar{X}| + 2.0s$

M	For $98.5 \le \bar{X} \le 101.5$, $M = \bar{X}$ For $\bar{X} < 98.5$, $M = 98.5$ For $\bar{X} > 101.5$, $M = 101.5$
$\bar{X}$	Average of the 30 assay values
s	Sample standard deviation of the 30 assay values

3. Calculate the limits for the individual dosage unit assays. The low limit for each individual assay is (0.75 M) and the high limit for each individual assay is (1.25 M).
4. If all assays are between (0.75 M) and (1.25 M) and the AV is NMT 15.0, the USP <905> testing criteria are met.

Multiple statistical approaches have been proposed as replacements for the procedures and acceptance criteria currently defined by USP <905>. While these approaches satisfy the statistical shortcomings of USP <905>, they require significant deviation from the current familiar implementation of that compendial test, such as comparing test results against large, table-listed acceptance limits (ASTM E2709/E2819), or determining acceptance by applying one- and two-sided tolerance intervals to the test results.[5] Both approaches require mathematical manipulation of the test results followed by individual determination of conformance to the acceptance limits.

To overcome obstacles associated with industry acceptance of a statistical methodology that may be unfamiliar, we attempted to develop a method that provides adequate statistical assurance in a manner that has the same familiar look and feel of the acceptance criteria test associated with USP <905>. The process presented here results in a single number that, when maintained within the defined numerical limit, satisfies the minimum statistical assurance provided by the acceptance criteria, a process very similar to that of the current application of USP <905>.

The CU approach presented here was selected and developed for two reasons: First, 50% confidence, 95% probability to pass USP <905> has been suggested as appropriate for release testing. Second, the methodology was developed to have the same practical look and feel as the current application of USP <905>.

DERIVATION

In this document, the percentage of individual CU results falling between 85.0 and 115.0 %LC is defined as "coverage." It has been shown that there is at least a 95% probability of passing the USP <905> test if coverage is at least 98.58%.[5] Based on this, a statistical approach to assess CU for batch release using a two-sided tolerance interval approach to provide 50% confidence and 95% probability to pass USP <905> (two-sided 50/95 UDU test), was established.

First, a two-sided tolerance interval is calculated:

$$\text{Lower Limit (LL)} = \bar{X} - k \times SD \quad (1)$$

$$\text{Upper Limit (UL)} = \bar{X} + k \times SD \quad (2)$$

where $\bar{X}$ is the mean of individual contents (expressed as %LC), SD is the sample standard deviation (expressed as %LC), and k is a constant that imparts the specified confidence level, coverage (corresponding with the probability to pass USP <905>), and sample size.

The constant k is calculated using the following equation:[9]

$$k = z_{\frac{1+p}{2}} \sqrt{\frac{v\left(1+\frac{1}{n}\right)}{\chi^2_{v;1-\gamma}}\left(1 + \frac{(n-3)-\chi^2_{v;1-\gamma}}{2(n+1)^2}\right)} \quad (3)$$

where:

- z is the critical value of the normal distribution associated with cumulative probability (1 + p)/2.
- p is the probability of individual values to fall within the range (coverage).
- n is the sample size (number of dosage units in a sample).
- v is the degrees of freedom (n – 1).
- γ is the confidence level (frequency with which the tolerance interval will contain the targeted number of individual values within the range (coverage)).
- $\chi^2_{v;1-\gamma}$ is the critical value of the chi-square distribution with degrees of freedom (v) exceeded with confidence level (γ).

Secondly, a determination must be made whether a CU sample passes the acceptance criteria. As expressed in Equations (4) and (5), the sample passes the acceptance criteria only if the interval (LL to UL) is completely contained within 85 to 115 %LC.

$$85.0 \le LL = \bar{X} - k \times SD \quad (4)$$

$$115.0 \ge UL = \bar{X} + k \times SD \quad (5)$$

For $\bar{X} \le 100.0$, the condition in Equation (5) can be met if the condition in Equation (4) can be met. Equation (4) can then be derived as:

$$100.0 - 85.0 \ge 100.0 - LL$$
$$= 100.0 - (\bar{X} - k \times SD)$$
$$= 100.0 - \bar{X} + k \times SD$$
$$= |\,100.0 - \bar{X}\,| + k \times SD \quad (6)$$

Which can be further derived as:

$$|\,100.0 - \bar{X}\,| + k \times SD \le 15.0 \quad (7)$$

For $\bar{X} \ge 100.0$, the condition in Equation (4) can be met if the condition in Equation (5) can be met. Equation (5) can then be derived as:

$$115.0 - 100.0 \ge -100.0$$
$$= (\bar{X} + k \times SD) - 100.0$$
$$= \bar{X} - 100.0 + k \times SD$$
$$= |\,100.0 - \bar{X}\,| + k \times SD \quad (8)$$

Which can be further derived as:

$$|\,100.0 - \bar{X}\,| + k \times SD \le 15.0 \quad (9)$$

Based on these results, it is concluded that $|100.0 - \bar{X}| + k \times SD$ should be NMT 15.0 to ensure the sample passes the release requirement. As such, $|100.0 - \bar{X}| + k \times SD$ is defined as the AV. Using this equation, an AV value can be established that satisfies any desired confidence (γ) and coverage (p) by calculating the corresponding k value using equation (3).

From the ISPE-sponsored Blend Uniformity and Content Uniformity Group's recommendation,[10] the proposed CU testing for CPV batches should consist of two stages (10 dosage units for Stage 1 and 30 dosage units for Stage 2). Additionally, a 50% confidence level and 98.58% coverage (corresponding to 95% probability to pass USP <905> test)[5] has been proposed as appropriate for release testing.[6] Therefore, to meet these recommendations using Equation (3), the corresponding k values for sample sizes of 10 and 30 are 2.664 and 2.521, respectively. As such, |100.0

Application

A stepwise summary of the proposed commercial testing procedure and application of the CU criteria for CPV is:

1. During manufacturing, collect at least one sample from at least 30 locations spaced equally across the batch, including the beginning and end of the run.
2. Assay a total of 10 dosage units from approximately equal locations across the batch, including the beginning and end of run. These samples should be taken from the 30 samples collected during manufacturing.
3. Calculate the average ($\bar{X}$) and SD of the 10 results.
4. Calculate $AV_{50/95} = |100.0 - \bar{X}| + 2.664 \times SD$
5. The sample complies if all individual values are within 75.0–125.0 %LC and $AV_{50/95} \leq 15.0$.
6. If $AV_{50/95} > 15.0$, assay 20 additional dosage units (one dosage unit from each of the remaining locations collected during manufacturing).
7. Calculate the average ($\bar{X}$) and SD of the 30 total results
8. Calculate $AV_{(50/95)} = |100.0 - \bar{X}| + 2.521 \times SD$.
9. The sample complies if all values are within 75.0–125.0 %LC and $AV_{50/95} \leq 15.0$.
10. If $AV_{50/95} > 15.0$, the batch does not meet the acceptance criteria.

CU acceptance criteria are summarized in Table A. If the acceptance criteria can be met, then with 50% confidence, there is at least 95% probability samples from the lot will pass the USP <905> UDU test.

Table A: CU acceptance criteria for CPV batches

CU Acceptance Criteria for two-sided 50/95 UDU	
Stage 1	1. n = 10 units 2. All individual values within 75.0% – 125.0% 3. $AV_{50/95}$ NMT 15.0 ($AV_{50/95} = \|100.0 - \bar{X}\| + 2.664 * SD$)
Stage 2	1. n = 30 units 2. All individual values within 75.0% – 125.0% 3. $AV_{50/95}$ NMT 15.0 ($AV_{50/95} = \|100.0 - \bar{X}\| + 2.521 * SD$)

Confidence level = 50%, Probability (passing USP <905> UDU) = 95%

$- \bar{X}| + k \times SD$ is defined as the two-sided 50/95 UDU test, for which an AV of NMT 15 ensures 50% confidence, 95% probability ($AV_{50/95}$), when k = 2.664 (n = 10), and when k = 2.521 (n = 30).

COMPARISON

As shown in Figure 1 (10,000 simulations), the probability of passing the USP UDU at any given coverage changes as the lot mean changes (e.g., 90, 97, and 100 %LC). This has been demonstrated previously by Bergum[5] and is a function of the "indifference zone" in USP <905> UDU, which introduces

Figure 1: Probability of passing a UDU test as a function of the percent of individual values between 85 and 115 %LC for various lot means

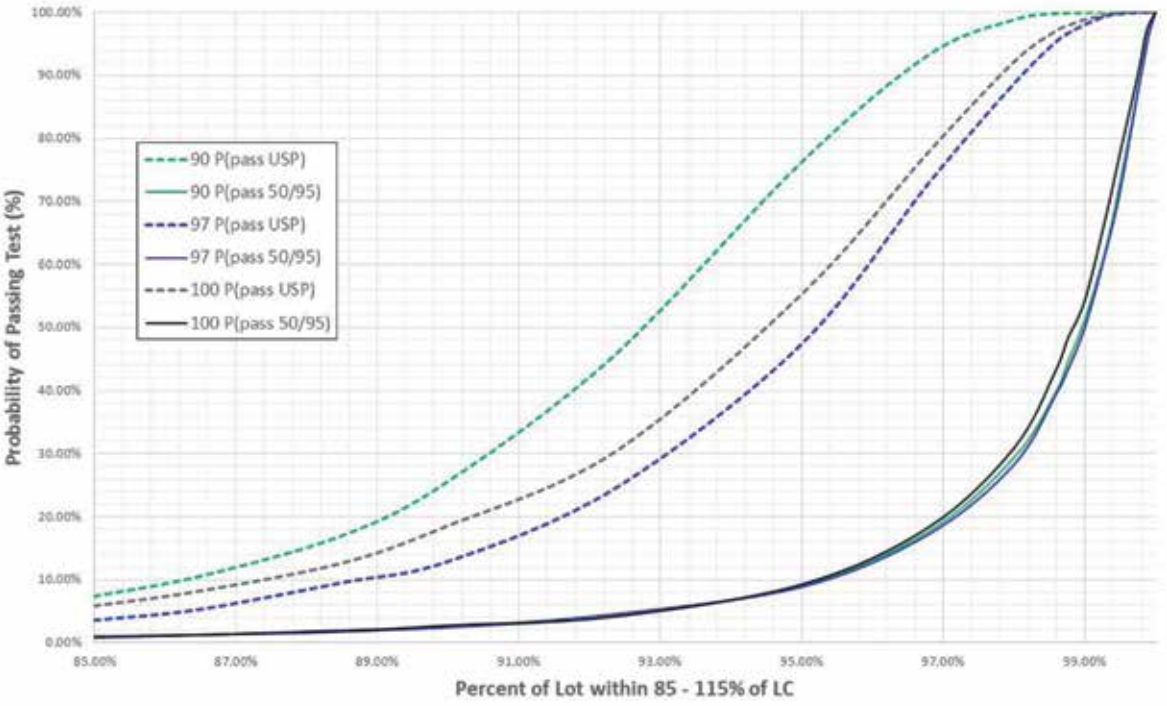
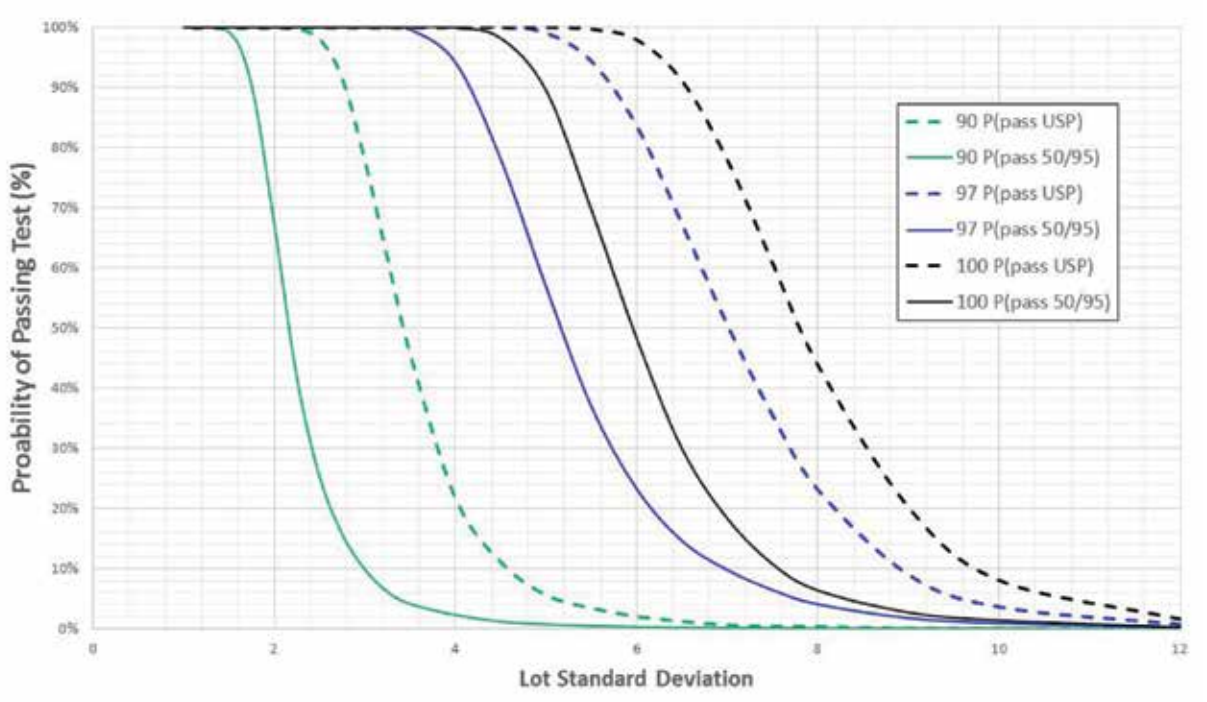


Figure 2: Probability of passing a UDU test as a function of the lot SD for various lot means



bias in acceptance probability when the lot mean deviates from 100 %LC.[11] As can also be seen in Figure 1, the phenomenon created by the indifference zone is absent in the operating characteristic (OC) curves created using the two-sided 50/95 UDU test. (This is expected since the methodology does not incorporate an indifference zone.) Also apparent in Figure 1 is the relatively conservative nature of the two-sided 50/95 UDU test compared to USP <905>. Overall, these observations demonstrate that the statistical assurance provided by the two-sided 50/95 UDU test remains consistent, regardless of the lot mean, and is more stringent than the USP <905> test.

Another comparison of USP <905> UDU vs. the two-sided 50/95 UDU approach is shown in Figure 2, which depicts OC curves demonstrating probability to pass the unit dose test as a function of SD for three different lot means (90, 97, and 100 %LC). A quick comparison of these curves reveals that for each lot mean, the corresponding curve is significantly right-shifted for the two-sided 50/95 UDU test vs. the USP <905> UDU test, demonstrating again the relatively conservative nature of this test as compared to USP <905>.

More quantitative comparisons of the two tests are depicted in Figure 3 and Figure 4. Figure 3 provides a graphical depiction of the confidence provided by USP <905> that future samples will pass the USP <905> UDU test as a function of the tested lot mean, when probability to pass is held constant at 95% (corresponding to 98.58% coverage) and the tested sample passes at the acceptance limit (i.e. AV = 15). Figure 4 provides a graphical depiction of the probability provided by USP <905> that future samples will pass the USP <905> UDU test as a function of the tested lot mean, when confidence is held constant at 50% ($\gamma = 0.5$) and the tested sample passes at the acceptance limit (i.e. AV = 15).

First, the maximum allowable SDs acceptable per USP <905> were calculated for the various tested lot means. These values (tested lot mean and corresponding allowable SD) were then used in the two-sided acceptance value calculation ($AV = |100 - \bar{X}| + k \times SD$), and the equation was solved for k. Then, using the new values for k and Equation (3), the corresponding confidence (γ) was solved for a coverage (p) of 0.9858 (corresponding to 95% probability to pass USP <905>).[5] The result for each lot mean was then plotted (Figure 3) against the 50% confidence and 95% probability to pass USP <905> assured by the two-sided 50/95 UDU test.

MULTIPLE STATISTICAL APPROACHES HAVE BEEN PROPOSED AS REPLACEMENTS FOR THE PROCEDURES AND ACCEPTANCE CRITERIA CURRENTLY DEFINED BY USP <905>

To compare the probability provided by passing the two tests, the k values determined above were used to solve for coverage (p, corresponding to the probability to pass USP <905>) with confidence fixed to 50% ($\gamma = 0.5$). Each calculated coverage (p) was then converted to a probability to pass USP <905> using an OC curve generated for the corresponding tested lot mean (similar to the OC curves depicted in Figure 1). The result for each lot mean was then plotted (Figure 4) against the 50% confidence and 95%

Figure 3: Confidence to provide 95% probability to pass USP <905> as a function of the tested lot mean %LC

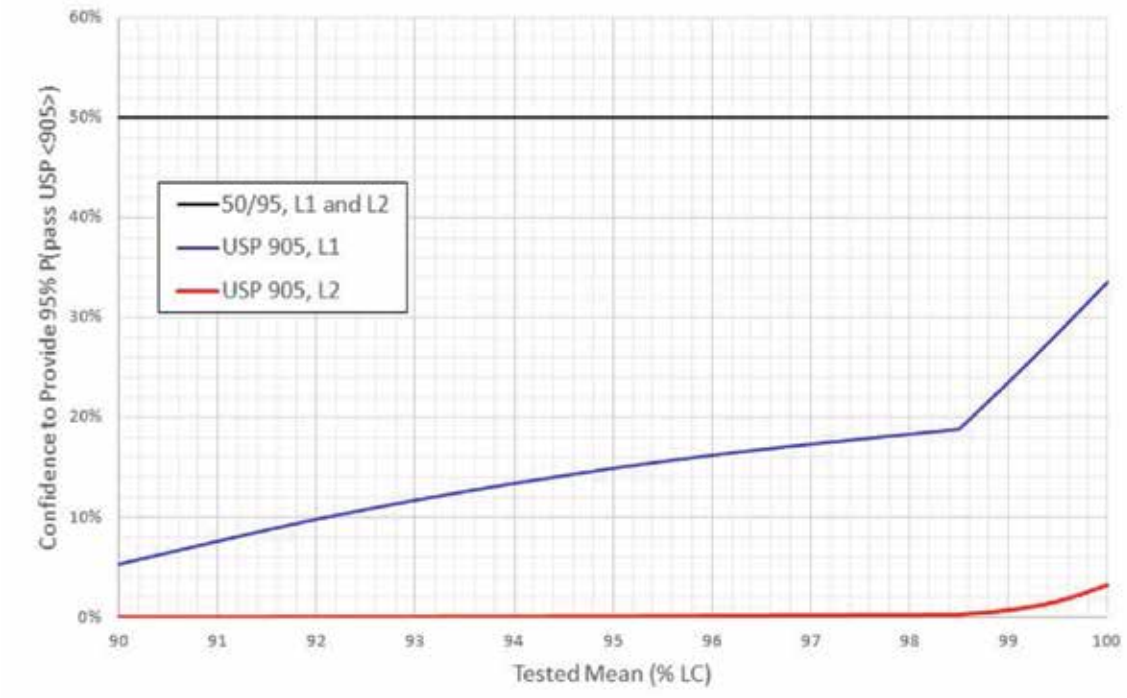
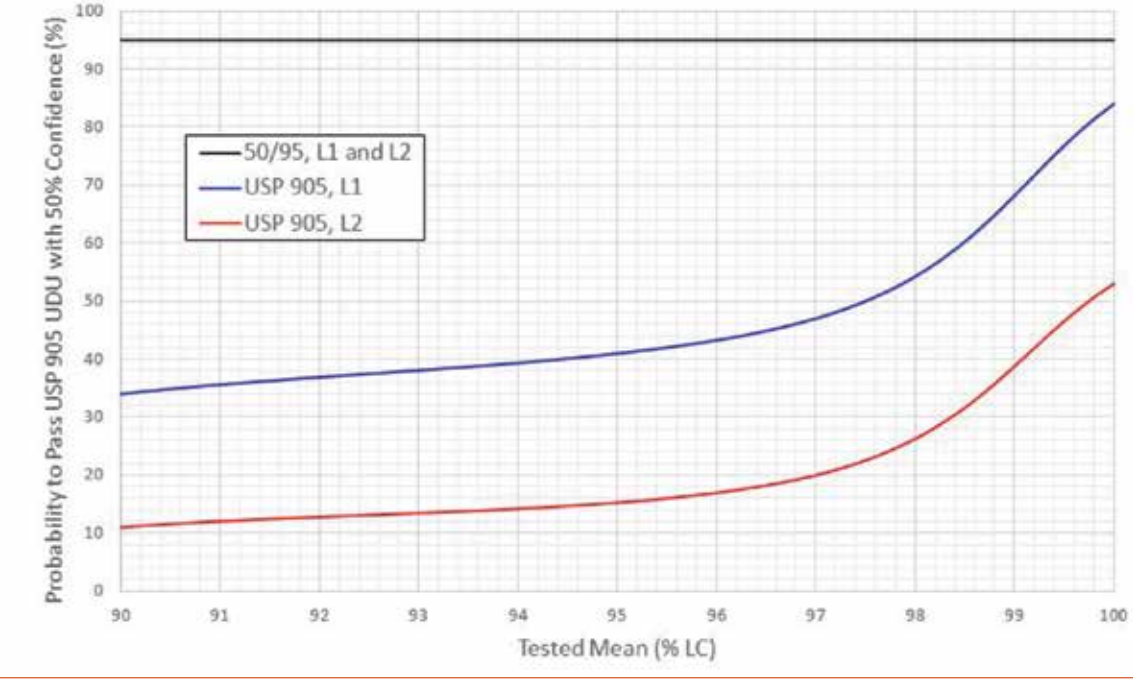


Figure 4: Minimum probability provided by USP <905> that future samples will pass the USP <905> UDU test as a function of the tested lot mean, when confidence is held to 50%



probability to pass USP <905> assured by the two-sided 50/95 UDU test.

As depicted in Figure 3 and Figure 4, when the acceptance criteria are met, the two-sided 50/95 UDU test consistently provides at least 50% confidence and 95% probability to pass USP <905>, regardless of the tested lot mean. The USP <905> UDU test, on the other hand, provides variable statistical assurance that future samples will pass the test, with minimal confidence and coverage assurances changing significantly as a function of the lot mean.

In addition to the variable statistical assurance provided by the USP

A TWO-SIDED TOLERANCE INTERVAL TEST HAS BEEN PROPOSED TO SATISFY CU RELEASE CRITERIA FOR BATCHES OF DRUG PRODUCT MANUFACTURED IN UNIT DOSES

<905> UDU test, a cursory glance at Figure 3 and Figure 4 also demonstrates the superior statistical assurance provided by the two-sided 50/95 UDU test at all acceptable lot mean values. In fact, a careful review of these comparisons suggests that the two-sided 50/95 UDU test is, if anything, more conservative than what is required to ensure CPV. That is beyond the scope of this manuscript, however, and a likely topic of future debate.

SUMMARY

A two-sided tolerance interval test has been developed and proposed to satisfy CU release criteria for batches of pharmaceutical drug product manufactured in unit doses. The two-sided 50/95 UDU provides consistent statistical assurance that if samples taken during manufacturing meet the proposed acceptance criteria ($AV_{50/95} \leq 15$), then with 50% confidence there is at least 95% probability that samples from the batch would pass the USP <905> UDU test. To ensure this level of statistical assurance, the test is significantly more stringent than the traditional USP <905> UDU. In addition, implementation of the methodology has a very similar look and feel to that of the current USP <905>, increasing the likelihood that it will be accepted by the pharmaceutical industry. ‹›

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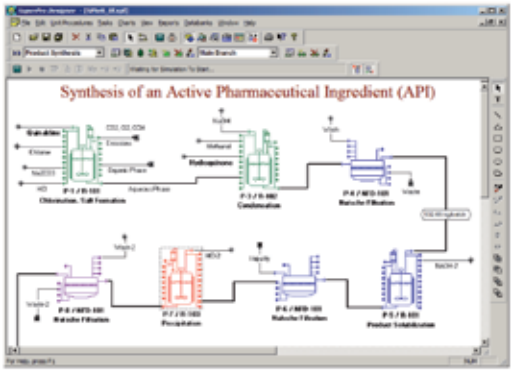

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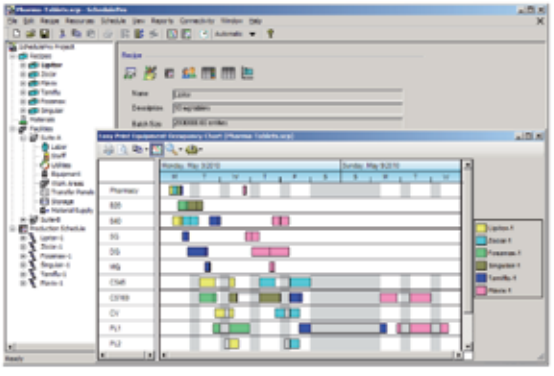

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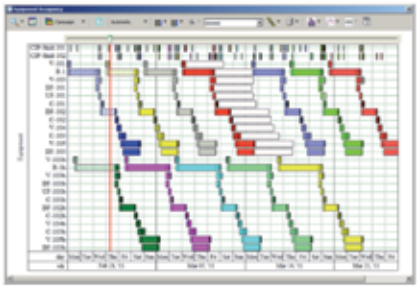

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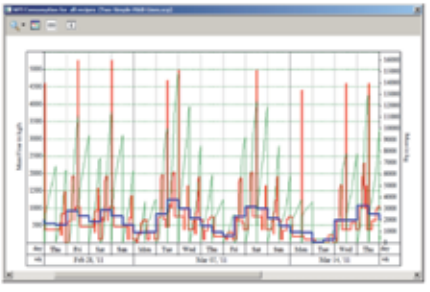
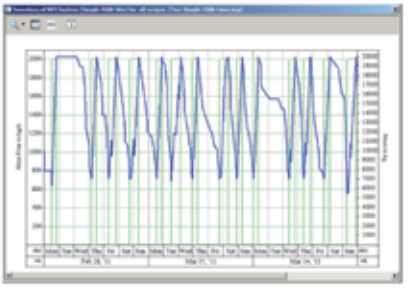


Tracking demand for resources (e.g., labor, materials, utilities, etc.)



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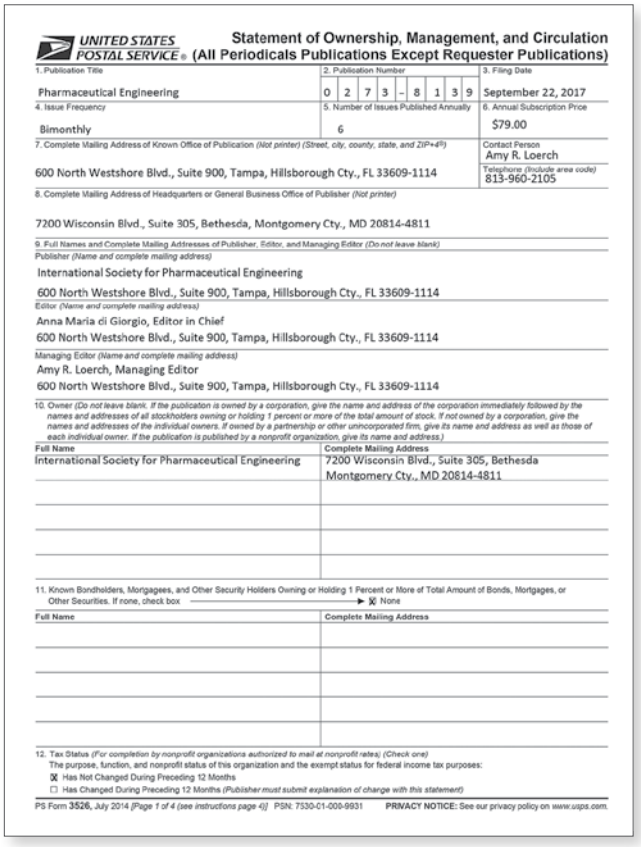

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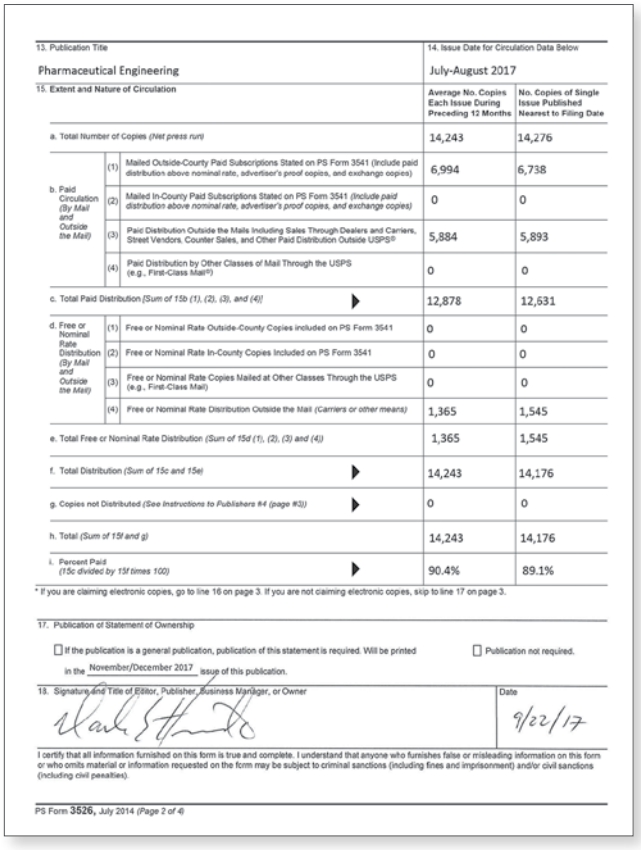

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MEDICAL ETHICS: CONFLICTING OBLIGATIONS

Beginning in 1932, the US Public Health Service conducted an infamous research project—the Tuskegee Syphilis Experiment—designed to follow the course of untreated syphilis. The unwitting participants were poor African-American men in Alabama, who were never told they had the disease. The experiment went on for 40 years, with the men receiving no treatment even after the discovery of life-saving penicillin in the 1940s. Many died of the disease, having infected their partners and fathered children born with syphilis.

As a graduate student of medical history, Yoram Unguru developed an interest in ethics after learning about events such as the Tuskegee Syphilis Experiment.

"It intrigued me how this profession that I viewed as noble was leveraged and prostituted," said Unguru, who is Chair of the ethics committee at the Herbert & Walter Samuelson Children's Hospital at Sinai in Baltimore, Maryland. "Once I got to medical school, I learned that ethics went much further than just Tuskegee or the involvement of doctors in Nazi Germany."

Unguru went on to study medicine at Technion—the Israel Institute of Technology—and after his pediatric residency, did a fellowship at the Berman Institute of Bioethics at Johns Hopkins University. He is currently a physician in the Pediatric Hematology/Oncology Division at Children's Hospital at Sinai in Baltimore, Maryland.

"Ethics is part of what we do every day, from the treatment decisions that are made in the clinic to our research," he said. "You can't divorce ethics from medicine and you certainly can't do that in my field of pediatric hematology/oncology."

In the clinical world, ethics is about conflicting moral obligations. The rights of Unguru's young patients is a paramount concern and he has written extensively on the role that children should have in the decision-making process.

"You want to respect the child's evolving ability to make decisions, but he or she may lack the necessary experience and not understand the consequences. Ethics is about justifying whether a particular decision is right or wrong."

One question is whether kids should be consulted about their treatment and if so, the limits to their involvement.

"How do we reconcile respecting the parents' wishes with what the kid wants? What happens if they disagree? Being able to navigate that type of situation with the appropriate tools is as important as doing a physical workup on a kid who comes in with a cough or a limp."

Unguru sees children from infancy to young adulthood, with some patients as old as 25. But involving these patients in decision-making is not primarily about age. It depends on the child, the decision, and the gravity of the consequences of that decision.

"Age is one factor, but not the most determinative. A younger child who has been dealing with a chronic disease all her life will probably be better equipped to make meaningful decisions about her treatment than a healthy older child coming in with his first diagnosis."

All hospitals are required to have an ethics committee, but ethics is not typically funded and doctors can't bill for consults of a purely ethical nature. As a result, Unguru observes, ethics is an afterthought in most places.

Despite needing his clinical work to take priority, he is grateful that the hospital recognizes the value of what the ethics committee does and gives them the time to do it.

While most hospital committees tend to be filled with providers and physicians, Unguru is keen on expanding the footprint so that ethics is omnipresent in his department.

"We have clinicians on the committee—doctors, nurses, and pharmacists—but we also have social workers, nutritionists, lay members, students, and residents."

Anyone with a vested interest in the care of the patient or who has an ethical concern can call on the committee. The first step is to determine if the concern is, indeed, an ethical issue. Sometimes it's an issue of scope of practice or professionalism. When it is an ethical issue, several committee members attend a consult. They listen and investigate, then make recommendations to the clinical team. Later, they present each of their consults to the larger committee at its regular meeting, providing an opportunity for others to contribute.

Often, the ethical issue arises because of a breakdown in communication between the care team and the patient and their family. In those cases, Unguru likens the committee's job to diplomacy.

"We arbitrate, we listen," he said. "If we expect our patients to listen to us, we have to start by listening to them. Clearing up problems can be as straightforward as getting everybody in the same room and getting the caregivers to speak plain English, not med speak."

Unguru acknowledges that pharmaceutical companies can't be involved in discussions of ethical decisions because they have separate responsibilities beyond clinical decision-making.

He does believe, however, that the pharmaceutical industry has a role to play in the ethics surrounding the allocation of scarce resources, which includes drug shortages.[1]

"At a minimum, pharma should serve as a gatekeeper, assuring that hospitals and GPOs (group purchasing organizations) do not overorder and hoard medications that are known or expected to be short," he said. "Pharma can do a better job making sure that local distributors play fairly when it comes to drug distribution. Within reason, pharma should be committed to continuing to produce lifesaving medications for which there is no alternative. I think a better place for them would be a national drug-shortage committee or a professional organization drug-shortage committee."

PERSONALIZED MEDICINE

"Ethics is going to have an integral role in personalized medicine, especially when it comes to treatments that affect the germline," he stated. "The technology is often way ahead of our ability for intervention. There are a lot of hard questions that require thoughtful analysis."

You can hear the compassion that Unguru has for the welfare of his patients in his voice, as well as his hope.

"Each successive decade has seen more and more kids with cancer survive. "Being able to be honest and to be present—almost omnipresent—is required. If you put yourself in the shoes of a kid who has cancer, they don't care that it's a weekend or late at night if they have a question. Yes, there are hard times, but kids want to be kids. Something in their mind as trivial as cancer is not going to get in the way." ‹›

—Scott Fotheringham, PhD

References

1. Fotheringham, Scott. "The Catastrophe of Drug Shortages in Pediatric Oncology." *Pharmaceutical Engineering* 37, no. 1 (January-February 2017): 33–34.

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