The Official Magazine of ISPE

PHARMACEUTICAL ENGINEERING®

January-February 2016 | Volume 36, Number 1

Sustainability in pharmaceutical manufacturing

INSIDE THIS ISSUE
Special Report:
QUALITY METRICS

ISPE®

www.PharmaceuticalEngineering.org

GENERAL VENTILATION TABLET PRESSES GRANULATING
TABLET COATING FILLING & PACKAGING
MIXING & BLENDING LOCAL EXHAUST
DRYING CENTRAL VACUUM
AND MORE

DUST PROBLEMS SOLVED

Farr Gold Series®
Industrial Dust Collector

Total Containment Safely and Economically


Bag-In Bag-Out

Scan QR Code, Place Phone Here

Turn your phone into a window to actually see inside the Farr Gold Series.

LOOKS LIKE A SAFE BECAUSE IT'S

BUILT LIKE A SAFE™

877-749-8664 www.camfilapc.com

camfil
AIR POLLUTION CONTROL

CHANGE IS OPPORTUNITY

Some see change as a problem; we see change as an opportunity. Adapting to the evolving trends and ever-changing regulations in the life sciences industry is what we're known for. We're driven to find the right solution to the most technically challenging problems. And we're satisfied only when we've produced results that make you successful.

crbusa.com

Biological
OSD
Fill/Finish
Vaccines
API's

Animal Health
Blood Fractionation
Oligonucleo/Peptides
Medical Devices
Nutraceuticals

Engineering | Architecture | Construction | Consulting

Il lancio dei cocci, not

Giorgio Morandi

In years gone by it was common practice in most parts of Italy to welcome in the new year by tossing all manner of pottery—plates, vases and such, from windows. Called *il lancio dei cocci*, (literally the tossing of pottery), the custom was to rid oneself of all that is old and broken and make room for the new; a nice idea, yet, not particularly practical for passersby.

I have heard much discussion this past year, my first at ISPE, about the older ways of doing things, the new issues facing the pharmaceutical industry, the rise of the millennials, outsourcing, insourcing, eBooks and print. It tells me that there is a form of disruptive innovation taking place at multiple levels within the industry: among scientists and engineers regarding the inevitable (continual) passing of the guard and the advent of new technology emerging alongside traditional operational paradigms; among regulators embracing sophisticated quality innovations and encouraging product reliability based on robust quality metrics; among patients about product convenience and consistency, which brands to trust and why; and among my colleagues about how best to serve your needs.

It is heartening that no one is suggesting we toss out all that we know and that may be deemed 'old' by some, in favor of a clean slate. Rather, I have heard only ideas about how to achieve harmony amid coexistence—of supply chains, processes, metrics, brands, people, tools and skill sets.

I shouldn't really be surprised. I have worked with engineers across many industries for some 30 years; and while they differ in profile and focus from one industry to the next, they share a common value: a belief in collaboration for greater knowledge.

On a fundamental level, that is what *Pharmaceutical Engineering* magazine is intended to do: share points of view, share information, share findings across our membership around the world. And that is what we shall deliver. Yet we want also to stimulate conversation, nurture debates and speak to like-minded professionals in other industries to see how they are dealing with shared problems, issues, or, if you prefer, opportunities.

With this first issue of 2016, we start the conversation about how what we are doing today, will manifest in the near future.

Redesigning the world, not just making it work, could very well become our collective mantra.

Anna Maria di Giorgio,
editor-in-chief

Comprehensive Compliance Solutions

Navigating the complicated and changing regulatory environment of the drug and device industries across the globe can be very challenging. ProPharma Group brings clarity and breadth of experience across the full lifecycle of your products. Let us be your single source with our complete suite of services:

- COMPLIANCE & QUALITY ASSURANCE
- COMMISSIONING & QUALIFICATION
- PROCESS & CLEANING VALIDATION, AIQ & EM
- COMPUTER SYSTEMS VALIDATION
- TECHNOLOGY TRANSFER & CMO SELECTION
- PHARMACOVIGILANCE
- MEDICAL INFORMATION

ProPharma Group

For more information, call **1-888-242-0559**
or visit us at **propharmagroup.com**

PHARMACEUTICAL ENGINEERING®

Volume 36, Number 1
Published since 1980

Cover photo: Shutterstock

Pharmaceutical Engineering editorial policy:

Pharmaceutical Engineering is a magazine that inspires engineers and regulators across all ranks, around the world, with provocative and useful articles that come from trustworthy and reliable sources.

From technical articles that provide how-to advice that is current and immediately applicable on the job, to thought-provoking features on current issues, *Pharmaceutical Engineering* offers readers a global picture of the profession and the industry.

Cover Story

10 Sustainability in pharmaceutical manufacturing

12 Industry embraces renewable energy

ISPE News

15 Annual meeting highlights

20 ISPE 2015 International Honor Award recipients

22 Study: Patient perceptions of IMPs
Sidebar: Pictograms, eLabels, and digital technology in clinical trials

24 A taste of things to come

25 New releases

28 Meet your new 2015-2016 executive

Affiliate Profile

30 ISPE Canada Affiliate: Adapting to meet the needs of the Canadian market

Young Professionals

32 A YP state of mind:
From student to successful YP

33 ISPE Ireland YP Committee:
A recipe for success

Feature Stories

36 How can I help ... ?

40 History and relevance of sustainability to the pharmaceutical industry

44 George Millili: 2015 Member of the year

LETZNER
Pharmawasseraufbereitung

Pharmaceutical Water and Pure Steam Systems

- 316 L
- DIN 11864
  Hygienic Design
- Anti Rouging Concept
- Green Planet Concept

Online Total Organic Carbon Analysis

- Multichannel (7)
  NDIR-Detection
- One system for
  hot and cold samples
- CFR 21 Part 11
- JP 16 compliance

Made in Germany
www.letzner.de

Special Report

50 Responding to the FDA Federal registry notice on quality metrics

53 Looking at quality metrics in the auto industry

54 Look outside, not just inside

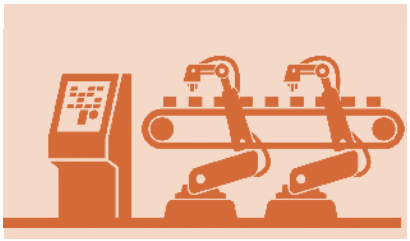
57 Cultural excellence: Ensuring that "Culture of Quality" is more than a slogan

Technical Articles

62 Metrics for the clinical trial material supply chain
Steven Yoder, Sandra Cook and Douglas Meyer

66 Cleaning buffer preparation tank air–liquid interface rings
Paul Lopolito, Dijana Hadziselimovic, Amanda Deal and Amy Thanavaro

74 Case study: Implementation of catalytic technology to improve the aeration Process for a ssyringe-filling line isolator
Donald Eddington, John Lanier, Michael Walsh, Jerry Shrake and Stefan Kleinmann



79 Managing computer system retrofit risks in a GMP manufacturing facility
Richard Parapar

87 Advertisers' index
Classified advertising

Back Page

88 The future of brand names

ISSN 0273-8139

Please address editorial correspondence to:
The editor, Anna Maria di Giorgio
amdigiorgio@ispe.org

For advertising and sale information, contact:
Chris Galione, director of global sales, 301-364-9212, ext. 409
Alisa Pachella, sales account executive, 1-813-960-2105, ext. 212
Diane Munda, sales coordinator, 1-813-960-2105, ext. 399
Robin Lane, sales coordinator, 1-813-960-2105, ext. 235

US Postmaster
Send change of address to:
Pharmaceutical Engineering magazine
600 N. Westshore Blvd.
Suite 900
Tampa, Florida 33609

Periodicals postage paid at Tampa, Florida, US

Canada Postmaster
Send change of address information and blocks of undeliverable copies to:
Pharmaceutical Engineering magazine
PO Box 122
Niagara Falls, ON L2E 6S8

Canada Post mail agreement #40012899

"Fristams are the best pumps going."

- Plant Maintenance Manager, Midwest Production Facility

Ultraclean Reliability From Fristam

Fristam FKL positive displacement pumps are designed to safeguard the integrity of your product and keep your critical path up and running. From its simple, complete CIP and SIP cleaning to its low-shear operation, Fristam's ultraclean FKL series PD pump provides high process purity and gentle, reliable flow.

In addition, the FKL is available with the most comprehensive BPE documentation and the best service and delivery time in the industry.

Biopharm and Pharma Applications:

- Cough syrups
- Enzymes
- Protein solutions
- Cell broths
- Gelatins
- Intravenous dyes

Personal Care Applications:

- Lotions & creams
- Shampoos & soaps
- Ointments
- Toothpaste

Contact Fristam, your trusted resource for pharmaceutical pumps, to learn more.

Fristam PUMPS®

Engineered For Lasting Performance®

1.877.841.5001 | fristam.com/pharma

January 2016

12 Delaware Valley Chapter January Program
Philadelphia, Pennsylvania

21 ISPE DACH Affiliate Stakeholder Management
Frankfurt, Germany

21–22 ISPE DACH Affiliate Stakeholder Management: Wie Geht Das?
Neu-Isenberg, Germany

23 Delaware Valley Chapter Future Cities Competition
Philadelphia, Pennsylvania

25–27 Basic Principles of Computerized Systems Compliance Using GAMP® 5, including Revised Annex 11 and Part 11 Update (T45)
ISPE Training Institute
Tampa, Florida

28–29 A GAMP® Approach to Data Integrity, Electronic Records and Signatures, and Operation of GxP Computerized Systems (T50)
ISPE Training Institute
Tampa, Florida

February 2016

1–3 HVAC (T14)
ISPE Training Institute,
Tampa, Florida

4–5 Biopharmaceutical Manufacturing Facilities (T31)
ISPE Training Institute,
Tampa, Florida

8–10 Process Validation (T46)
ISPE Training Institute,
Tampa, Florida

9 Delaware Valley Chapter 26th Annual Symposium and Exhibition
Philadelphia, Pennsylvania

11 ISPE Nordic Affiliate Cleaning Validation Conference
Copenhagen, Denmark

11–12 Process Validation in Biotechnology Manufacturing (T32)
ISPE Training Institute,
Tampa, Florida

18 Rocky Mountain Chapter 21st Annual Vendor Exhibition
Westminster, Colorado

18–19 Technology Transfer (T19)
ISPE Training Institute,
Tampa, Florida

19 Rocky Mountain Chapter Denver Networking Event
Copper Mountain, Colorado

20 Delaware Valley Chapter Windows on Industry
Philadelphia, Pennsylvania

22–23 Auditing (G07)
ISPE Training Institute,
Tampa, Florida

25–26 Science and Risk-Based C&Q (T40)
ISPE Training Institute,
Tampa, Florida

29 – March 1
GAMP® 5 Process Control Systems (T21)
ISPE Training Institute,
Tampa, Florida

ISPE 25th Aseptic Conference
Arlington, Virginia

March 2016

2–3 Pharma 2025 - Trends in Aseptic
Basel-Allschwil
ISPE DACH Affiliate

7–8 Practical Application of GAMP® 5 (T11)
ISPE Training Institute,
Tampa, Florida

7–9 European Annual Conference
Frankfurt, Germany

8 ISPE DACH Affiliate CoP GAMP D/A/Ch Forum
Stuttgart, Germany

10 San Francisco/Bay Area Chapter 25th Annual Vendor Night
San Francisco, California

14–15 QRM (T42)
ISPE Training Institute,
Tampa, Florida

17 ISPE France Affiliate Risk Analysis in Distribution Chain
Paris, France

17–18 Risk-Based Verification of Facilities, Systems and Equipment Workshop (T48)
ISPE Training Institute,
Tampa, Florida

21–22 Cleaning Validation (T17)
ISPE Training Institute,
Tampa, Florida

30 Delaware Valley Chapter Delaware Valley Science Fair
Philadelphia, Pennsylvania

31 ISPE DACH Affiliate Automation in Der Pharmaindustrie
Reinach, Switzerland

CaSA Chapter
23rd Annual Life Sciences Technology Conference
Raleigh, North Carolina

April 2016

8 Delaware Valley Chapter
Volunteer Day

11–12 China Spring Conference
Shanghai, China

11–14 ISPE Manhattan Beach Training
GAMP® 5; Biotechnology; Project Management*; OSD, Water
Manhattan Beach, California

12 Chesapeake Bay Area
Mid-Atlantic Life Sciences Showcase
Rockville, Maryland

14 Carolina–South Atlantic Chapter
Educational Event
Education & Therapeutic Thursday
Raleigh–Durham, North Carolina

14–15 April 2016
ISPE Japan Affiliate
Annual Meeting

19–21 ISPE Facility of the future and
Continuous Manufacturing Conference
Baltimore, Maryland

20 ISPE Nordic Affiliate Critical Utilities
Conference
Copenhagen, Denmark

22–23 ISPE India Affiliate Annual Conference
Mumbai, India

Training

High-quality, in-depth skill development

ISPE has been delivering training courses since 1998. We've earned the title of the "Industry's Trusted Source of Knowledge" and are viewed by manufacturing professionals and regulators worldwide as the go-to resource for expert-knowledge.

Our robust body of knowledge is delivered onsite, online, or at our new ISPE Training Institute.

ISPE Training Institute
Classroom training courses delivered at ISPE's office in Tampa, Florida. Visit http://www.ispe.org/training for more information.

ISPE eLearning
Convenient access to our global knowledge through online training courses and webinars. Visit www.ispe.org/elearning to learn more.

ISPE Onsite Training
We can help stretch your training budget by bringing our courses to you. Contact Training@ispe.org to request a quote.

eLearning

Online courses and webinars help you expand your skills from the comfort of your desk.

- Expanded Online Training
- General Industry Knowledge Courses
- Fundamental Industry Knowledge Courses
- GMP Courses
- Webinars

Onsite training

Bring customized ISPE training courses to your company.

Topics include:

- Biotechnology
- Cleaning
- C&Q
- Facilities
- GAMP®
- GMPs
- HVAC
- Manufacturing
- Process Validation
- Project Management*
- Quality by Design
- Validation
- Water

* ISPE has been reviewed and approved as a provider of project management training by the Project Management Institute (PMI®)

GAMP® is a set of guidelines for manufacturers and users of automated systems in the pharmaceutical industry and a registered ISPE trademark.

Industry's Trusted Source of Knowledge

"Drug manufacturing has a sustainability problem it needs to address. Fortunately, many companies are doing just that."

Sustainability in pharmaceutical manufacturing

Sasja Beslik, head of responsible investments at Nordea Asset Management, took a filmmaking crew to India to investigate the impacts of pharmaceutical manufacturing in the area around Hyderabad. The locals they spoke to were concerned about the quality in and around the facilities that act as suppliers of bulk drug products to the pharmaceutical industry.[1] What Beslik saw shocked him.

"This is the worst example of water pollution I've seen in a long time," he says in the film, standing by a river covered in white foam into which facilities were dumping their process wastewater. "It looks terrible. The smell is unbearable."

Nordea is the largest financial group in the Nordic and Baltic regions and includes investments in pharma companies in its portfolios. It conducts research – like Beslik's mini-documentary, *Polluting to Heal* – as a way to understand what it invests in and to engage in conversations with companies in which it invests.

India is the largest supplier of APIs to the pharmaceutical industry in the world. Nordea discovered that government authorities responsible for the environment either don't have the power to force the pharmaceutical companies to comply with regulations, or won't. The problem is obvious, severe and little is being done to correct it.[2]

"It's become quite clear during this visit to India that water, which is a huge issue in India, is also important to the industry," Beslik said in the film. "If they don't address water recycling and their pollution of the water, they create a long-term problem that will decrease their ability to grow and create the returns that we need to deliver returns to our customers."

Lack of treatment of process effluent isn't the only way the industry is polluting. Pharmaceuticals that escape into the environment – on agricultural land and into rivers, lakes and our drinking water – are a growing problem. About 90 percent of those detected are excreted or flushed medications.[3] These include antibiotics, diabetes drugs, opioids, beta-blockers, synthetic estrogens and antipsychotics. A German study found over 600 APIs, or their metabolites, in the environment.[4]

Examples like these make it clear that drug manufacturing has a sustainability problem it needs to address. Fortunately, many companies are doing just that, looking at their energy and water use, sourcing of materials for API production and embracing green building.

How is industry improving?

The US Environmental Protection Agency puts it succinctly:

> *"Everything that we need for our survival and well-being depends, either directly or indirectly, on our natural environment. Sustainability creates and maintains the conditions under which humans and nature can exist in productive harmony, that permit fulfilling the social, economic, and other requirements of present and future generations."* [5]

The recent COP21 climate change talks in Paris show how the world can come together to solve the ecological crises before us. Encouragingly,

Sanofi was one of the official partners of the conference, stating that it wanted to raise awareness of the health consequences of climate change. It has committed to reduce its greenhouse gas emissions and develop ways to treat wastewater.

Also encouraging is the number of Big Pharma firms that made it onto Newseek's annual ranking of corporate sustainability and environmental impact of the world's largest companies.[6] Biogen was in the top spot of the green rankings that take into account such metrics as energy, greenhouse gas, water and waste productivity. Other pharmaceutical manufacturers that made the list are Shire (2), Allergan (3), Roche (9), Novo Nordisk (15), Johnson & Johnson (23) and AstraZeneca (30).

Among the companies that have won a US Presidential Green Chemistry Challenge award are Bristol-Myers Squibb, Eli Lilly, Merck, Roche, and Pfizer, for, among other avenues of research, their work designing drugs that biodegrade more readily.[7]

Johnson & Johnson is among the companies with an extensive sustainability policy that addresses its sourcing of raw materials, water use, greenhouse gas emissions, pharmaceuticals in the environment, waste treatment and the use of renewable energy sources. A wind turbine in Cork, Ireland is part of the reason that seven percent of the energy used by the company is obtained from clean or renewable sources.[8] [See sidebar]

Perhaps the most widespread example of sustainability in action among industry players is the way they have embraced green building concepts and LEED certification.

The sustainability of manufacturing facilities

LEED is a sustainable green option with benefits for both industry and the communities in which they operate. It provides both indisputable PR and a good ROI.[15] Leadership in Energy & Environmental Design (LEED) is a green building certification program created and administered by the US Green Building Council (USGBC) to provide a standardized rating system for assessing sustainability of buildings in the United States. It is also used by the Canada Green Building Council and in 150 other countries around the world.[9] Part of its mandate is to promote a "sustainable built environment for all within the next generation."[10] The USGBC certifies 1.85 million square feet of construction every day.[10]

"LEED is a voluntary tool and has been since its inception," said Corey Enck, director, LEED technical development at the USGBC. "There is a significant marketing benefit to certification. We're using that marketing benefit to also drive change. We hope that projects that certify, advertise that they're certified."

Indeed, they do. Among the companies that have embraced LEED, Genzyme has ten LEED-certified buildings, including its corporate headquarters in Cambridge, Massachusetts, which received LEED Platinum, the highest level possible.[11] GlaxoSmithKline's US headquarters in Philadelphia was awarded Double LEED Platinum in 2013. Shire has a LEED-certified single-use system manufacturing facility in Lexington, Massachusetts where it produces biopharmaceuticals.[13] The company claims it uses 80 percent less water and half the energy of conventional facilities. Alexion Pharmaceuticals received LEED Gold certification for its headquarters in Connecticut in 2010.[14] Johnson & Johnson requires that sustainability be applied to most of its new construction and renovations worldwide and to all buildings that cost over $5 million. As of 2014, J&J had 25 LEED-certified buildings, including the corporate headquarters of Janssen Pharmaceuticals, the drug-making arm of the company. [See sidebar]

Beyond the positive PR, there are sound financial reasons that the pharmaceutical industry chooses to LEED certify existing and new construction. The cost for retrofitting a building to achieve LEED certification can carry a premium of roughly two percent of construction costs when compared with non-LEED buildings.[15] These additional costs can be done away with on new construction, which offers design options taking advantage of passive design approaches.

For an owned building, such as any of the corporate headquarters listed above, the savings in energy and water costs usually exceed the expense of meeting LEED standards, with average energy savings and reduced water usage of at least 30 percent.[15]

Staff productivity is enhanced in green buildings

Keith Robertson is an architect and president of Solterre Design in Halifax, Nova Scotia, who won a Green Building Champion Leadership Award from the Canada Green Building Council in 2013. He sees great benefits in LEED for improvements to employee productivity.

"It's interesting to me that pharmaceutical companies are getting their corporate buildings LEED certified because the benefits are not always easy to quantify," Robertson said. "But good green features have been shown to result in less absenteeism, more productivity and less employee turnover."

The green features Robertson refers to are part of the LEED category, Indoor Environmental Quality, which gives credits for such aspects as having a view to outside, access to natural light, high-quality indoor air and control of the temperature and air flow of one's workspace. Studies have shown significant increases in productivity with improvements in each of these categories.[15]

"In fact, these numbers can be significant," Robertson said. "I've seen studies that show improvements in such things as absenteeism can be as high as 15 percent."

He has a simple illustration to show the effect of incorporating green features. "A good estimate is that it costs $2 per square foot to run a building, $20 per square foot to own or rent the space and $200 per square foot for staffing costs. This means that even a one percent improvement in staff productivity – never mind 15 percent – is equivalent to having a zero energy building."

Robertson pointed out that, while LEED was developed around a model of designing, constructing and maintaining office buildings, it has expanded to include other building types.

Use of LEED in manufacturing facilities

"We often see corporate headquarters certified," Enck said. "But over the last six years, we've been working with manufacturers to certify their plants as well. There are a lot of benefits for manufacturing and it's quite an easy sell.

"There's a shared mission between what a manufacturing facility needs to do and what LEED certification does," Enck continued. "Both are trying to conserve natural resources and be as efficient as possible. How can I

streamline my processes? How can I reduce my energy and water consumption? How can I have a healthier indoor environment? Manufacturing facilities are doing this anyway, so LEED gives them a framework to follow to optimize their processes. But then it rewards them so they can use it as brand recognition. We're seeing many manufacturers are liking to advertise things such as that 100% of their products are made in a LEED-certified factory."

There is great diversity in manufacturing, from companies making toothbrushes to semiconductors; pharmaceutical manufacturing falls toward the end with tightly controlled indoor environments. Genzyme has four manufacturing plants that are LEED certified, including a bio-manufacturing plant in Lyon, France.[11] Pfizer has broken ground on a factory it expects to achieve LEED certification for production of its vitamins and dietary supplements.[16]

"We find that the LEED framework works for manufacturers to save energy, to drive energy-efficient projects through the company and help them with their bottom line," Enck went on. "It gets people motivated. That's largely what the LEED rating system is intended to do, to get the project team and the company working toward the same goal."

LEED v4 and the future of pharma manufacturing

The USGBC is introducing LEED v4, incorporating feedback the council has received from project teams since LEED was first introduced in 2001. The current version, from 2009, will continue to be available to the market until October 2016 when LEED v4 will become the sole rating system.

"Data from the market was that projects were scoring higher and higher," Enck said. "The average was a high Silver certification. LEED was becoming more common to get certified. We felt it was the time to release a new version. LEED itself is an evolving tool and LEED v4 raises the bar. It's a stringent tool and a credible tool in terms of quantifying benefits. We require an improvement over business as usual for all categories.

"We're trying to get to holistic building performance and quantify that performance more than we have thus far. We want to ensure that when projects are earning credits they are actually realizing the environmental benefit that was intended."

As with the current system, LEED v4 will have four levels of certification – Certified, Silver, Gold and Platinum. The new standard evaluates high-performing materials more holistically, including lifecycle analysis for the first time, which considers the environmental costs of the full life of a material, as well as the whole building in terms of structure, enclosure and building materials.

"We've really taken a stand on a couple of issues, with human health, energy efficiency and water conservation," Enck said. "The changes we've made signal the next generation of green building."

The focus on human health addresses indoor environmental quality and more testing of indoor environments. It considers the emissions that products offgas and encourages the purchase of materials that emit fewer volatile organic compounds (VOCs). LEED v4 introduces a credit for material ingredients, rewarding transparency about what's in building materials, which adds a health component to the lifecycle assessment.

"We anticipate that uptake will be slow, as we always see when we put a new product on the market," Enck explained. "Market leaders adopt first, then slowly it becomes widely adopted and then common practice. We always see this dynamic between LEED and the market when we release a new version. At first, people are upset that it's so hard, but when we have a version out there for a long time we see that projects are earning LEED certification quite easily because they understand how to use it. We use this dynamic to effect market transformation. We incentivize projects to use this voluntary tool. Then what we put out there becomes business as usual and we raise the bar again."

Industry Embraces Renewable Energy

Electricity use for process manufacturing can account for a substantial portion of a factory's energy budget, not to mention contributing to CO_2 emissions. Big Pharma is addressing its energy needs using renewable resources in a number of notable ways.

RE100

Biogen, Novo Nordisk and Johnson & Johnson are part of RE100, an initiative that requires participating companies to commit to obtaining 100 percent of their electricity from renewable sources by a date each of them sets.[1] RE100 defines renewable energy as electricity generated from biomass, geothermal, solar, water and wind sources, either from on-site installations or off-site generation.[2] Nordea Asset Management, mentioned in above, is also a member.

Big Pharma is addressing its energy needs using renewable resources in a number of notable ways.

Biogen achieved its goal of procuring all of its electricity from renewable sources in 2014. Novo Nordisk set its RE100 target of 100 percent renewable energy at all its production facilities by 2020, while Johnson & Johnson intends to meet its target by 2050. J&J also claims to have cut CO_2 emissions by almost 10 percent in the past five years and has 10 MW of solar systems either built or under construction in Puerto Rico.[3]

Harvesting the wind

GlaxoSmithKline, Novartis, Janssen and DePuy Synthes (which makes medical devices for J&J)

LEED v4 takes into account the unique nature of buildings with high process loads, making it more practical for manufacturing facilities. For energy, LEED v4 references the predominant energy standard in the US – ASHRAE 90.1 – as the baseline, then requires improvements above that. In general, it is 14 percent more stringent than the previous standard. To make it work for manufacturing, LEED v4 allows projects to meet the minimum requirement with a five percent improvement in process loads. The threshold for renewable energy has been adjusted to account for large process loads.

"We addressed process energy so a facility can meet the minimum standards," Enck said. "You're allowed to split out your process energy from your building energy and show an improvement in both of those to meet the prerequisite."

Under review is an adjustment to consider more sources of water in the building, no longer solely focusing on fixtures and fittings. This is an important development, because it includes process water, a potential opportunity for pharmaceutical facilities, which use a lot of water in production.

"We're allowing them to total water usage in the facility and show an improvement from their whole building water usage, not just from fittings and fixtures," Enck said.

So, while there are still serious environmental issues to be dealt with – particularly in the global supply chain – Big Pharma is making strides in environmental sustainability on many levels. ■

By James Hale and Scott Fotheringham, PhD

1. Nordea.com – Polluting to heal – Mini documentary on field visit to India. http://www.nordea.com/en/responsibility/responsible-investments/news/2015-11-08-polluting-to-heal.html
2. Global Research – India: Environmental Damage Caused by Western Pharmaceutical Companies. http://www.globalresearch.ca/india-environmental-damage-caused-by-western-pharmaceutical-companies/5457296
3. GreenBiz – Downstream Drugs: Big Pharma's Big Water Woes. http://www.greenbiz.com/article/downstream-drugs-big-pharmas-big-water-woes
4. Weber, F.A., and T. aus der Beek, and A. Bergmann. "Pharmaceuticals in the Environment – the Global Perspective." Available at https://pharmaceuticals-in-the-environment.org
5. EPA – Learn About Sustainability. http://www.epa.gov/sustainability/learn-about-sustainability#what
6. Newsweek – 2015 Green Rankings. http://www.newsweek.com/green-2015/top-green-companies-world-2015
7. EPA – Presidential Green Chemistry Challenge Winners. http://www.epa.gov/greenchemistry/presidential-green-chemistry-challenge-winners
8. Johnson & Johnson – 2014 Citizenship & Sustainability Report. http://www.jnj.com/sites/default/files/pdf/cs/2014-JNJ-Citizenship-Sustainability-Report.pdf
9. Canada Green Building Council – Going Green with LEED http://www.cagbc.org/CAGBC/LEED/CAGBC/Programs/LEED/Going_green_with_LEE.aspx?hkey=54c44792-442b-450a-a286-4aa710bf5c64
10. USGBC – About USGBC http://www.usgbc.org/about
11. Genzyme – Green Building. https://www.genzyme.com/Responsibility/Environmental-Action/Green-Building.aspx
12. Inhabitat – GSK's US Headquarters Awarded Double LEED Platinum in Philadelphia's Navy Yard. http://inhabitat.com/gsks-us-headquarters-awarded-double-leed-platinum-in-philadelphias-navy-yard/
13. PRNewswire – Shire Announces FDA Approval of Manufacturing Facility for VPRIV Drug Substance. http://www.prnewswire.com/news-releases/shire-announces-fda-approval-of-manufacturing-facility--for-vpriv-velaglucerase-alfa-for-injection-drug-substance-245523021.html
14. Alexion - Alexion Pharmaceuticals Earns the Connecticut Green Building Council Green Advocate Award and Two LEED Gold Certifications for Environmental Sustainability. http://news.alexionpharma.com/press-release/company-news/alexion-pharmaceuticals-earns-connecticut-green-building-council-green-ad
15. GreenBiz – How to Measure the ROI of LEED. http://www.greenbiz.com/blog/2012/10/04/how-measure-roi-leed
16. Business Wire - Pfizer Consumer Healthcare To Expand Caltrate And Centrum Production In China. http://www.businesswire.com/news/home/20150615005638/en/Pfizer-Consumer-Healthcare-Expand-Caltrate-Centrum-Production

have collaborated to build a wind farm to supply a substantial portion of the electricity needs at each of their facilities in Cork, Ireland. When it's complete, there will be a 3 MW wind turbine on each site and three of them were in operation by mid-2014.[4] Energy-related CO_2 emissions were reduced over one-third while energy savings of 24M kWh accrue each year.

Sanofi invested in a 2.1 MW windmill at its API production facility in Ankleshwar, India.[5] The turbine provides 30 percent of the plant's electricity needs, which the company estimates reduces CO_2 emissions by 4.5 kilotonnes annually. The savings in energy costs are anticipated to pay for the windmill project within six years.

Solar arrays

Janssen Pharmaceuticals, an affiliate of J&J, has demonstrated a commitment to using renewable energy at its facilities, as part of its commitment to green building standards and to impact its bottom line.[6] The Janssen site in Titusville, NJ, received LEED Gold certification in 2004 and was recertified Gold in 2014. Almost 85 percent of the facility's yearly electricity demand comes from 5.1 megawatt array of sun-tracking solar panels. The building also scored well for water efficiency.[7]

Ram Pharma in Jordan, built a solar steam system to replace its need for expensive diesel fuel.[8] The steam it produces is used in the facility's steam grid for sterilization, drying and fermenting. The company that built the system estimated that the system would pay for itself within seven years.[9] ■

By James Hale and Scott Fotheringham, PhD

1. RE100 http://there100.org/re100
2. RE100 – Technical Criteria. http://there100.org/technical-criteria
3. RE100 – Johnson & Johnson. http://there100.org/johnson-johnson
4. SEAI – Cork Lower Harbour Energy Group. http://www.seai.ie/lienreport/company-cork-lower-harbour-energy-group.html
5. Sanofi – Energy and Carbon Footprint. http://en.sanofi.com/csr/planet/in_action/energy_carbon_footprint/energy_carbon_footprint.aspx
6. Janssen – Committed to Clean, Renewable Energy. http://www.janssen.com/sustainability/renewable-energy
7. USGBC – Janssen Titusville Recertification. http://www.usgbc.org/projects/janssen-titusville-recertification
8. Solar Thermal World - http://www.solarthermalworld.org/content/jordan-fresnel-collectors-supply-160-degc-steam-pharmaceuticals-producer-ram-pharma
9. Haagen, M., et al. "Solar Process Steam for Pharmaceutical Industry in Jordan," *Energy Procedia*, 2015, 70, pp. 621-625.

25th Annual Aseptic Processing Technology Conference

29 February – 1 March 2016

Crystal Gateway Marriott, Crystal City

The two day conference is filled with track presentations, case studies and group discussions highlighting technological achievements in robotics, dispensing systems, disposables and recently developed best practices.

Each day will kick off with an opening plenary followed by Aseptic and Barrier breakout sessions and concluding with a closing FDA question and answer session.

What's New at **2016** Aseptic Conference?

- Qualification and Validation of Disposables in Production Processes
- Single-use Disposable Technology and Components
- Robotics within Isolators
- New Trends in Aseptic Vial Fillers
- Case studies on the Use of Disposables in Fill-Finish
- Leachables, Extractables and SUD Components
- Legacy Facilities and RABS Upgrades

And Much More!

REGISTER NOW! www.ISPE.org/2016-Aseptic-Conference

ISPE

Annual meeting highlights

Gathering sets attendance record; focuses on change, transformation and innovation

ISPE's 2015 Annual Meeting, held 8–11 November in Philadelphia, Pennsylvania, hosted 28 regulators, 34 speakers, 204 exhibitors and a record 1,934 attendees—a 22% increase from 2014—with 72 sessions covering five subject tracks: biopharmaceuticals, China/Asia–Pacific facilities, data integrity, metrics, risk-based approaches, and single-use technologies. [Table: By the Numbers]

The organization also unveiled its highly anticipated Drug Shortage Assessment and Prevention Tool, available exclusively to members and conference attendees, and hosted its first Global Regulatory Town Hall, with a panel of regulators from the European Medicines Association (EMA), US Food and Drug Administration (FDA), UK Medicines and Healthcare Products Regulatory Agency (MHRA), and the Pharmaceutical and Medical Devices Agency (PMDA).

Opening remarks

John Bournas and François Sallans, Johnson & Johnson Vice President and Chief Quality Officer, Chair of ISPE's Drug Shortages Prevention Program (DSPP) task force, and honorary conference chairman opened the keynote session of the ISPE Annual Meeting on Sunday, 8 November. The trio announced a number of new developments within the organization, including a new strategic plan, purpose statement, and logo; the return of chapter and affiliate dues sharing; the new Tampa Training Institute, and the Drug Shortage Prevention and Assessment Tool.

Andrew Skibo, Executive Vice President and Head of Global Biologics Operations and Global Engineering for MedImmune/AstraZeneca, and Past Chair of the ISPE Board of Directors, was next at the podium.

"The state of the society—our careers—is directly wired to the state of the industry," he told his listeners. "We are entering a period of profound change. . . . Our strategic focus has to recognize the tectonic forces shaping our industry. We as a society and as members have to adapt and be prepared."

Worldwide pharmaceutical sales are expected to hit $1 trillion by 2020; that's 5% to 6% year-on-year growth, he said, a change that is being propelled by four drivers: New products, driven by large molecules and oncology drugs; biologics, which are expected to command 27% of the market in 2020; a shift from primary care to specialty care; and emerging markets, especially China.

In an industry that's changing so rapidly, ISPE provides value to members and companies by offering:

- Training in new technology and execution in challenging areas
- Access to regulators for knowledge of changing demands
- Networks, benchmarks, and best-in-class information

Keynote addresses

Kathy Wengel, Worldwide Vice President, Johnson & Johnson Supply Chain and the first of two keynote speakers, talked about quality as a competitive advantage in an era of change.

"There has never been a better time to be an engineer in our industry than right now," she told the audience, who applauded in agreement. "We hear about new technology or molecules every day."

The landscape is changing fast, she said, with accelerating challenges: pricing pressure, health care reform and regulation, and disruptive competitors. Decision makers are changing as well: While the company formerly sold to physicians, surgeons, and small pharmacies, they now target hospital C-suites and global firms like Walgreens.

"And as science shows us more than we knew before," she explained, "we have to adjust to regulations. We have to balance risk and benefit. We have to have seats at the regulatory table—we have to have a voice in the deliberations. We have to deliver innovation into a regulated world."

Innovation is especially needed in pharmaceutical production, she continued. "We're still making tablets the same way our dads did 50 years ago. We know we can do better—and we are." Wengel said that "leveraging and adapting technology from other industries" to pharmaceuticals and the life sciences is "the key to our future."

Most of all, she concluded, "Everything we do must be of high quality. It's about bringing all of that together. It's all about the patients, and the moms, and the babies, and the lives we can change."

John Cox, Executive Vice President of Pharmaceutical Operations and Technology for Biogen,[1] gave the final keynote address, speaking about Biogen's drive for success through innovation. The company's pipeline programs, he noted, are focused on specialty, neurodegenerative, and rare diseases with many different therapeutic modalities: monoclonal antibodies, small molecules, gene therapy, and drugs for orphan diseases.

Like the speakers before him, Cox said that the life sciences industry is undergoing a transformation that began with the development of molecular and cellular biology, and was expanded by the science of genomics. These two "revolutions" led to a third: the integration of life sciences at the molecular level with engineering, physical sciences, mathematics, and computational sciences.

In this new phase, Cox said, "We have tremendous potential to change lives," and that new treatments like PD1 molecules for oncology give life sciences the potential to change the world. "The future and promise of that is in the hands of people in this room," he said. "We can make that happen."

But researching ways to slow or reverse neurodegenerative and rare diseases requires an understanding of biology we have not had in the past. Those who work on the engineering side of this business must realize that there will be challenges to make these types of drugs. These challenges are not exclusive to Biogen.

Cox defined Biogen's strategy as "success through innovation":

- Develop a world-class biologics manufacturing network to deliver on future need.
- Increase productivity by modernizing existing technology and developing novel facility design
- Update existing drug substance, process, and equipment technology
- Implement advanced process control, with the goal of eliminating batch failures due to process variability

One piece of Biogen's approach is its planned 10-metric-ton high-throughput antibody production facility that the company plans to build in Solothurn, Switzerland. An industry first, the plant is expected to be 3 to 5 times more productive than existing facilities, with a modular design that provides flexibility for growth.










Cox ended urged his listeners to "care deeply; work fearlessly. If we follow these principles, we can change lives. It's in your hands, this third revolution. I hope you will make the most of it."

Drug shortage prevention and assessment tool

Fran Zipp, President of Lachmann Consultant Services, ISPE Board of Directors Member, and a member of the Drug Shortages Initiative steering committee, debuted ISPE's Drug Shortage Prevention and Assessment Tool[2] on day two.

"It's a privilege to work in this industry," she began. "We're not here making eyeglasses, we're making drugs. And if you're not focused on what you can do to mitigate and prevent shortages, maybe you should be making eyeglasses."

Drug shortages are an ongoing international issue and a critical concern for every pharmaceutical professional, she continued, presenting an FDA infographic that linked quality and manufacturing issues to 37% of all drug shortages.

"Quality and manufacturing are prime issues in shortages," she noted, "but even with great quality and manufacturing you can still have shortages. Contract manufacturing organizations, marketing authorization holders, and suppliers can create problems.

"You're only as good as your neighbor," she continued. "It's easy to say it's the business decision, it's the market, it's the hospital. Look in the mirror—it's you. If you have any part in the pharmaceutical industry, you have a part in preventing shortages."

"We take this very seriously," Zipp said. "ISPE provides education and guidance to enable manufacturing and compliance excellence throughout the product life cycle to prevent drug shortages. We've designed a tool so you can assess your state of basic compliance to prevent shortages. It's a self-assessment. It's not to dictate what you do—it's to give you ideas."

ISPE's Drug Shortages Prevention Initiative formed in 2012, she explained, and deployed an industry-wide survey in 2013. This became the basis for the "Drug Shortages Prevention Plan" (DSPP), published in 2014, which identified the six key dimensions of shortage prevention.

"But how do you make it real?" Zipp asked. "How do you operationalize it?" Answer: the assessment and prevention tool, built on the six dimensions of the DSPP.

"Our team took the best and the brightest from across the industry and put it in this document," Zipp said. Each section is very organized ("We're pharmaceutical nerds," she admitted, laughing), and the tool is interactive, allowing users to enter data on the tables. Regulator feedback was also incorporated.

Zipp encouraged the audience to download the tool, which is free to ISPE members and conference participants. "It puts theory into practice. We're convinced this tool will help industry to improve the robustness of product supply chain."

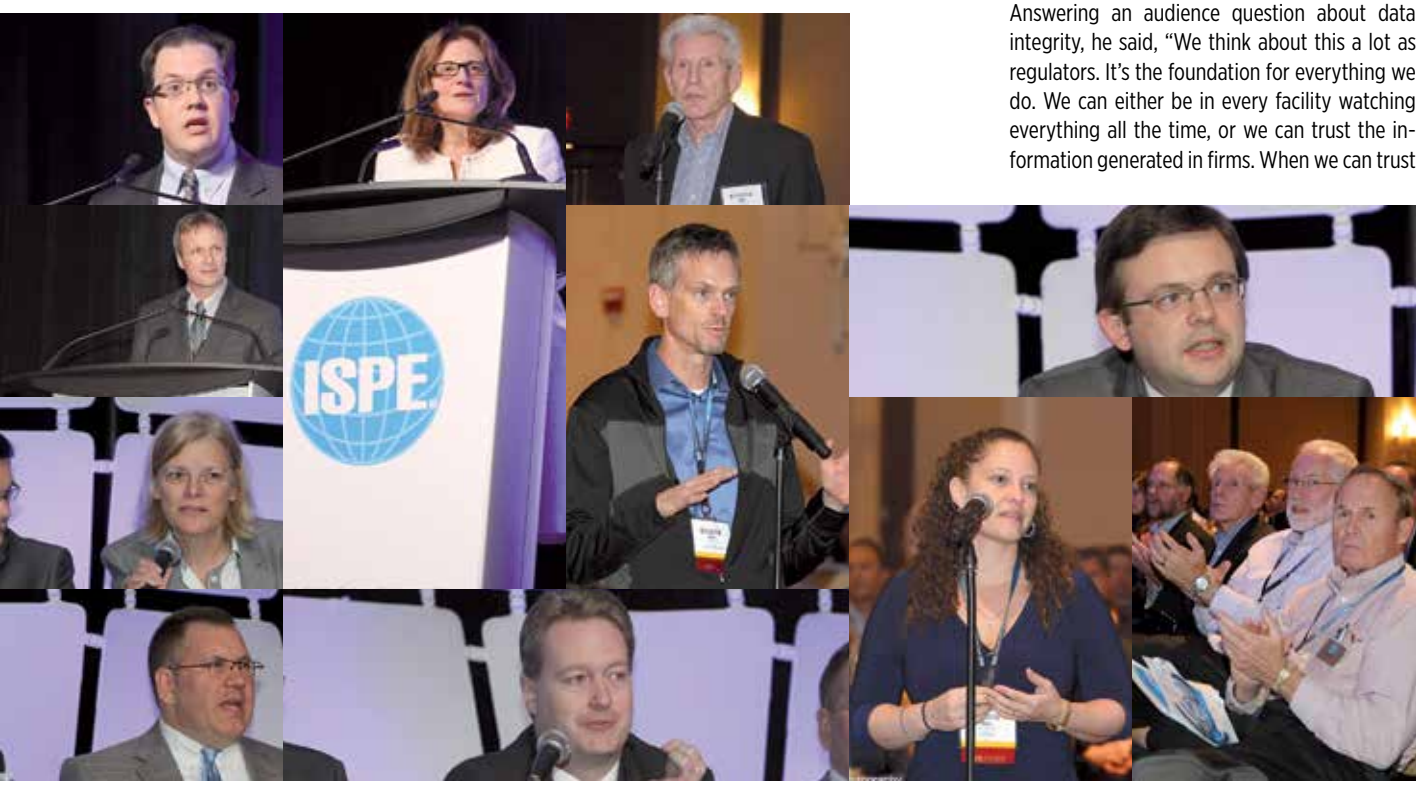
Regulatory town hall

Thomas Cosgrove, Director, Office of Manufacturing Quality, Office of Compliance (OC), FDA/CDER, began by noting that while "people come to these gatherings to hear from regulators, it's just as important for us to hear from industry in a collegial atmosphere."

"This is an amazing time to be a regulator," he said. Regulators have to learn how to deal with, lasso, and promote innovation, but "how do we innovate and keep up with the increasing pace of change?" he asked. "How can we best promote patient health and safety in the context of new health and regulatory abilities?

Cosgrove applauded China's steps to join the Pharmaceutical Inspection Co-Operation Scheme (PIC/S). "This is a huge development," he said, "especially given the amount of commerce going on in China."

Answering an audience question about data integrity, he said, "We think about this a lot as regulators. It's the foundation for everything we do. We can either be in every facility watching everything all the time, or we can trust the information generated in firms. When we can trust



the data, it allows a more flexible relationship between business and industry. But when we can't, regulators must intervene."

Cosgrove urged the audience to be sure that data they receive from contractors is reliable. "Every firm deals with contractors around the world," he said. "Each of you must be 100-percent confident that your contractors are above board with their data and information. Audit carefully and deeply to ferret out problems before we ever know about them."

He assured listeners that CDER's Office of Pharmaceutical Quality (OPQ) is making significant investments in understanding the drug manufacturing process. "Ask hard challenging questions," he said. "We're here to provide answers."

Sabine Haubenreisser, EMA/FDA, OC, Office of Global Regulatory Operations and Policy/Office of International Programs, talked about the EMA's scheme for priority medicines (PRIME), intended to optimize the development and accelerated assessment of medicines of major public health interest. PRIME is based on enhanced interaction and early dialogue with medicine developers. Haubenreisser said the new scheme, which seeks to provide enhanced regulatory support for drugs in development designed for unmet medical need will accelerate development and review. EMA expects to launch PRIME in the first quarter of 2016.

Mark Birse, Group Manager Inspectorate, Medicines and Healthcare Products Regulatory Agency (MHRA), UK, talked about the launch of the PIC/S Inspectors' Academy (PIA), a web-based educational center and accredited qualification system designed to help harmonize and standardize good manufacturing practice (GMP) training at an international level. PIA will deliver general or advanced training and also serve as a platform for discussion and sharing among regulators. The academy became operational in the third quarter of 2015.

Birse also discussed the International Coalition of Medicines Regulatory Authorities (ICMRA), a new global collaboration that brings together senior regulatory leaders to provide coordinated strategic leadership to address global regulatory challenges.

Over time, ICMRA will enable a global architecture to support enhanced communication, information-sharing, and crisis response. The coalition will also focus on strengthening regulatory systems and capacity, increasing both awareness of and appreciation for the importance of strong regulatory systems and functions within national, regional, and global contexts.

David Churchward, Expert Good Manufacturing and Distribution Practice Inspector, MHRA, talked about need to extend the compliance management process across the European Union, noting that early intervention in response to poor compliance trends is an important enabler of compliance. Educational components like symposia, conferences, and articles on training are also important.

"Shortages are a key issue for us," he said. "We are also looking at intrinsic risk separate from compliance risk. For these sites we may want additional oversight."

Data integrity is another key topic for the UK, especially in support of national and international guidance to industry.

Churchward also discussed the MHRA's promising innovative medicine (PIM) designation, which can be granted when early clinical data indicates that a product may be a candidate for the early access to medicines scheme (EAMS), which gives patients with life-threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorization when there is a clear unmet medical need. The PIM designation will be issued after an MHRA scientific meeting and could be given several years before a product is licensed.

In addition, Churchward cited MHRA's support for regional strengthening activities, saying that the United Kingdom has signed a memorandum of understanding with India to facilitate info sharing between the two countries.

David Doleski, Acting Deputy Director, FDA/CDER/OPQ, Office of Process and Facilities (OPF), explained that OPQ, a new office within CDER, was created to elevate the role of quality. The office has specialized divisions that assess different products. It's responsible for assessing manufacturing process and facilities as well as microbiology functions.

OPF members go to previous inspection sites, look through inspection reports, perform risk assessments, and weigh them against a product. The office also evaluates the need for future preapproval inspections related to that product. "We combine review and inspection functions. We've done this for biologics, and now we're carrying it into small molecules as well."

The nature of inspections will change with the agency's new inspection protocol (NIP), Doleski said. "We don't have a depth of experience in these innovative technologies, so we do preapproval reviews in an attempt to understand it better. We'll provide Informal feedback of what the agency's expectations are. We want to have discussions about the manufacturing process and facility. For breakthrough therapies, we want to meet with companies early in the process to foster communication."

OPF encourages innovative technology in facilities. "We're willing to meet with companies that embrace innovative technologies," he said. "We'll give you the best feedback possible and do preapproval reviews at the facility. When firms go above and beyond, we want to acknowledge and capture that."

Masatohsi Mirsue, Director, GMP Inspections, PMDA, Japan, discussed a Japanese government initiative to boost generic drug market share to at least 60% by the end of fiscal 2017. Others have suggested raising the target to 80%.

Because many of the active pharmaceutical ingredients (APIs) in generic drugs come from Asian countries, the PDMA's challenge at PDMA is how to pursue inspections in Asian countries. To this end, PDMA wants to increase its number of inspectors—currently about 25—by 50%.

"Focusing on the Asian market and inspections," he said, "we would like to use cooperation with countries that are PIC/S members and to use mutual reliance agreements as much as possible."

Japan will host joint symposium with China, Taiwan, Thailand, and Indonesia to introduce GMP inspections performed by PMDA.

After hours

Networking and social events rounded out the four-day gathering. The organization's annual 5K charity run/walk raised money for the Center for Information and Study on Clinical Research Participation. ISPE also announced a number of honors and awards at the membership and awards breakfast, including the 2015 Facility of the Year Overall Award Winner, AstraZeneca China. The meeting ended with a party at Philadelphia's famous Reading Terminal Market, followed by exclusive facility tours on the last day of the conference.

"ISPE hosts our Annual Meeting with one goal in mind: to provide pharmaceutical manufacturing professionals with world-class education in order to take our evolving industry to the next level," said ISPE President and CEO John Bournas. "Thanks to our staff, planning committee, board, members, speakers, exhibitors, and attendees, we accomplished our goal—and we achieved new paradigms for manufacturing excellence." ■

References

1. See ISPE's profile of John Cox and Biogen, "Future Factories for Manufacturing Flexibility," in the October 2015 issue of *Pharmaceutical Engineering*.
2. See Fran Zipp's article "Six Degrees of Shortage Prevention: ISPE Debuts New Gap Analysis Tool," in the October 2015 issue of *Pharmaceutical Engineering*.

By the numbers: ISPE 2015 Annual Meeting	
5	Subject tracks
28	Regulators
34	Speakers
72	Education sessions
200	Exhibitors
1,934	Attendees

Photos: © 2015 Robb Cohen Photography

ISPE 2015 International Honor Award Recipients

ISPE's International Honor Awards were presented at the annual meeting member breakfast on Tuesday, 10 November. These awards honor ISPE groups and members who have demonstrated remarkable dedication and service to our organization. Thank you to the ISPE International Honor Awards Committee for reviewing the nominations and administering the awards process.

ISPE congratulates the 2015 awardees

Award	Recipient
Joseph X. Phillips Professional Achievement Award	George P. Millili, PhD
Max Seales Yonker Member of the Year Award	Alan S. Levy
Company of the Year	Novartis
Committee of the Year	Quality Metrics Core Team
Chair	Mairead M. Goetz
Former Chair	Diane O. Hagerty
Team Members	Nuala F. Calnan, PhD Laura Cannon Michael G. Davidson Betsy P. Fritschel Steve Greer Steven Lynn Lorraine E. McClain Matthew Pearson Christopher Potter, PhD Peggy Speight Lorraine K. Thompson Paul J. Weninger Bryan Winship
Affiliate and Chapter Excellence Award	ISPE Italy Affiliate ISPE Delaware Valley Chapter ISPE New Jersey Chapter
Roger F. Sherwood Article of the Year "Risk Analysis and Annual Training Program Definition," *Pharmaceutical Engineering* 35, no. 1 (2015)	Luca Falce
Undergraduate Student Poster of the Year	Neeraja Ravi
Graduate Student Poster of the Year	Sydney Shaw

Joseph X. Phillips Professional Achievement Award: George P. Millili, PhD

Company of the Year: Novartis

Committee of the Year: Quality Metrics Core Team

Affiliate and Chapter Excellence – ISPE Italy Affiliate

Affiliate and Chapter Excellence – ISPE Delaware Valley Chapter

Affiliate and Chapter Excellence – ISPE New Jersey Chapter

Graduate Student Poster of the Year – Sydney Shaw

Photos: © 2015 Robb Cohen Photography

Patient perceptions of IMPs

Eight members of the EU ISPE Investigational Products (IP) Community of Practice (CoP) served as the task team partnered with UK National Health Service (NHS) and European Patients Academy on Therapeutic Innovation (EUPATI) to undertake a study of patient perceptions of investigational medicinal products (IMPs) in European Union (EU). In a similar time frame five members of the China ISPE Investigational Products (IP) Community of Practice (CoP), with support from pharmaceutical company sponsors and an execution team, completed a similar study in China. The survey had been translated into the local language using most of the questions from the EU survey and the survey was made available to patients in paper and mobile versions, or were conducted in person at clinical sites.

These further studies were prompted by results from the "ISPE Project Concerning Patient Experiences with Clinical Trial Materials" conducted by the ISPE Patient Survey Project Team. The study surveyed 1,425 clinical trial patients predominately in the United States to learn about the suitability of clinical materials, obtain patients' opinions about their experiences, and gather suggestions for improvements. While results indicated that while patients were generally satisfied with the IMP medicine kits they received, they also revealed a number of areas for consideration in improving medicine kits.

After the original US survey was published in 2013, the IP team was curious: Did these study results about IMP design, packaging, and labeling apply only in the United States, or were they consistent with other geographies? The question is significant, because clinical trials are often run in multiple countries and/or regions; pharmaceutical companies must be sure that their IMP kits meet the needs of patients wherever they are in the world

Background

The IP teams decided to expand the study into other parts of the world, including China, a region that had never provided feedback on IMP before. If these new surveys revealed major geographic differences, it could affect how IMP kits are designed, labeled, and packaged.

To establish access to patient groups in the EU, the CoP joined forces with the NHS and EUPATI, who were also interested in collecting data from patients about the clinical trial process. The survey was conducted electronically and only in English.

Key questions in both studies centered on whether IMP kit design, packaging, and labeling influenced patient compliance and retention. Compliance and retention are important cost drivers in clinical trials, because noncompliance can lead to patient failure and un-evaluable data. Even a small percentage of failures can

Pictograms, eLabels, and digital technology in clinical trials

An education session presented by members of the eLabeling and pictogram task teams at the 2015 ISPE annual meeting explored industry's search for alternative ways to label investigational medicinal products (IMPs). Pharmaceutical and life sciences companies are also seeking opportunities to use digital technology to enhance clinical site operation, investigator and patient access to information, and patient compliance.

The session also presented TransCelerate's efforts to develop digitally supported clinical supply chains, and Pfizer's real world experiences with eLabeling.

Pictograms and eLabels

Sascha Sonnenberg, Vice President, Commercial Operations for Marken, Ltd., began the session with a discussion about the use of pictograms and eLabels in clinical supplies.

Pictograms are recognizable symbols that provide instruction or convey information without words. Some pictograms used on IMPT labels have already been established, such as those for temperature and storage conditions, for example. Pictograms take up less space on IMP labels; this requires less information to be conveyed in writing and frees more label space for text, permitting the use of larger, easier-to-read font sizes.

eLabels provide information required to be on the outer label of a medication kit and additional info about this medication kit via a mobile device that is operable by the subject to whom the medication kit is dispensed. eLabels can allow clinical supply chain coordinators and/or investigators to move the medication kit decoupling point (KDP)—the point in the supply chain where a kit becomes country- or even patient-specific—closer to the patient.

Both pictograms and eLabels can help support patient compliance, improve the way labels are formatted, and expand options for providing clear information—such as how to take medications. ELabels, in particular, can help deliver information on protocolled dose changes, and can also be used to remind/alert the patient to take his/her medication. Both can help reduce the risk for errors on a clinical site, make labels easier to read, and reduce country-specific review times.

As with any new technology, eLabels present legal, regulatory, and technical challenges. Who owns and is allowed to access electronic data?

be detrimental, since each lost patient has been estimated to cost the study sponsor as much as $47,000 per patient, even if they're not replaced.

Initial analysis

Both studies went live in August 2015 and the combined initial results were presented at the ISPE annual meeting in Philadelphia, Pennsylvania on 9 November. Data analysis for the EU the interim was conducted by the Robertson Centre for Biostatistics in Glasgow on results for 405 patients, 78 of whom were given medication in a clinical trial. The China response was phenomenal—evaluable data from over 1,900 patients.

The IP team initially expected that patients would complain most about the size, weight, and ease of transporting the kit, but they didn't. This mirrors results from the US study. Overall our industry can take some satisfaction in that the results demonstrated that 87% of patients found their medication easy to use and over 75% of the patients in all the surveys managed the transportation and storage of the medication kits provides by the hospital.

All of the surveys—the original US survey and the recent survey EU and China—indicated that patients value clear instruction and explanation from the medical staff on how to take, store, use, and transport the medication. While still significant, kit design appears to be less important in ensuring dosing adherence.

In the US study, for example, 60% of patients said that the kit design helped them take the medication on schedule. In the EU survey, 40% found kit design important. The Chinese population split evenly: 46% said the design was helpful, and 46% said it didn't.

When asked "What would help you take the medication on schedule?" 81% of EU patients indicated a preference for clear dosing information on the label; 77% of Chinese patients felt that while dosing information on the label was important they valued more highly "instructions from my physician/nurse/pharmacist at every visit."

As had been seen in the original US study, there was a significant percentage of patients that did not return unused medication to the clinical sites, with around 19% of patients keeping the medication for future use; a result that the industry needs to mitigate against globally. It was also interesting to note that as patients are often having to travel longer distances to participate in studies and thus some clinical trials are implementing more localized care, over 70% of patients in both the EU and China reported that having IMP delivered direct to their home would be helpful.

Conclusions

These interim results have provided some interesting observations suggesting that while IMP kit design is important to ensuring compliance, personal explanations and clear label dosing information could be more significant. The full study results will provide some clarity on how various design changes for IMP kits, label dosing information, and patient instruction can be incorporated into future studies to improve patient compliance and reduce the cost of patient failure for pharmaceutical companies and other organizations that run clinical trials.

Full results of the EU survey will be presented at the March 2016 ISPE European meeting in Frankfurt, Germany, with the Chinese data being presented at the ISPE China annual meeting in April 2016. Additionally, detailed results from both data sets will be published in *Pharmaceutical Engineering* in the first half of 2016. ■

By Esther Sadler-Williams

The IP task team welcomes your questions and feedback on this study. Please contact Lynn Wang (Lynn.L.Wang@merck.com) and Esther Sadler-Williams (Esther.SadlerWilliams@Catalent.com).

Is the system compatible with a variety of platforms? How will the data be transferred and where will it be stored?

eLabels: Just the beginning

Many of these questions are being addressed by TransCelerate, a nonprofit entity created to drive industry collaboration in research and development (R&D) across the biopharmaceutical research and development community. The organization is dedicated to identifying common issues and modeling solutions that will drive efficiencies in the R&D process.

The organization was formed in 2012, with five projects. Three years later, their to-do list has grown to 14 projects and 2 "ideation efforts." TransCelerate currently works with over 40 people in 12 companies.

The Food and Drug Administration is interested in eLabels' potential for the industry, said Jodi Smith-Gick, Senior Advisor Product Delivery and Supply, Eli Lilly and Company. ELabels and other interactive response technologies not only have the potential to link investigators with regulators and get feedback much earlier, they may also help speed product to patients more cost effectively.

TransCelerate's eLabels workstream is a long-term initiative that will help the industry develop digitally supported patient-centric clinical supply chains and a collaborative approach to health authority engagement.

Real world questions

Michael Moorman, Executive Director, Global Clinical Supply Systems and Support at Pfizer, says it's not a question of if there will be a digital transformation, but when it will occur.

Pfizer's long-range vision is global digital clinical supply chain, part of a range of clinical strategies to expand insights on enhanced site and patient experiences. Like all innovations, however, it prompts a number of questions: How can we redesign our medications so patients can best use them? How do we eliminate errors, digitize our current processes, and enable future capabilities?

While these questions will be answered as technology continues its rapid development, others will certainly emerge to take their place. ■

Find these presentations at www.ispe.org/2015-annual-meeting/presentations:

- "Concept Paper: eLabels/JIT Labeling, English Only or Pictograms as a Universal Language on Primary Packaging," by Sascha Sonnenberg
- "eLabeling: It Is Just the Beginning," by Jodi Smith-Gick
- "Real-World Experiences with eLabeling" by Richard Moorman

2016 Aseptic Processing Technology Conference

A taste of things to come

With the 2016 Aseptic Processing Technology Conference fast approaching, we thought it the right time to give you a taste of what you might expect in Crystal City, February 29-March 1. We've selected five questions from the 2015 conference's Q&A session with the FDA to whet your appetite.

The four 2015 panel members responding to questions from conference attendees were:

- Richard Friedman, Associate Director of Risk Science, Intelligence and Prioritization, FDA/OMPQ
- Robert Sausville, Director, Division of Case Management, FDA/CBER/OMPT/OCBQ
- David Doleski, Director, Manufacturing and Product Quality, FDA/CDER/OC/DGMPA
- Destry Sillivan, (current) Owner, TCubed Regulatory Consultants, LLC – at the time of the 2015 Aseptic conference he was FDA/CDER/OCBQ/DMPQ/MRBII

Q1 This question is about UAF patterns and velocities at work surface. How should we establish acceptable UAF patterns and velocities, verify and validate them, at work surface of Grade A?

A1 **Robert Sausville:** You should use smoke studies to show unidirectional air flow, there is guidance to provide direction.

Destry Sillivan: First you have to evaluate what your system is — there are so many different set-ups out there.

Richard Friedman: You should correlate air velocity with the smoke studies to fit the purpose of avoiding contamination via airflow.

David Doleski: You should map your air flow throughout the equipment and then set your requirements accordingly.

Q2 In the case of isolators and RABS, when we can decontaminate a high level, is the high-pressure steam sterilization of the rubber stopper bowl necessary?

A2 **Destry Sillivan:** First of all, I want to put out something that I have heard during the conference that is troubling me. I hear people saying that they have a sterile isolator, which would be a 12-log reduction, while most of you only have decontamination at 6 log. Anything that you can sterilize should be sterilized, therefore also the vibrator bowl.

Richard Friedman: Just to confirm this, if you can steam sterilize it, you have to. It is in the guide. If you only do a surface decontamination, you have to put together a good justification to the agency, yet it can be done.

Q3 Qualification for HEPA filters is supposed to be required and performed twice a year. Actually, however, the testing work load is usually highly challenged, especially in a system with membrane diffusers (CG screens) below the HEPA filters. So, if a RABS or an isolator equips such membranes in order to maintain uniform air flow below the HEPA filter, we think it might be acceptable to perform the scan leak testing below the screens without disassembling the membranes. If acceptable, can you elaborate what is the necessary condition to justify the test?

A3 **Robert Sausville:** The way we read it, there seems to be more work involved to remove the diffusors and therefore you would like to avoid that. Yet the diffusors in place are what you really need to test because this is what the product sees.

Q4 Numerous sites produce small batch clinical trial materials using hand fills, forceps stoppers and seal placement in simple hoods. (Assume this is not a biotech product customized for individual patients.) Is this still an acceptable practice? If not, how are you handling this type of filling and will you be increasing the scrutiny and enforcement in the future?

A4 **Richard Friedman:** Do you want us to increase the scrutiny and enforcement? We had to get involved with sites that did get warning letters where they were doing clinical supplies, even with hand fills! You should find more reliable sources also in clinical fills, put extra attention here when outsourcing. In the end, the product is given to a patient! We need to protect those patients.

Robert Sausville: This seems to be related to the small batch sizes, where you also have small media fills that don't tell you much.

Richard Friedman: We were tipped off by the CMC reviewers, and we went in to investigate the clinical site, and it was ugly.

Q5 Per FDA guidance on aseptic processing, processes conducted in an isolator can be simulated with a lower number of units as a proportion of the overall operation. What does the FDA consider appropriate for a "proportion," and/or how should we approach the assessment of an appropriate proportion?

A5 **Richard Friedman:** It is risk based, if the isolator is properly designed and operated, it provides additional safety for the operation. Your media fill program should start at 5,000 to 10,000 units, and it should adequately reflect your operation with all interventions, so this quantity of units might not be enough. Whatever you do in routine operation, you should be doing a simulation in the media fill and be sure that there is no risk to the product. ■

New releases

ISPE is pleased to announce that the *Sustainability Handbook* is now published (December 2015). Another new guidance document, the *Operations Management Good Practice Guide* is scheduled for release shortly (Q1 2016).

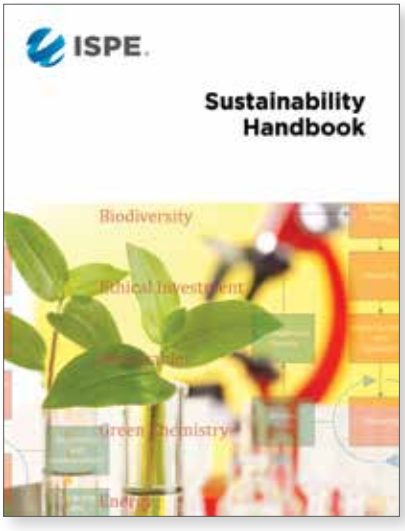
Sustainability handbook

ISPE's first handbook is written to provide information at the front end of projects that will be useful to the project team in understanding sustainability criteria, with examples where considered useful. It is based on the premise that there is a viable path to achieving sustainability that corresponds to all of the precepts of the life sciences industry. This is an especially important ethical consideration for the health care industry, which has a focus centered on maintaining or improving the health of the patient.

Objectives

Key objectives of this guide are to:

- Provide a reference point for sustainability in the life sciences industry for project teams



- Provide a global pharmaceutical sustainability baseline for the life sciences industry through promotion of the reduction of consumption of finite resources and consideration of the effects of environmental shifts.
- Respect the industry's advanced engineering traditions by providing an informative and easy-to-use document.
- Directions of research for project teams are given in each of the engineering areas from product development through to facility development.
- Provide a route map to understanding the legislative conditions worldwide that either exist at the time of writing or are understood to be in progress.

The *ISPE Sustainability Handbook,* taken with suitably amended Baseline and Good Practice Guides will help in aiming to provide that opportunity for a sea change toward ensuring an ethically acceptable yet financially viable and secure pharmaceutical industry.
Visit http://www.ispe.org/ispe-handbooks/sustainability to order your copy today!

Operations management

The *Operations Management Good Practice Guide* establishes a framework for all of the major topics in operations management. It's an impressive body of knowledge representing tremendous experience from around the world and throughout the industry; it's intended to promote excellence and integrate the complex body of knowledge within pharmaceutical operations enterprises and systems.

This Good Practice Guide is the first ISPE document that pulls together topics like facility design, validation, regulatory and quality assurance, goods import/export in a in a ready-to-use "toolbox." This multidisciplinary document provides a 360-degree review of everything involved in the manufacture and supply of life sciences products in pharmaceuticals, biotechnology, and medical devices. It also defines a common language with which to discuss operations management, and introduces lean concepts—a pharmaceutical industry first.

The authors call Operations Management a toolbox because it's designed as a reference to help identify appropriate solutions for specific problems, whether readers are addressing issues in manufacturing plants or need guidance in developing a manufacturing strategy or establishing an operational excellence program. Where it doesn't provide an answer, it will help users frame the questions necessary to move their projects forward.

This GPG is designed for pharmaceutical professionals who:

- Are involved in the manufacture and supply of products, irrespective of discipline
- Are in operations management, regardless of seniority,
- Work anywhere in the industry, from management to the shop floor
- Aspire to operational excellence

Objectives

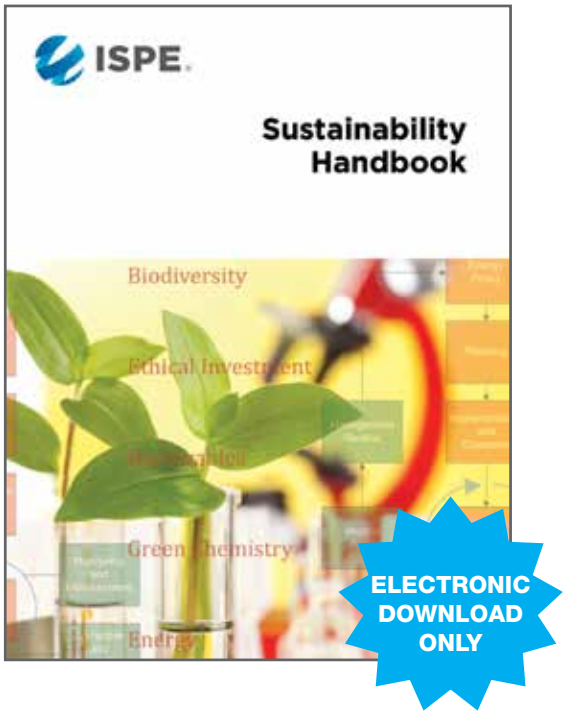
The guide addresses all operations along the supply chain from the selection of raw materials through the distribution of drug products to customers, and ultimately patients. It provides many tools for measurement that will help readers become more effective and efficient. Finally, it provides up-to-date information that supports good practices across the board.

Key concepts include:

- Supply chain strategy and management
- Manufacturing operations strategy and management
- Key performance indicators
- Continuous improvement and innovation
- Lean simulation for continuous improvement, capacity analysis, planning, and scheduling
- Industry benchmarking
- Lean Six Sigma
- Facility/site master planning ■

Our Newest Release Now Available

ISPE Sustainability Handbook



Individual PDF Download Item#:
HBSUSTDLUS

Pricing:

Member	$145 / €140
New Member*	$429/ €378
Nonmember	$455/ €400

This handbook—ISPE's first—is written to provide information at the front end of projects that will be useful to the project team in understanding sustainability criteria, with examples where considered useful. It is based on the premise that there is a viable path to achieving sustainability that corresponds to all of the precepts of the life sciences industry. This is an especially important ethical consideration for the healthcare industry, which has a focus centered onmaintaining or improving the health of the patient.

Key objectives of this guide are to:

- Provide a reference point for sustainability in the life sciences industry for project teams.
- Serve as a global pharmaceutical sustainability baseline for the life sciences industry through promotion of the reduction of consumption of finite resources and consideration of the effects of environmental shifts.
- Respect the industry's advanced engineering traditions by providing an informative and easy-to-use document.
- Directions of research for project teams are given in each of the engineering areas from product development through to facility development.
- Supply a route map to understanding the legislative conditions worldwide that either exist at the time of writing or are understood to be in progress.

Meet your new 2015-2016 executive

We announced ISPE's 2015–2016 ISPE Board of Directors in the last issue of Pharmaceutical Engineering. In this issue and the next, we will ask the newly elected officers to provide some insight their new roles as well as their plans for the year ahead.

This issue, we get insight from the Chair, Joseph Famulare, and Vice Chair, Michael Arnold.

2015-2016 officers

Chair
Joseph Famulare, Vice President, Global Quality Compliance and External Collaboration at Genentech/Roche, Pharma Technical Operations

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

Treasurer
Timothy P. Howard, CPIP, PE, Vice President of Global Operations, Commissioning Agents, Inc.

Secretary
James Breen, Jr, PE, Vice President, Worldwide Engineering and Technical Operations, Johnson & Johnson

Joseph Famulare, Chair

1. How do you see your new role on the Board?

As Chair, I see my new role as one that primarily meets the needs of the members. Having been honored by the membership who selected me for this role, I see this as a daunting task given the wide breadth, expertise, experience and diversity of our global membership.

2. What are the top 3 items on your list of things to do in 2016?

My top 3 are to set the priorities for this year, set the strategy for the coming years, continue to build ISPE's business acumen and make the society sustainable for many years to come.

3. What role will you play in the execution of ISPE's strategic plan for the next 3 years?

Execution will be the key area of strategic focus. I will drive on those topics that are relevant to the direction of pharmaceutical manufacturing, such as the continued globalization of the supply chain, maintaining a supply of critical drugs and the vital need to find a path to regulatory convergence.

The industry is quickly catching up on the mounting pipeline of drugs in the biotech space, and drugs in the small molecule realm that are produced in smaller volumes and more directed to the disease treatment. Many of these also have may specialized containment requirements.

In addition, drug delivery systems are changing; and while we come to grips with combination products we are just at the beginning of saying technology will change how patients receive their medicines and how medicines are delivered. The demand for innovation in manufacturing and facilities will continue and we must stay ahead of the curve as we serve patients. We simply can not fall behind.

4. What do you believe is the most difficult part of your role?

We have so much talent, experience and ability to drive education, training, important information dissemination and collaboration that we will need to prioritize what is needed by the membership, the industry they work for and the patients they serve. Delivering on a priority basis and being agile enough to respond to needs as they arise will be most challenging for me.

Fortunately, ISPE has fantastic volunteers who can deliver on these needs and will help us deliver in our training, education events, conferences and publications content, strategy and value that you can take back to your workplace and advance your career. Only through collaboration can we really advance the science of manufacturing, quality, engineering and regulation for pharmaceuticals.

5. What can ISPE members expect from you?

They can expect me to drive the strategic plan as best as I can with the combined effort and work of all that makes ISPE of value to its members, from both industry and regulatory health authorities alike. I will make sure the strategic plan is evident in all our events and publications in the coming year and will be foundational in the future. I will be sure that I communicate with our chapters, affiliates, COPs, knowledge networks, and all of the committees relevant to ISPE on our direction and progress and ask that you let myself know those areas we can continue to improve.

Michael Arnold, Vice chair

1. How do you see your new role on the Board?

I see my role as co-leading and aligning the ISPE organization so that it generates solutions that address industry and member needs and expectations.

2. What are the top 3 items on your list of things to do in 2016?

My 3 priorities are to: (1) Build and sustain a strong financial base for ISPE; (2) drive member value; and (3) develop an effective project decision-making process coupled with appropriate ISPE support staff to ensure project success.

3. What role will you play in the execution of ISPE's strategic plan for the next 3 years?

As Vice Chair, I will work closely with our Chair, Executive Committee and Board of Directors to ensure the strategy continues to be directionally correct and appropriately supported to ensure successful outcomes. And in my other new role, as Chair of the New Content Advisory Committee (NCAG), I will work with other leaders to provide guidance and feedback on projects that will be "fit for purpose" as they relate to the strategic plan. Does it add value to our members, to industry and/or the support of our financial strategy?

4. What do you believe is the most difficult part of your role?

The most difficult part of my role is making decisions on what subset of projects, from a set of highly desired projects, would most optimally serve our members and the industry as a whole. While most all of the projects that come to ISPE are very interesting and have relevance to everyone to some degree, we can't be all things to everyone and will need to make tough decisions. I believe if we focus on our member needs and what is best for the patients we serve, we will make the correct decisions most of the time.

5. What can ISPE members expect from you?

Members can expect commitment, communication and leadership from me:

- Commitment to the success of ISPE and its delivery of member value;
- Ensuring members are aware of what projects we are working on at ISPE and how they might either get involved or benefit from them; and
- Leadership. I am in the role of Vice Chair because of our members and I want to ensure that while business decisions may be difficult at times, they will be made with their best interests in mind. ■

ISPE Canada Affiliate: Adapting to Meet the Needs of the Canadian Market

A season of change has arrived in Canada. As the cold winter months settle in and blanket the country's vast landscapes in snow, the ISPE Canada Affiliate looks ahead to 2016 and beyond with a new name, a new structure, and a new president at the helm.

The former ISPE Central Canada Chapter recently became ISPE Canada Affiliate. "We completed the change in 2015," says Richard Fecteau, President of the ISPE Canada Affiliate. "This provides more flexibility with our bylaws, allowing us to make changes that are specific to the needs of our Canadian members."

Fecteau, an industrial engineer with 25+ years in the pharmaceutical industry, was appointed President of the ISPE Canada Affiliate in September 2015. Born and raised in Montréal, Québec, he studied industrial engineering at l'École Polytechnique de Montréal.

"I came to pharmaceuticals a bit by chance," he says. "I had a mandate as a project manager at an intravenous facility, and I fell in love with the industry. It was nice to work in an environment where people care about what they do, because someone will take our product and feel better. At the end of the day, we're doing something that helps make the world better. I think everyone who works in this industry has this as a driver somewhere in their chain of values."

He is currently Vice President, Business Development, at SNC-Lavalin's Industrial division, which specializes in pharmaceutical, biotechnology, and agrifood projects. He has been a member of ISPE for more than 20 years and in recent years has become more involved in local leadership. "ISPE is relevant to my job; it makes my job easier," he says. "The guidance documents are very useful, and the training has been especially helpful. When I was in Operations, I would send my team for training. Plus, at the local level, industry networking is very valuable."

"ISPE is relevant to my job; it makes my job easier."

"The guidance documents are very useful, and the training has been especially helpful."

"Industry networking is very valuable."

Two main hubs

Based on landmass, Canada is the largest country in the Americas and the second-largest country on the planet. Its pharmaceutical industry is the ninth largest in the world, according to Industry Canada, and features many of the global industry's biggest names. Activities in the pharmaceutical sector are mainly concentrated in the country's two largest cities: Montréal, Québec, and Toronto, Ontario; with smaller hubs in Québec City; Winnipeg, Manitoba; and Vancouver, British Columbia.

As with many national Affiliates, the distance between activity hubs creates somewhat of a challenge for the Canada Affiliate. According to Fecteau, it is becoming increasingly difficult to attract members to attend events, especially given the current economic environment where travel and training budgets are limited.

"Getting a Québec City engineer to come to Toronto is nearly impossible," he says. "That's why we are currently assessing more effective ways to reach our audience with educational programs, and borrowing ideas from other chapters like Boston by starting to webcast our seminars." The webcasting solution addresses part of the problem; however, Fecteau acknowledges that it leaves out one very important aspect of ISPE events for remote attendees: networking. "We really encourage networking because people get a lot of benefit from it," he says. "If you are a project engineer at Company A, these events provide an opportunity to share your tips and experience with people from Company B. And when you network with other people in the industry, you know who to speak to if you run into trouble—and not necessarily a vendor."

A changing industry

Fecteau has noted a shift away from manufacturing in the Canadian pharmaceutical market—another challenge shared with other Chapters and Affiliates. "In Canada, the industry is really focused on R&D," he says. "There are fewer large investments in manufacturing, although we do hear about the Green Cross, Sanofi Canada, and Glaxo[SmithKline] projects."

In addition, says Fecteau, there are fewer pharmaceutical companies with large numbers of engineers onboard. "If you look at the number of companies in Ontario and Québec, 90 percent of them have 10 employees or fewer, and they are R&D focused. That's not a prime target for our membership, so that's one of the challenges for us."

Overall, says Fecteau, while the trend in the pharma industry is to centralize manufacturing, there are still a number of companies that have manufacturing facilities in Canada, with many employees involved in the manufacturing process. It is these employees that will benefit from being a member of ISPE Canada Affiliate which we need to do a better job of attracting.

The next generation

With a current membership of approximately 400, the ISPE Canada Affiliate isn't considered either small or large. And while Fecteau would love to see those numbers grow, he's more concerned about the average age of his current membership, which, he says jokingly, is much closer to his own age than that of a graduate. "We see a lot of the same people who have been involved in the ISPE over the years; we need to rejuvenate our membership," he says. "We need to find new ways to reach out to the young professionals so that we can make them aware of all the benefits of being part of ISPE."

To help attract this next generation of members, the Affiliate has recruited two young professionals—Entela Brahimi from SAGE Engineering in Toronto and Maša Ivanković from SNC-Lavalin in Montréal. Fecteau is pleased. "They're two young chemical engineers involved in the industry—one in Toronto and one in Montréal —and we hope that through them, we'll be able to rejuvenate the membership and attract more young professionals," he says.

In addition, Fecteau says that the recent change to Affiliate status will provide more tools to attract new members. "It gives us more flexibility on how we price and invite the young professionals," he says. "We can more easily decide that a particular event is a lower price for the young professionals and the regular price for members."

Growth opportunities

Despite the challenges, Fecteau and his Canada Affiliate colleagues see an interesting trend in the industry. "More and more, this industry is open to cross-pollination," he says. "Fifteen to 20 years ago, if you talked about technologies with a pharmaceutical engineer in a pharma facility, it had to be pharma specific, otherwise they would not even look at it. Nowadays the younger generation, who were born with technology, are more open to cross-pollination from other industries that are often more advanced, especially in the automation and control fields."

Fecteau and his Board are also looking at ways to further entrench ISPE in the Canadian market. "We want to get closer to the regulatory bodies in Canada," he says. "It is important for our organization to develop a relationship with Health Canada, so through the leadership of two executives on our board [Affiliate Vice President Dina Iezzi and Past President Vern Solomon], we initiated discussions in 2015 to better understand how we can work together. Like ISPE's relationship in the US with the FDA, we hope to collaborate on educational events and provide expertise on various issues affecting our industry to ensure we continue to produce reliable supply of quality medicine. We have a common goal, which is simple: Safeguard the drugs and health products to which not only Canadians have access, but people in general, as Canadian facilities manufacture drugs for other countries."

In terms of membership growth, Fecteau's high-level objective is to add one member per week in 2016 to finish the year at 450 members—a 10-percent growth rate. ISPE Canada Affiliate intends to hold events on the third Thursday of each month and, whenever possible, webcast the events for those who cannot attend. To encourage local attendance, Fecteau says they will continue to use flexible pricing strategies. "We started to offer corporate pricing for various activities," he says. "For example, if the price is $35 per attendee for a specific seminar, we offer a rate of $250 for 10 people or more from the same company, bearing in mind that a lot of people come to our activities, even if they're not members. This strategy will provide ISPE with greater exposure."

On the whole, Fecteau is optimistic about the Canadian pharmaceutical market. "I find the industry is in better shape than I thought it would be. I see the high end of the drug manufacturing being done here and the more traditional in emerging markets." ■

By Mike McGrath

Contacts

President:
Richard Fecteau, SNC-Lavalin

Vice President:
Dina Iezzi, Therapure Biopharma Inc.

Treasurer:
Marie-Christine Leblond, Pharmascience

Secretary:
John Rydall, BioAcuity Consulting

Past President:
Vernon Solomon, Environmental Systems Corporation

Case study:
From student to successful YP

Pharmaceutical Engineering is pleased to present this new column, written by Robert W. Landertinger, on all things YP.

The power of networking, knowledge sharing, and experience

I'm Robert W. Landertinger, a 29-year-old Technical Marketing Manager (or bioprocess engineer working in marketing) at Sartorius Stedim Biotech, a company that provides single-use technologies and engineering services for the pharmaceutical industry.

When I was studying to earn my bioprocess engineering degree, I became fascinated by the role biotechnology plays in producing lifesaving medicines. Today I have an active role in shaping the pharmaceutical industry. In retrospect, I have identified three challenges that I turned into opportunities:

1. Student knowledge
2. Find a job
3. Young professional success

Student knowledge

During daily life at university, the main focus lies on attending classes, getting good grades, and (of course) enjoying student life. As a student, the faculty helps you to navigate the knowledge blocks you need for your degree.

When trying to understand the pharmaceutical industry as whole, you would most likely Google "pharmaceutical industry" and get a Wikipedia description and a World Health Organization definition. You would learn about history, sales, and therapeutic areas, and would spend many more hours in research, trying to filter the information that is relevant for you.

It's a great challenge to decipher industry trends, gain process knowledge, understand the business of producing medicines, and identify all the different parties that are involved: engineering companies, service providers, technology suppliers, contract manufacturing organizations, and innovators. It's an even greater challenge to learn how the markets work in the United States, South America, Europe, and Asia.

This knowledge gap can easily be closed with industry internships during summer breaks or even during classes. Invited lectures from industry members are essential to help students gain their first insights. In some countries, it's possible to work in industry while still completing your studies.

This all sums up to building your own industry network of industry experts, which will help you through future challenges.

Find a job

Shortly before finishing your degree you should be asking yourself "What do I want to do in my first job in the industry?" Looking at job posting is always a good idea, but having a good understanding of the job description is even better. Talking with your professors who have industry connections is a must. Ask yourself: "Who are the companies looking for?" and "Does that job really fit my personality?"

Navigating through these questions can be hard at times, but working with an industry mentor you trust and who you feel comfortable talking to can be really valuable. But even without a mentor, the need remains to understand what the departments—such as process development, quality, and engineering—in different organizations are doing. Being a student member within a strong industry organization such as ISPE can also help you identify a job that fits your individual development needs, will allow you to thrive, be fulfilled, and have fun.

Young professional success

When you start working, the excitement of learning new topics is one of the main sources of motivation. Gaining knowledge, understanding, optimizing, and becoming an expert in your field is essential. Later on, leading your own projects in your organization gives you opportunities to thrive. So the velocity at which you can achieve success and minimize failures is of utmost importance.

At ISPE there are experts in all topics regarding our industry and opportunities for networking with other experts. Both help build and broaden your perspective of the industry. Further, a mentor outside of your own organization will provide you with new insights. Through ISPE Good Practices Guides and conferences you can obtain still more expert knowledge and build even larger networks with peers.

Choose a job you love, and you will never have to work a day in your life.

By taking responsibility at ISPE you gain valuable leadership experience, which you can put directly into practice in your own organization.

Bringing it all together

The power of networking, sharing knowledge, and experience is fundamental in transforming professional challenges into opportunities. This additional focus will yield results and create self-fulfilling success.

What was your experience? Which opportunities did you use to achieve your goals? Please share your thoughts, as I learn just as much from you as you do from me. ■

Robert W. Landertinger Forero is a bioprocess engineer and a marketer at Sartorius Stedim Biotech. He is Chair of the ISPE Young Professionals Committee and a core team member of the Drug Shortages Initiative team. Fluent in 5 languages (German, Portuguese, Spanish, French and English) Robert is an invited speaker in countries like Mexico, Ireland, China, the USA, and Germany. He has written for or been covered by *Pharmaceutical Engineering*, *BioPharma-Reporter*, and other publications.

ISPE Ireland's YP Committee: A Recipe for Success

Ireland YPs Committee founding members from left Ross Slevin, Caroline Rocks, Grainne Ryan, Ian O'Connor

Building a successful Young Professionals (YP) group is an objective and a major challenge for many ISPE Affiliates and Chapters. The four founding members of the ISPE Ireland Young Professionals Committee—Caroline Rocks, Grainne Ryan, Alan O'Connor and Ross Slevin—may have come up with a recipe for success; they have grown their own group from four to 14, having held five events in the past 18 months.

"The origin of the Young Professionals group goes back several years," says Gerard Coey, former chair of the ISPE Ireland Affiliate. "We tried to get Student Chapters established to varying levels of success. Then speaking to a number of companies and engineering firms in 2012, we received very strong feedback suggesting that we really needed to target young professionals and grow the amount of influence we were having with the younger members in the industry in Ireland."

And so the ISPE Ireland Affiliate Committee set a plan in place. In early 2012, Kyran Johnson, the ISPE Ireland Affiliate Chair at the time, published an article outlining the benefits of ISPE membership and challenged colleagues across the industry to encourage young professionals to broaden their experience and interact with the various elements of the pharmaceutical industry.

"We established a professional target to have an event in the first half of 2014 where our committee endorsed and gave full financial backing and support to the establishment of a Young Professionals group," says Coey. "That allowed us to host events to try to set up a committee as well as a Young Professionals group."

A groundbreaking event

Through its members Coey, Johnson, Donal Higgins, Conor O'Meara, and Emmet Cronin, the ISPE Ireland Affiliate Committee, planned an event in Dublin in early 2014 and reached out for support from Robert Landertinger, the European Chair of ISPE Young Professionals.

There, Landertinger gave a presentation on ISPE Young Professionals and spoke about the objective of developing a group in each country in Europe. He also encouraged the attendees to use the networking session after the event to learn more about it. His presentation piqued the interest of Rocks and Ryan, both of whom were also presenting at the event, as well as O'Connor. "When Robert spoke about the ISPE Young Professionals and gave its advantages, it struck a lot of chords within myself," says O'Connor, who at the time was in the midst of a change in his own career in pharmaceuticals. "I got back to him and said I'd be interested in helping any way I could." Landertinger collected the email addresses of the four future founding members of the ISPE Ireland YP Committee and put them in touch with one another.

"We're all from different parts of the country, and we actually arranged the next YP event by conference calls and emails," says Rocks, Chair of the ISPE Ireland YP Committee. "We received a lot of support from the main committee, who gave us advice on how to organize the event. And then just prior to the event, we had our first face-to-face committee meeting at the hotel across the road from the venue. It was there that we defined a committee structure that mirrored the main committee: a chair, a vice chair, a secretary and a treasurer—and we all took on a role and came up with a mission statement that we'd speak about at each event going forward."

> **"I have no particular skill or qualification to be part of the committee, just an interest and motivation to be part of it.**

"From that first event, it was quite evident that there was a lot of support for something like this," says Ryan, Vice Chair of the ISPE Ireland YP Committee. "We had 110 people, all like-minded young professionals trying to improve. That's a big driver of why we have been as successful thus far."

Recipe for success

Following the success of that first event, the newly formed committee has since gone on to hold four more equally popular events. From the beginning, the committee decided on a structure that fits the profile of the industry's young professionals.

Ireland YP mission statement

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

To begin with, each event is held at a different venue. For example, one event was held at a rooftop pavilion that towers over the city of Cork, while another was held at the Light House Cinema in Dublin. As Rocks explains, the committee feels it is important to "provide a refreshing change from hotels and conference rooms."

Second, each event features presentations on a technical topic important to the pharmaceutical industry in Ireland, and includes presentations from both a young professional and an industry role model/mentor speaking about their career and involvement in ISPE. Sessions are kept at a short 20 minutes, similar to a TED Talk. This structure provides "a platform for young professional speakers and an opportunity for them to develop their public-speaking skills while participating in an ISPE event," says Rocks.

Perhaps one of the more useful elements of the committee's successful events is the opportunity for attendees to network. "It's important to provide a link for people across different companies— opportunities to get to know one another," says Rocks. "It means moving forward from not only a professional level but also a personal level."

"We've had very senior people come and talk openly about how they got to where they are and what's happening in the industry," says Ryan. "That's another huge benefit of networking. It's not just talking to peers about issues in the industry; it's talking to people who are much higher up whom we would otherwise not have had the opportunity to meet."

The committee also collects feedback at each event and acts on those suggestions at subsequent events. In fact, one modification to the event structure came about following feedback from attendees. "We moved the networking to the middle of the event, at the break, instead of having it at the end, when people are more likely to start heading home," says Rocks.

In terms of industry participation, the committee members say they've had tremendous support thus far. "Industry employers are very supportive of the young professionals developing personally and professionally, so they have been eager and quite positive," says Ryan. "I think that that's part of the change in the industry; employers are happy to see young professionals go that extra mile in wanting to improve the industry in whatever way they can and as a result are quite happy to support it."

They have also had support from the main ISPE Ireland Committee members, who have used their wide- reaching relationships within the industry to enable the ISPE Ireland YP Committee to approach speakers for the events. "Even though the industry is growing in Ireland, it has been so very much like a small community," says Rocks. "Even with their busy schedules and workloads, they are still very happy to travel to events, prepare presentations, and share with young professionals."

In addition, the main ISPE Ireland Committee provides financial support for all YP events.

Advice for Other YPs

Other Young Professionals groups from around the world may be able to learn from the Ireland committee's experience, and the members are quick to offer some advice.

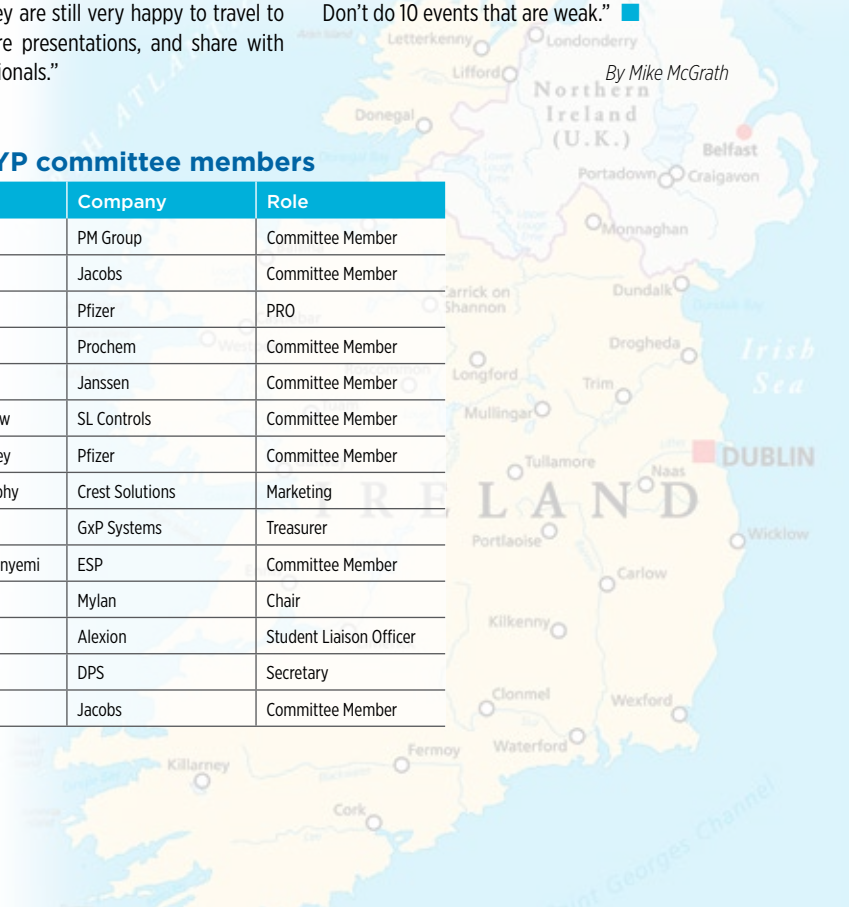
"I'm just a motivated young professional working in the industry," says Rocks. "I have no particular skill or qualification to be part of the committee, just an interest and motivation to be part of it. We're not experts; we are learning as we go along, and at every event we change a little thing here and there and we collect feedback, both positive and negative."

"This is more of a marathon than a sprint," adds Ryan. "It's about looking ahead to see what other events are happening at the same time, what's happening in the industry at the moment, and making sure that you can ensure the quality of the event. If that means the Young Professionals can hold only two events per year, that's fine. Don't do 10 events that are weak." ■

By Mike McGrath

Ireland YP committee members

Name	Company	Role
Tom Bannon	PM Group	Committee Member
Elaine Clarke	Jacobs	Committee Member
John Clarke	Pfizer	PRO
Conor Eighan	Prochem	Committee Member
Seamus McHugh	Janssen	Committee Member
Dermot McMorrow	SL Controls	Committee Member
James McSweeney	Pfizer	Committee Member
Anne-Marie Murphy	Crest Solutions	Marketing
Alan O'Connor	GxP Systems	Treasurer
Samusideen Ogunyemi	ESP	Committee Member
Caroline Rocks	Mylan	Chair
Grainne Ryan	Alexion	Student Liaison Officer
Ross Slevin	DPS	Secretary
Emer Somers	Jacobs	Committee Member



ISPE®

ISPE/FDA/PQRI Quality Manufacturing Conference

Operational Excellence in Manufacturing

Integration of Regulatory Review & Inspection Strategies

Frontiers in Manufacturing Science & Quality

6 – 8 June 2016

Bethesda North Marriott Hotel
and Conference Center
Bethesda, MD

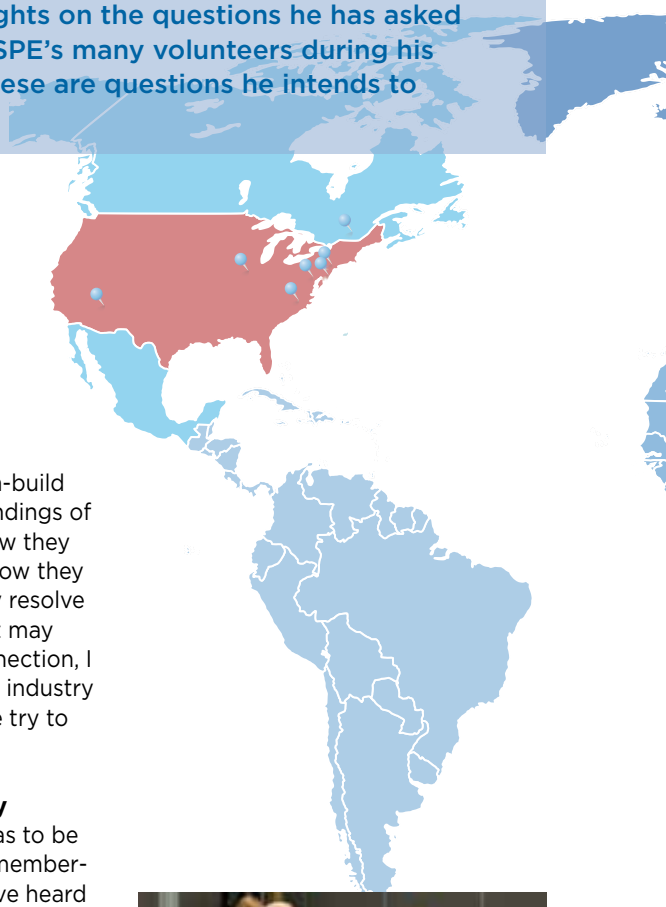
FDA PQRI Product Quality Research Institute

Register Today!

www.ISPE.org/2016-Quality-Manufacturing-Conference

Pharmaceutical Engineering met with ISPE President and CEO John E. Bournas to talk about his first year at the helm of the organization, what lies ahead, and how he intends to build upon ISPE's foundation and continue to meet the needs of its global membership.

Following are his thoughts on the questions he has asked himself, his staff, and ISPE's many volunteers during his first year of service. These are questions he intends to keep asking.



How can I help ... ?

... members?

Continue to shape the organization to meet the changing landscape of the global pharmaceutical and biopharmaceutical industries.

Historically, the bulk of our membership has been in North America and Western Europe. These centers continue to be an important base. But the organization's growth will reflect new areas of production: Asia-Pacific, Latin America, Eastern Europe, Turkey, the Middle East, where new facilities are being built.

ISPE will continue to globalize, with well-rounded and diverse human resources that can understand cross-cultural complexities. These are ongoing issues for many associations, regardless of geography. The human element is always one of the most complex aspects of management in an international association. And when you take it one step further, trying to create a cross-cultural teams, it becomes even more challenging.

That said, cross-cultural dialogue—trying to approach and understand issues from different cultural perspectives—is extremely important. It's not a facile endeavor, and I don't know if there is one model that fits all. The goal for managers is to team-build by having a better understandings of their members' locations, how they experience the daily grind, how they perceive work, and how they resolve conflict in environments that may not be their own. In this connection, I believe our organization and industry face similar challenges as we try to achieve our objectives.

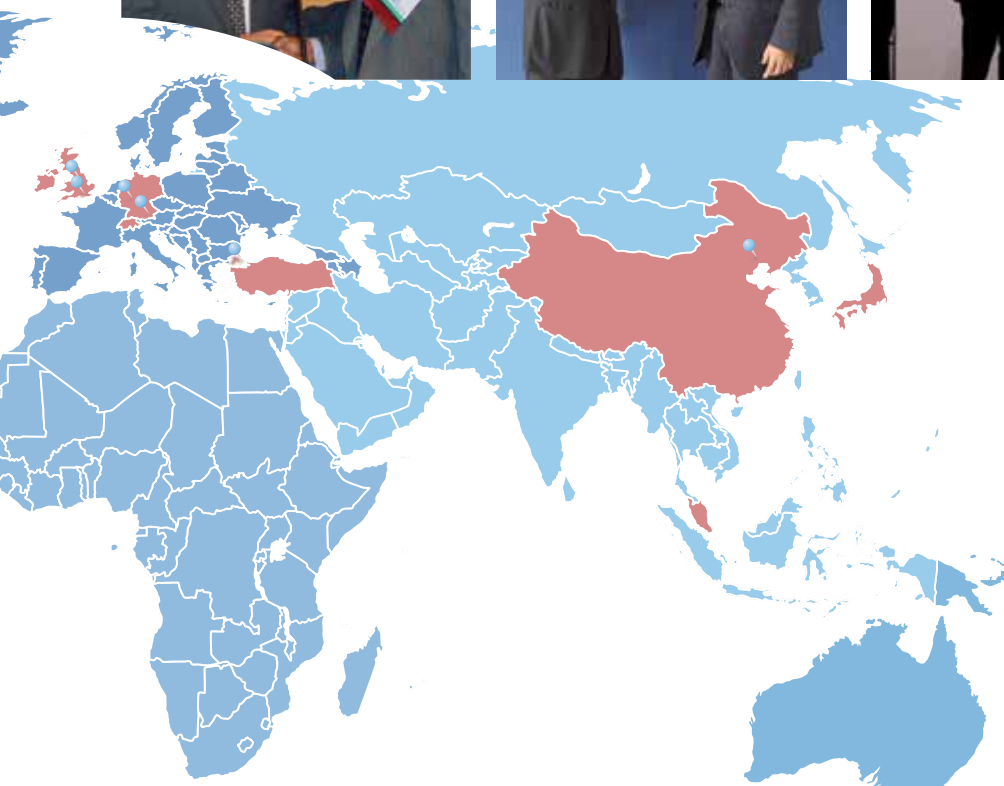
A lifeline ... and neutrality

Global knowledge sharing has to be the biggest benefit of ISPE membership. Certainly it is what I have heard time and again this past year. Being able to pick up the phone and speak to a fellow member in any part of the world—that is, to coin a phrase, invaluable. Long-standing members have told me that the network ISPE has built is one of its strongest assets. And I can confirm it is one the Board and I intend to maintain and grow.

ISPE's ability to reach into different geographies, converse with regulators around the world—well, that's an essential service to our members. ISPE provides a neutral setting for discussion and that is unique to us.

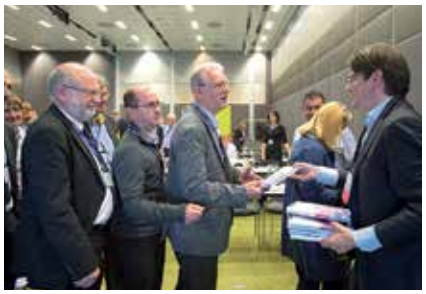
Global knowledge sharing has to be the biggest benefit of ISPE membership

A year in review—left to right: with Merck & Co. Executive Vice President Willie A. Deese at the 2015 ISPE Quality Metrics Summit; touring China's Center for Food and Drug Inspection; delivering the keynote speech at the 2015 ISPE China Annual Spring Conference.



Silent majority

I'm often surprised by the number of volunteers who work quietly behind the scenes, who want to do the right thing, give back, contribute to their space. There are so many of them who have so many good words to say about what we are doing. Funnily enough, they're the silent majority, they truly are.



… staff?

I am very pleased with the modernization the organization has undergone in the past 12 months. We were a traditional society, with one prime location, one predominant way of doing business. Yet in the last year we have established a physical presence in Washington, D.C., so that we can have timely, robust, and ongoing dialogue with regulatory agencies.

At the same time, we've kept all the strengths Tampa has to offer and founded the ISPE Training Institute there. We've recruited and blended the new health care association talent in D.C. with our Tampa-based employees, who have done so much for members and ISPE in past years. Walking that fine line and finding the right skill sets has been complex, but I'm confident that it has greatly helped us be better able to work closely with our members.

We are moving further into positive territory in 2016. And we'll begin to implement the strategic plan—that will be exciting. ISPE's new strategy will further focus our approach so that we can be more responsive to members' interests and be a platform for active engagement.

A truly inernational society: We speak 13 languages and come from 11 countries.

… YPs?

I am intent on giving young professionals a louder voice, a greater voice, and more space in which to engage.

We need to learn how to speak their language. Associations tend to be very committee oriented, yet that isn't necessarily the prime mode of interaction for YPs entering the nonprofit space. That's my perception. We need to think outside the box and develop better ways of relevant and sustained engagement.

One of our greatest assets at ISPE is diversity. It's also one of our greatest challenges. We must determine how to be pertinent to all our members. For instance, pharmaceutical manufacturing today is leading us into 3D pills. That is a completely new mode of production. YPs may be more in tune with that type of drug delivery system since they have a better grasp of technology, simply because that is how they have learned and adapted.

John B's 3 Ps:
Perseverance
Prudent growth
Prioritization

… patients?

Providing safe and quality medicines to patients—that is my personal vision statement. It is what I would like ISPE to influence most. And I believe we can achieve it by providing continuous education and training to our members. This ought to apply in the holistic sense, encompassing engineering and manufacturing, inclusive of quality. You simply can't cut corners. The repercussions of not being able to comply with basic GMPs are significant for businesses, but are even more so for patients, who rely on our consistent supply of medicines.

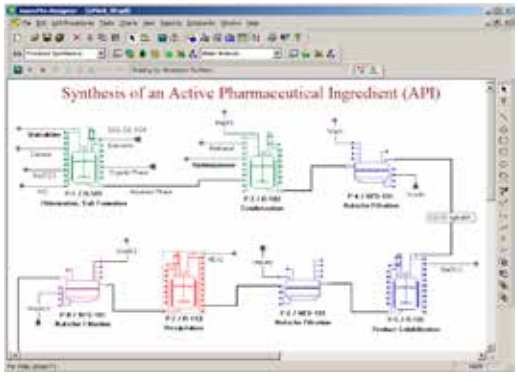
ISPE is perfectly positioned to provide not only knowledge-sharing, networking, and socialization that members expect, but also to offer that education on a regular basis anywhere in the world where it's needed. That's what I trust will be our legacy in the long term.

ISPE's growing footprint—clockwise from far left: Bethesda offices; Tampa headquarters; a classroom in the new Tampa Training Institute.

Intelligen Suite®

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

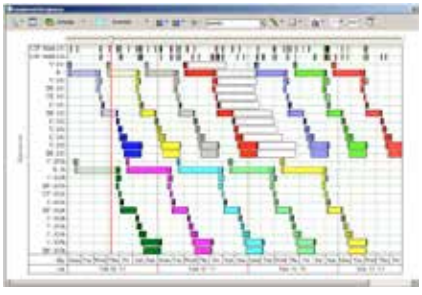
SuperPro®



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

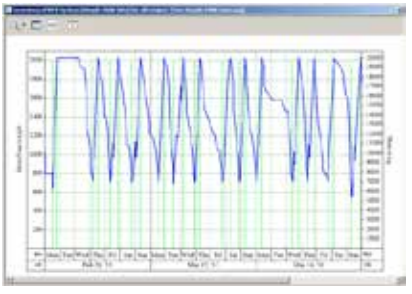
SchedulePro®

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



Easy production tracking, conflict resolution and rescheduling

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



Managing inventories for input, intermediate, and output materials

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

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

Visit our website to download detailed product literature and functional evaluation versions of our tools

INTELLIGEN, INC. • 2326 Morse Avenue • Scotch Plains, NJ 07076 • USA
Tel: (908) 654-0088 • Fax: (908) 654-3866
Email: info@intelligen.com • Website: www.intelligen.com
Intelligen also has offices in Europe and representatives in countries around the world

History and Relevance of Sustainability to the Pharmaceutical Industry

Corporate sustainability has its global foundation in the International Union for Conservation of Nature publication "World Conservation Strategy: Living Resource Conservation for Sustainable Development," [8] which was the initial attempt to integrate conservation into sustainable development.

Sustainable development became mainstream through the Brundtland* Commission's publication of "Our Common Future" in 1987. [23] The publication "Caring for the Earth" [9] and the adoption of Agenda 21, a declaration on environment and development presented at the Rio Earth Summit in 1992, reinforced sustainability. [4, 19, 20] Sustainable development aims to reduce poverty, thus economic growth was needed. Collectively, these documents add the third pillar of environmental protection and restoration to the financial and social pillars typical of development, aka, the "Triple Bottom Line."

The United Nations Global Compact (UNGC) is a corporate sustainability initiative for businesses that are committed to aligning their operations, eco-innovations, and business strategies. Its 10 principles cover human rights, labor, environment, and anticorruption. [15] UNGC established the "Caring for Climate: Business Leadership Platform" in 2007 [18] and catalyzed actions aligned with the Millennium Development Goals (MDG) identified at the UN Millennium Summit in 2000. [16] World governments and leaders built upon the MDG accomplishments by adopting the Johannesburg Declaration on Sustainable Development [17] and Plan of Implementation [27] at the UN World Summit on Sustainable Development in 2002. These were followed in 2015 with the 2030 Agenda for Sustainable Development, which lists 17 Sustainable Development Goals (SDGs) and 169 targets that encompass economic growth, environmental dimensions, and social inclusion. [25]

Governments have been implementing sustainability initiatives that affect businesses worldwide. India's Company Act of 2013, for example, mandates certain companies to develop a corporate social responsibility (CSR) policy and to invest 2% of net profit on CSR. The 2014 European Union "Directive on Disclosure of Non-Financial and Diversity Information by Certain Large Undertakings and Groups" with more than 500 employees was implemented; topics encompass the environment, social issues, human rights, and diversity, as well as anticorruption and bribery. [6] Recognized frameworks include the Global Reporting Initiative (GRI) sustainability

* *Dr Gro Harlem Brundtland: Norwegian physician, prime minister (1981, 1986–89, and 1990–96), and director general of the World Health Organization, 1998–2003.*

reporting guidelines, [7] UNGC, UN Guiding Principles on Business and Human Rights, Organisation for Economic Co-Operation and Development Guidelines, ISO standard 26000, and the International Labour Organization Tripartite Declaration.

Market regulators and investors are mandating or recommending that companies listed on stock exchanges to report on sustainability metrics—i.e., environmental, social, and governance (ESG)—with commentary on risks, opportunities, and effects on performance; ESG is commonly used interchangeably with sustainability. The Sustainable Stock Ex changes (SSE) Initiative, the Investor Network on Climate Risk, and the World Federation of Exchanges Sustainable Working Group (WFE SWG) champion requests for increased ESG disclosure. The SSE collaborated with WFE SWG, releasing the "Model ESG Guidance on Reporting ESG Information to Investors" for companies that report on global exchanges. [14] This guidance contributes to the priorities outlined in the UN SDG's such as SDG Goal 12, Target 12.6 ("encourage companies, especially large and trans-national companies, to adopt sustainable practices and to integrate sustainability information into their reporting cycle") while demonstrating the value proposition or business case. WFE SWG subsequently authored the "WFE ESG Recommendation Guidance and Metrics," [24] which outlines 33 specific metrics that correlate ESG to bottom line effects, and promote harmonizing disclosure by referencing the leaders in defining material ESG metrics and reporting:

- Carbon Disclosure Project (CDP) [3]
- GRI
- International Integrated Reporting Council
- Sustainable Accounting Standards Board (SASB)
- UNGC

SASB is developing nonfinancial material metrics that may drive financial performance for 79 industries in 10 sectors. [13] Health care is a defined sector, and the pharmaceutical industry is covered by a current guidance document; sustainability topics identified as material include drug safety and side effects; safety of clinical trial participants; affordable and fair pricing; ethical marketing; employment, recruitment, development and retention; employee health and safety; counterfeit drug prevention procedures; energy, water, and waste efficiencies; and corruption and bribery.

SASB enables US companies to select material metrics, embed them into their corporate strategy, and disclose the material sustainability metrics in mandatory US Securities and Exchange Commission 10-K or 20-F filings. SASB's standards provide consistent data such that peer performance and benchmarking are possible within an industry. A recent *Harvard Business Review* working paper highlights that positive performance on material sustainability metrics correlates with improved financial performance. [11]

GRI is an independent international organization that has developed an index based on ESG metrics purported to be most the widely used for sustainability disclosure and standards. GRI has 10 industry-sector-specific supplements, although it does not have a specific supplement for the health care or pharmaceutical sectors.

CDP works with investors, governments, cities, and companies in using CDP's questionnaires to collect data regarding climate change, water, and deforestation risk. Disclosure in their database increases awareness of business risk and proactively innovating or finding opportunities to future-proof businesses from these environmental threats.

Green chemistry can drive innovation, reduce costs — which may increase access to medicines — reduce carbon footprint, and benefit the environment.

Industry initiatives are championing aspects of sustainability relevant to the pharmaceutical industry.

- The Pharmaceutical Supply Chain Initiative released the "Pharmaceutical Industry Principles for Responsible Supply Chain Management" in June 2015. [26]

- The American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable was developed in 2005 to "encourage innovation while catalyzing the integration of green chemistry and green engineering in the pharmaceutical industry. . . . [T]he pursuit of green chemistry and engineering is imperative for business and environmental sustainability." [1] This roundtable provides tools for green chemistry implementation: Solvent Selection Guide, Process Mass Intensity Calculation Tool, Process Mass Intensity-Lifecycle Assessment, and Reagent Guide.

- PhRMA is engaging in initiatives to address pharmaceuticals in the environment.

- The European Chem21 Project provides a unique opportunity for academia to engage with pharmaceutical companies and other SMEs to develop innovative catalytic processes that may replace pharmaceutical syntheses that use precious finite resources such as previous heavy metals. [5]

Green chemistry can drive innovation, reduce costs (which may increase access to medicines), reduce carbon footprint, and benefit the environment. Common focus areas for pharmaceutical companies include energy and climate, access to water, sustainable packaging, access to medicine, health and safety, injury prevention, ergonomics, and stress management. [12]

Businesses play a crucial role in implementing SDGs. Pharmaceutical companies have begun to embed sustainability into their corporate strategy and product stewardship. For example, Johnson & Johnson's Healthy Future Goals [10] aim not only to improve chemical and material safety, increase product manufacturing efficiency, and use less hazardous materials in products, processes, and packaging, but also to incorporate social sustainability goals. Select elements are the foundation of company's Earthwards process, which facilitates development of more sustainable products. Biogen has adopted context-based sustainability principles that take into account local conditions and ecological thresholds. [2] In January 2014, Biogen ranked second on Corporate Knight's annual "Global 100" list of most sustainable companies.

Sustainability implementation involves governance strategies, disclosure (to include relevant standards, systems, and materiality agreement of disclosure metrics); stakeholder engagement from investors, employees, customers, and C-level; along with a performance strategy to ensure success within a corporate structure. Value drivers identified by the WFE SWG include access to capital; profitability and growth; compliance and risk management; branding and reputation; harmonized information flow to stakeholders; enhanced stakeholder relationships and engagement; and measurable achievements. [24]

Common focus areas for pharmaceutical companies include energy and climate, access to water, sustainable packaging, access to medicine, health and safety, injury prevention, ergonomics, and stress management.

The SDGs, regulations, and global market drivers from stock exchanges, investors, and customers are players in driving the sustainability narrative. Leaders include SASB, GRI, CDP, UNGC, and the WFE SWG. The pharmaceutical industry is engaging in the global sustainability narrative and has ample opportunity to further incorporate sustainability into their business strategy and value proposition while communicating how companies are helping to solve the world's pressing challenges: poverty, social justice, climate change, water, resource constraints, and biodiversity. ■

By Dr. Clarice Hutchens

References

1. American Chemical Society. Green Chemistry Initiative. "ACS GCI Pharmaceutical Roundtable." www.acs.org/content/acs/en/greenchemistry/industry-business/pharmaceutical.html.
2. Baue, Bill. "#SustyGoals 7: How Biogen Uses Context-Based Sustainability to Set Environmental Goals." Sustainable Brands website, 3 March 2014. https://www.2degreesnetwork.com/groups/2degrees-community/resources/how-does-biogen-use-context-based-sustainability-set-environmental-goals.
3. Carbon Disclosure Project. https://www.cdp.net/en-US/Pages/HomePage.aspx.
4. Castro, C. "Sustainable Development: Mainstream and Critical Perspective." Organization & Environment 17(2): 195–225.
5. Chem21. "Pharmaceuticals and Universities Working Together on Multi Million Pound Project." www.chem21.eu.
6. Council of the European Union. "New Transparency Rules on Social Responsibility for Big Companies." Press release, 29 September 2014. www.consilium.europa.eu/uedocs/cms_data/docs/pressdata/en/intm/144945.pdf.

7. Global Reporting Initiative. “Learn about Our Reporting Guidelines.” https://www.globalreporting.org/standards/Pages/default.aspx. .
8. International Union for Conservation of Nature and National Resources, United Nations Environment Programme, and the World Wildlife Fund. “World Conservation Strategy: Living Resource Conservation for Sustainable Development.” 1980. https://portals.iucn.org/library/efiles/edocs/WCS-004.pdf.
9. ———. “Caring for the Earth: A Strategy for Sustainable Living.” October 1991. https://portals.iucn.org/library/efiles/edocs/CFE-003.pdf.
10. Johnson & Johnson. “Healthy Future 2015 Sustainability Goals Progress.” www.jnj.com/caring/citizenship-sustainability/performance/healthy-future-2015.
11. Khan, Mozaffar, George Serafeim, and Aaron Yoon. “Corporate Sustainability: First Evidence on Materiality.” Harvard Business Review, 9 March 2015. http://papers.ssrn.com/sol3/papers.cfm?abstract_id=2575912.
12. Schneider, Jennifer, Anna Wilson, and Joseph M. Rosenbeck. “Pharmaceutical Companies and Sustainability: An Analysis of Corporate Reporting.” Benchmarking: An International Journal 17(3): 421-438. https://www.researchgate.net/publication/243460210_Pharmaceutical_companies_and_sustainability_An_analysis_of_corporate_reporting.
13. Sustainable Accounting Standards Board. Sectors. “Health Care.” http://www.sasb.org/sectors/health-care.
14. Sustainable Stock Exchanges Initiative. “Model Guidance on Reporting ESG Information to Investors.” 2015 www.sseinitiative.org/wp-content/uploads/2015/10/SSE-Model-Guidance-on-Reporting-ESG.pdf.
15. United Nations. “What Is UN Global Compact?” https://www.unglobalcompact.org/what-is-gc.
16. ———. “Millennium Development Goals and Beyond 2015.” http://www.un.org/millenniumgoals.
17. ———. “Johannesburg Declaration on Sustainable Development.” World Summit on Sustainable Development, Johannesburg, South Africa, 26 August–4 September 2002. http://www.un-documents.net/jburgdec.htm.
18. ———. «Caring for Climate: Business Leadership Platform.” 2007. http://caringforclimate.org/wp-content/uploads/C4C_Statement.pdf.
19. ———. Conference on Environment and Development. Agenda 21. Presented at the United Nations Conference on Environment and Development, Rio de Janeiro, Brazil, 3–14 June 1992. https://sustainabledevelopment.un.org/content/documents/Agenda21.pdf.
20. ———. Conference on Environment and Development. Report of the United Nations Conference on Environment and Development. Annex I: Rio Declaration on Environment and Development. Presented at the United Nations Conference on Environment and Development, Rio de Janeiro, Brazil, 3–14 June 1992. http://www.un.org/documents/ga/conf151/aconf15126-1annex1.htm.
21. United Nations Environment Programme. “Global Environmental Outlook 3: Past, Present, and Future Perspectives.” London: Earthscan Publications, 2002. http://www.unep.org/geo/geo3/english/pdfs/prelims.pdf.
22. United Nations. “Global Drylands: A UN System-Wide Response Report.” 2011. http://www.unccd.int/Lists/SiteDocumentLibrary/Publications/Global_Drylands_Full_Report.pdf.
23. ———. World Commission on Environment and Development. “Our Common Future.” Annex to document A/42/427: Report of the World Commission on Environment and Development. 4 August 1987. http://www.un-documents.net/our-common-future.pdf.
24. World Federation of Exchanges. “WFE ESG Recommendation Guidance and Metrics.” October 2015. Download available at: http://www.world-exchanges.org/home/index.php/news/world-exchange-news/world-exchanges-agree-enhanced-sustainability-guidance.
25. United Nations. “Transforming Our World: The 2030 Agenda for Sustainable Development.” https://sustainabledevelopment.un.org/content/documents/21252030%20Agenda%20for%20Sustainable%20Development%20web.pdf.
26. Pharmaceutical Supply Chain Initiative. “The Principles.” June 2015. PDF download available at: http://pscinitiative.org/resource?resource=1.
27. United Nations. “Plan of Implementation of the World Summit on Sustainable Development.” 2002. http://www.un.org/esa/sustdev/documents/WSSD_POI_PD/English/WSSD_PlanImpl.pdf

2015 Member of the Year

George Millili: Giving back to an industry he loves

At the 2015 ISPE Annual Meeting held in in Philadelphia, Pennsylvania, George P. Millili, PhD, received the organization's Joseph X. Phillips Professional Achievement Award. It was no surprise to anyone in the room—except Millili himself. But it was his acceptance speech, delivered with passion and emotion, that revealed as much about the man as his 37 years of professional experience.

Currently an individual contributor as Senior Principal Technical Advisor at Genentech, a member of the Roche Group, Millili, now 62, has built a stellar career in the pharmaceutical industry in the formulation, process development, scale-up, and technology transfer of new drug products.

Born and raised in the Philadelphia area, Millili currently lives in Cherry Hill, New Jersey, with his wife Patricia. In their spare time, they spend as much time as they can at their house in Naples, Florida, where they enjoy the warm weather and as much golf as they can fit in. Millili also enjoys deep-sea fishing with his two sons, Peter and George. Peter has followed in his father's footsteps in the pharmaceutical industry: He is an engineer at Bristol-Myers Squibb and an active member of ISPE.

Two lifelong mentors

Everyone has their own story as to how they became interested in the field in which they chose to pursue a career; Millili's story can certainly be described as unique. He was first introduced to the pharmaceutical industry at the Annunciation Greek Orthodox Church in Elkins Park, Philadelphia. It was there that he met Theodore Kallelis, PhD, and Nicholas Batuyios, PhD, who became his mentors.

"Dr. Kallelis was a professor at the Temple University School of Pharmacy, and we had discussions at church about pharmacy school," says Millili. "I read a good bit about pharmaceuticals when I was younger, and I was fascinated. The whole key is that I wanted to help people—help the patients—and I thought this would be a really neat profession." Millili would go on to earn his bachelor of science degree in pharmacy at the Temple University School of Pharmacy.

Batuyios was director of research for McNeil Laboratories at the time. "Dr. Batuyios was working on perfecting the various formulations for Tylenol," says Millili. "He knew that I was going to pharmacy school and offered me a summer job at McNeil in Fort Washington, Pennsylvania. I worked there for four summers and really gained an interest in research and formulation/process development. I ended up working there for 12 years as a bachelor-level pharmacist."

During the same period, Millili became a licensed pharmacist and would moonlight on evenings and weekends at a second job filling prescriptions to support his growing family. Then, through Batuyios's further encouragement, Millili moved on to attend school full time at the Philadelphia College of Pharmacy and Science, where he completed his PhD in pharmaceutics in 1990.

Building a career

Following the completion of his PhD, Millili joined Schering-Plough (now a subsidiary of Merck & Co.) in Kenilworth, New Jersey, where he took on increasing levels of responsibility in the Biotechnology group as well as in the Process Improvement group.

From there, he moved to DuPont Merck Pharmaceutical in Wilmington, Delaware, where his responsibilities included supervising the technical activities of DuPont's Worldwide Manufacturing Technology organization. He eventually became Executive Director of that organization and was responsible for all technical activities at the company's worldwide manufacturing sites and contract manufacturing locations. This included the contract manufacturing DuPont did for other organizations as well. .

It is in speaking about his time at DuPont that Millili reminisces about his work on a product for which he feels most proud: an antiviral medication called Sustiva that helps prevent HIV cells from multiplying in the body.

"I was the Manufacturing Technology program lead for Sustiva," says Millili. "This was the early stages when multiple drugs with varied mechanisms (cocktails) were being utilized to treat HIV, where mono therapy would not work because the patient would develop resistance to the drug. But this drug in combination with other drugs would control the spread of HIV. I worked with R&D in perfecting the formulation and with a team of scientists led the process development, scale-up, and technology transfer resulting in 'expanded access' and early accelerated approval of the drug."

Under normal circumstances, a drug product takes 4 to 6 years to go through the development and US Food and Drug Administration (FDA) approval process to reach the wider patient market. Given the urgency of the HIV crisis at the time (mid-1990s), however, Millili and the DuPont team worked closely with the FDA after smaller-scale clinical studies demonstrated that Sustiva was helping HIV patients.

> "At Genentech, the position allows me to utilize my career experiences, and to give back to the industry that has been good to me."

"The FDA worked very closely with us and allowed [the drug] to be used for expanded access quickly to extend those peoples' lives and to get the drug approved quicker so that we could get it out to more people," says Millili. "So that's one that I'm particularly proud of because it has been a life saver or a life extender for a lot of patients." Even today, Sustiva is still a top drug in its class.

Following his time at DuPont, Millili moved to Merck & Co.'s West Point, Pennsylvania, facility in 2001, where he was responsible for the Technical Operations groups at Merck's Latin America and Puerto Rico sites. There, he led the technology transfers and technical operations groups supporting the manufacture of products in the Latin America region.

In 2005, Millili joined Johnson & Johnson Corporation (GSPG group) as Senior Director of Pharmaceutical Technology Services. There he was responsible for new-product introduction, pharmaceutical technology, packaging, graphic services, pharmaceutical process engineering, contract manufacturing technical support, and site technical operations groups throughout North America.

He returned to Merck in 2008 as Senior Director of Pharmaceutical Commercialization Development, taking responsibility for a technical staff of scientists and engineers developing formulations and processes from Phase IIB through validation and commercialization.

In 2013, Millili moved to his current position as Senior Principal Technical Advisor for Genentech. He is a full-time technical advisor to the company's Pharmaceutical Technology Quality organization and is responsible for external collaboration with the industry and regulators for the Americas.

As Millili explains, his position at Genentech allows him to give back to the pharmaceutical industry: "In all those years at Johnson & Johnson and Merck, in leading development teams and technical teams, I had the management responsibilities for budgets, performance reviews, personnel development etc., which was very rewarding," he says. "At Genentech, part of my job is as a technical advisor to the quality organization on any technical issues that may arise providing the technical perspective to Quality management when needed. The second part of my job is to be responsible for external relations with industry and regulators for the Americas, helping influence regulatory policy and technical standards that result in the manufacturing of high Quality products for patients. This position allows me more time to work with associations like ISPE, keeping my company current in latest trends and leading industry technical teams and groups who work with regulators to help develop standard practices that improve the quality of products being manufactured for the patient. The position also allows me to utilize my career experiences, and to give back to the industry that has been good to me."

Involvement with ISPE

Membership in industry associations like ISPE can provide many benefits to the members as well as the association itself. That has certainly been true when it comes to Millili's association with ISPE. He joined ISPE in the early 1990s and has been an active participant ever since. "I've been involved with ISPE for a good part of my career," he says. "It has been my key association."

Millili has represented ISPE internationally on numerous occasions through presentations, white papers, and articles on subjects touching the best practices for technology transfers, quality, and process improvement, such as his 2013 presentations on the International Conference on Harmonisation guideline on Pharmaceutical Quality Systems (ICH Q10) in China, Brussels, and Washington, among others.

For the past 3 years, Millili has also led ISPE's Product Quality Lifecycle Implementation (PQLI®) technical team. "All of the technical teams and subteams that ISPE sponsors fall under this group," he says. "We have monthly meetings with international technical leaders within ISPE. We have committees under numerous work streams—process validation, process capability, breakthrough therapy, knowledge management etc.—and they work on such things as white paper publication conference content that provide a positive contribution to the industry."

As of 2016, Millili will co-lead ISPE's Global Regulatory Compliance Committee (RCC), a committee comprising international members from North America, Latin America, the Asia–Pacific region, Europe, and the Middle East and Africa (EMEA). "Each region has regulatory experts who are active with regulators in their country who keep track of the key trends from a regulatory perspective," he explains. The committee will "help us build conference content on topics of interest in those regions as well as work with regulators to help bring positive change from a regulatory perspective," he adds.

2015 award

On 11 November 2015, at ISPE's Annual Meeting membership breakfast in Philadelphia, Millili was named the 2015 recipient of the Joseph X. Phillips Professional Achievement Award. The award honors an ISPE member who has made a significant contribution to the industry. It is named in honor of the late Joe Phillips, a former FDA official who was a longtime supporter of ISPE and a leader in establishing the organization as an "integrator" of industry and regulators.

According to the ISPE website, Millili received the award because throughout his career he has focused on building a strong relationship between regulators and industry to collaboratively tackle the issues they both face. He is regarded as a leader among his peers for his technical expertise, energy, and enthusiasm as well as his inclusive and collaborative style. His dedication and commitment to ISPE has been consistent for years, and his contributions to the industry and the organization have gone above and beyond expectations.

Receiving the award "was very emotional for me and an extreme honor," says Millili. "Joe Phillips worked closely with ISPE in a huge capacity; when he retired from the FDA, he became a regulatory scientific advisor for ISPE. He was involved with bringing regulators and the industry together in a lot of different ways. He had a fantastic personality; I worked closely with him, and he became a later-stage mentor for me. He taught me about doing the

"I've been involved with ISPE for a good part of my career," he says. "It has been my key association."

right thing when working with the industry and the regulators for the benefit of the patient. We did a lot of good things together. We traveled and attended many meetings together, and, over the years, we became good friends. I respected his approach to how he did things. He taught me the importance of giving back to the industry."

On the morning that Millili received his award, 800 to 1,000 people were in attendance, including his wife and one of his sons. As Millili describes it, the moment that John Bournas, CEO of ISPE, announced the award was a surreal and emotional experience. "I went up to the podium, and I was shocked. John Bournas was reading about my accomplishments, and I'm there listening, holding the plaque, and looking down at the teleprompter. When I looked down at the teleprompter, in the corner was the face of Joe Phillips. Then they asked me to say a few words, but when I walked up there, I choked up, and it took me about 5 to 8 seconds—which felt like 5 hours—to just pull it back in."

"It was a very proud moment for me because of what's getting recognized," he says. "I'm toward the end of my career, so it's a nice time to have this type of recognition. And, secondly, it was really special that it was under the name of Joe Phillips, a mentor who was a great friend and someone I loved."

Motivation

A relentless drive to succeed is a common motivator for high achievers like Millili. Another common motivator is the desire to give back, which also holds true for Millili. "Two things motivate me," he says. "The utmost thing in being a pharmacist—a pharmaceutical engineer—is to work on things that benefit patients, that help them live more productive lives or extend their lives. [Our] working in this industry and making drugs available to patients worldwide helps their quality of life. It motivates me when I get up in the morning to know that the little piece that I do on these things … someday someone is going to need this medication and some patient is going to benefit from it.

"The second thing is mentoring young people in the industry to do the same, to have that same drive and enthusiasm to help the patient with high quality and compliance," continues Millili. "To really mentor these young engineers and scientists coming out of school to do it the right way, to do the right thing for the patient using good science, high-quality standards and compliance with regulations. If I see young people doing that and succeeding to bring a product to market; it really makes me feel good when I see that I was part of that person's development."

Advice for YPs

And it is to those young professionals that Millili offers some sage advice:

"Number one is to get hands-on experience and be patient with your progression in your career," he says. "Which means don't work for 6 months and then ask for your first promotion. I know these young scientists are aggressive, and they should be, but get out there and get some experience and be patient. Be patient with the progression of your experience; build your technical quality and scientific base well. That will lead to your first promotion so that you can really accelerate from there.

"The second thing is to have fun when you're working," he adds. "If you're having fun, you're going to be motivated. If you're motivated, you're going to be productive.

"And, finally, work well with people," says Millili. "Treat each person as an individual and work with [him or her] as an individual; try to get the best out of that person and understand the areas where [he or she] needs to grow and try to help."

As Millili reiterates, understanding individuals will become more important as the industry becomes more globalized. "A lot of work is being transferred to places like India, China, Japan, and Korea, etc., so they are really going to have to understand varying cultures and styles." ■

By Mike McGrath

1

"Number one is to get hands-on experience and be patient with your progression in your career"

2

"The second thing is to have fun when you're working"

3

"And, finally, work well with people"

ELETTRACQUA

pure water technologies

SINCE 1966

PHARMACEUTICAL WATER SYSTEMS

OSMOSIS + EDI UNIT HOT WATER SANITIZABLE

DOUBLE PASS REVERSE OSMOSIS

HIGH TEMPERATURE SANITIZATION + CONCENTRATE RECOVERY SYSTEM

MULTIPLE EFFECTS DISTILLATION UNIT

PURE STEAM GENERATOR

DESIGN AND CONSTRUCTION OF PURIFIED WATER PACKAGES • DOUBLE PASS REVERSE OSMOSIS • R.O. + ELECTRODEIONIZATION HOT WATER SANITIZABLE • ULTRAFILTRATION • MULTIPLE - EFFECT DISTILLATION UNITS • PURE STEAM GENERATORS • STORAGE AND DISTRIBUTION LOOP • COMPLETE TURN KEY PROJECTS • VALIDATIONS IQ, OQ

www.elettracqua.com

Energy is Expensive. Why Waste it?

High Efficiency BioPure LSX

Minimized Energy Consumption. Economical Price.

The BioPure LSX USP Purified Water System for pharmaceutical applications features high efficiency motors with variable frequency drives and self-modulating valves minimizing energy usage while in operating mode. Additionally, USB ports and Ethernet compatibility allow real time tracking of operational parameters and electrical output. Minimized Energy Consumption is only one of the many features that make the BioPure LSX the logical choice for a pharmaceutical research and manufacturing USP water system.

View the BioPure LSX video at www.mcpur.com to find out more.

MAR COR
A Cantel Medical Company

ISO 9001 & ISO 13485 Certified · US: 800-633-3080 · Canada: 800-268-5035
For more information email us at info@mcpur.com or visit **www.mcpur.com**

PHARMACEUTICAL ENGINEERING®

Special Report

QUALITY METRICS

January-February 2016

ISPE®

Responding to the FDA Federal Notice on Quality Metrics

There is an argument to be made – and some industry insiders make one – that pharmaceutical manufacturers are willing and capable of self-regulating process and product quality. Additionally, those insiders say that, beyond the obvious desire to produce safe and effective drugs, application of continual improvement makes good business sense. Application of continual improvement may require changes to manufacturing processes and in turn this may require changes to manufacturing process and control procedures documented in drug applications.

"We'd like to see a shift to more industry self-regulation and self-driven continual improvement," said Mairead Goetz, head of compliance at Novartis and chair of the ISPE Quality Metrics Core Team. "I believe the FDA sees this as a step in the journey to provide more latitude, flexibility and agility within the industry."

How does introduction of FDA's Quality Metrics program[11] fit with this vision?

There are many quality issues that continue to concern the FDA. For example, it issued 36 warning letters to prescription drug manufacturers in 2015.[1] As of December, there were shortages of more than 60 drugs,[2] including 5 oncology products and 14 anti-infectives, and 40 Class I drug recalls.[3]

With the expansion of overseas operations and the increasing number of drug applications and post approval supplements, the inspection burden has become a problem for the agency.[5, 6] For example, all eight warning letters issued to API manufacturers were to API makers based outside the United States, underscoring the inspection challenges the FDA faces with the globalization of the industry's supply chain.[5]

"I get questions all the time, like 'What about manufacturing in India? What is the level of quality?'" said Janet Woodcock, the director of the Center for Drug Evaluation and Research (CDER) at the FDA, in her keynote address at the ISPE quality metrics meeting held in Baltimore, MD in April 2015. "Well, I don't know. All I know is the result of some different observations that are made. I know there is a lot of variability, but there is in the U.S. as well, and all around the world."[14, 15]

Last year there were many cited data integrity issues, which are red flags for the FDA, particularly regarding a company's quality culture.[7] One facility was testing drugs in a lab that was unknown to the agency and had shipped products that had failed tests.[8, 9]

To address these problems, the FDA is leveraging a risk-based approach to inspection as provided under the Food and Drug Administration Safety and Innovation Act (FDASIA) rather than to inspect manufacturing facilities biannually to ensure they comply with GMPs.[4] Part of the requirements of FDASIA is that information could be provided in advance or in lieu of an inspection. Some of this information are quality metrics data. In February 2013, the agency announced its Quality Metrics Program via a *Federal Register* notice[10] and over the past two years, the agency sought feedback from industry on choosing standardized data and metrics that would be reported. In July 2015 FDA released its *Request for Quality Metrics: Draft Guidance*.[11]

In their draft guidance FDA indicates how they expect their Quality Metrics Program can help FDA and industry:

> *Quality metrics are used throughout the pharmaceutical industry to monitor quality control systems and processes and drive continuous improvement efforts in drug manufacturing. These metrics can also be used by FDA: to help develop compliance and inspection policies and practices, such as risk-based inspection scheduling of drug manufacturers; to improve the Agency's ability to predict, and therefore, possibly mitigate, future drug shortages; and to encourage the pharmaceutical industry to implement state-of-the-art, innovative quality management systems for pharmaceutical manufacturing.*

The draft guidance explains what facilities are covered by the guidance, the required data and data provider and which quality metrics the FDA intends to calculate.

"[W]e at FDA do not know or have a good handle on where the industry is," Woodcock said. "I have said this before. Quality metrics, in fact, are part of our effort to ascertain in a quantitative manner, what the status of quality is in pharmaceutical manufacturing. We do not know that right now."[14] She also pointed out that the industry has failed to embrace continual improvement.[14, 15]

Preliminary responses from ISPE and other industry groups to the Request for Quality Metrics were presented initially to the FDA in a public meeting with industry in August 2015.[12, 13]

Formal responses were provided before the end of November. The agency has said it will publish its Quality Metrics Program, complete with selected metrics soon.

Some of the data the FDA proposes collecting – which it believes is already collected by companies following cGMPs – is the number of lots attempted, specification-related rejected lots, attempted lots pending disposition for more than 30 days, out-of-specification (OOS) results, product quality complaints and annual product reviews (APRs) and product quality reviews (PQRs) for the product.[13]

The agency would then use these data to calculate metrics such as lot acceptance rates, product quality complaint rate, invalidated OOS rate and APR or PQR on time rate. It also asked for comments on optional metrics, such as quality culture measured by engagement of senior management and CAPA effectiveness, and process capability/performance.[11]

Does the industry need a standardized quality metrics program?

There is no doubt that there are quality issues and that some regulatory oversight is necessary. But is collecting industry-wide standardized metrics the way to meet the FDA's stated goals?

"A large segment of the pharmaceutical industry has quality systems that are robust and reliable said Goetz. "We have many of our own metrics. The selection that the FDA is considering is a small piece of that and, generally, a variant of those that companies already will have. But we realize that we don't represent the whole industry and it's the diversity of the industry that makes regulation challenging from a burden/benefit perspective."

Chris Potter, ISPE advisor, agrees that ISPE works in a world of quality converts that may not be indicative of the entire landscape that the FDA is regulating.

"The quality of most of the industry is acceptable," Potter said. "The number of major crises is low. The generics and OTC companies are big players in volume terms and their quality standards are in most cases at least as good, if not better, than the major Rx firms. It's the outliers of cavalier companies or sites, and some products within some companies that pose problems. A potential criticism of the FDA's quality metrics program is that they are imposing a big program to hunt a relatively small part of the industry."

Potter believes the large companies will buy in if they can see the benefits: reduced inspection frequency, risk-based inspections and a reduction in post-approval change processes. The latter are currently often necessary to support implementation of continual improvement opportunities, however, submission and approval is bureaucratic and difficult to manage because of different procedures and time scales between countries around the world.

Prospective submission of quality metric data could be considered a step in the direction of the industry vision where provision of information may increase regulator's confidence that industry's quality systems are performing to a high standard.

ISPE's response to the FDA draft guidance

ISPE's response to the FDA draft guidance, Request for Quality Metrics, was based on the society's data findings from its Quality Metrics Pilot Program Waves 1 and 2.[16] Wave 1 sought to determine whether industry could practically collect and report standardized quality metrics and concluded this objective could be achieved. ISPE is continuing its research, canvassing participants in Wave 2 to determine the amount of effort and burden involved in gathering product-based data with Wave 2 including the quality metrics proposed by the FDA. Wave 2 results will be published by the ISPE in the spring of 2016.

"We at ISPE appreciate the opportunity to provide input to the FDA and support the agency's effort to implement a quality metrics program," Goetz said. "Our comments are based on our experiences and are genuinely designed to assist FDA with successful implementation of their program. We look forward to maintaining this objective data-driven dialogue with the FDA."

In its response to the FDA, ISPE is largely silent on the relationship of standardized quality metrics to drug shortages.

"Standardized metrics across the industry are likely not the solution to predict drug shortages," Goetz said. "Metrics need to be relevant to the situation to monitor and be predictive of a drug shortage. They need to be pertinent to the risk, to the situation, to the lifecycle of the product."

"There's no doubt that some metrics help alleviate drug shortages," said Goetz, who wrote the chapter on metrics in I*SPE Drug Shortages Prevention Plan*,[17] which includes a suggested list of performance indicators that could be used to assess a quality metrics program. "But the metrics we highlight are not necessarily the standardized metrics that are in the FDA's draft guidance and are not advocated for consistent cross-industry implementation. Rather the key message there is selection of the KPIs that are pertinent to the risk at hand. There is potential for confusion."

"FDA proposed standardized metrics might well help predict the potential for drug shortages, but from ISPE's perspective, we're not sure how," Potter said. "We haven't seen any published or public information showing that they will alleviate drug shortages."

In addition to supporting the FDA's overall effort to implement the QM program, ISPE responded with six other points with clear rationale justified based on the findings of its Quality Metrics Pilot Program:

1. ISPE believes the program needs to start with a small, targeted approach, so both industry and the FDA can learn and evolve the program over time.

2. ISPE recommends a phased introduction that will maximize learning, minimize burden on both the industry and FDA and enhance the chances of a successful implementation such as allowing clear benefits to be evident. ISPE suggests voluntary reporting for firms that are not participating during the initial period with a possible incentive of reduced inspection frequency.

   In their responses to the draft guidance, a number of organizations also want the FDA to take a phased approach to implementation, including the Pharmaceutical Research and Manufacturers of America (PhRMA), the Biotechnology Industry Organization (BIO) and the Generic Pharmaceutical Association (GPhA).[18, 19, 20, 21]

3. ISPE advocates starting with only three of the proposed metrics:

- Lot Acceptance Rate (report by site differentiated by product, evolving to product differentiated by site)
- Product Quality Complaint Rate (report by product only)
- Invalidated Out-of-Specification Rate (report by site)

Additional clarity is requested on definitions

It is very important that definitions are clear and have the most appropriate denominator.

ISPE also addressed the issue of collecting metrics from contract manufacturing organizations (CMOs). Currently, the quality data the FDA wants to collect is not routinely gathered or shared between CMOs and license holders. This will add an additional burden on firms and CMOs because the license holder prior to its submission should verify the data. Thus, ISPE recommends that data be reported by the CMO after agreement of the data with the license holder.

4. ISPE recommends deferring some metrics and data points, including APR or PQR on Time Rate, optional metrics related to quality culture and process capability and the complementary data point of "lots pending disposition for over 30 days", given the relatively high burden for collection.

5. ISPE is concerned that the burden to the industry is underestimated, based on the industry's experience, both in terms of upfront investment and ongoing cost. The burden estimate should include the additional time required to collect the proposed metrics, the anticipated costs to establish routine governance practices, adjust internal IT systems and incorporate additional review and retention of data to support verification during inspection.

   ISPE considers that the recommendations given above will contribute to reducing the burden with the additional recommendation that data are reported annually rather than quarterly.

6. ISPE requests greater transparency in the manner in which data will be assessed, and outcome and conclusions determined and communicated.

ISPE was engaged in in the Cross-Industry Quality Metrics Collaboration Group, which represents interested parties across the pharmaceutical industry, including PhRMA, BIO, GPhA and others.[16] This group proposes that quality metrics should be part of a continual improvement program, not used as a punitive measure; and requested that the FDA adopt a phased-in approach to its quality metrics program. The Collaboration Group also recommended that:

- The reporting period begin at least six months after the FDA issues its final guidance
- Reporting be done annually with specific submission dates determined by each firm to balance workload and align with existing quality system procedures
- Trending should be incorporated into the analysis model
- The FDA provide time to make adjustments and provide clear guidance about who is accountable for reporting which metrics
- The FDA clarify if and under what circumstances API manufacturers should report their own data and how that date should be reported

"The feedback we got from our colleagues who participated in Wave 1 suggested that the logistics of implementing a program like this are enormous, which is a challenge for both the FDA and industry," Potter said. "It involves getting the definitions right, then having the industry and the agency know how to collect and manage the data. For us, the $64,000 question is, once the FDA has all this information, what is it going to do with it? Analyzing the information to get some benefits will be a huge challenge and hence small, carefully managed steps are appropriate."

Toward a more self-regulating industry

"For ISPE, the short-term perceived benefits of this program include reduced inspection frequency, say from annual for some to every two years for others," Goetz said.

The FDA has suggested that recognition of a company's robust quality system program would offer a perceived benefit among one's peers. A company might, for example, list its ranking in an FDA classification system, say as a Tier 1 or Tier 2 manufacturer. "ISPE doesn't necessarily see it this way," Goetz said, "but you will see that in the discussion."

"It's possible that, with classification, you could assess your partners – CMOs or joint venture partners – more robustly than you can now," said Potter. "It might help with your selection criteria."

Goetz suggested that the biggest benefit from an industry perspective could be to improve the post-approval change process. "This could lead to less agency reporting, which will facilitate navigating the global regulatory post-approval change process and the complicating differences that exist in this landscape," she said. "There's a deliberateness around making changes today because of the complexity of the process. So some changes are not made because of the burden of the process."

Goetz reflected that having standardized quality metrics could provide assurance to agencies about the level of compliance. This should, in the long term, give them confidence in the ability of industry to self-regulate.

"This may be a step in the journey to provide more flexibility and agility within the industry," Goetz said. "The upside for us is we'd have more latitude to be self-controlling. Janet Woodcock says the industry needs to lead continual improvement ourselves. If we realize the benefit of, for example, post-approval changes, it is getting closer to the vision of industry being in control of its own destiny. The FDA believes that these metrics could indicate the system's health and the likelihood we can be self-controlling, with less regulatory oversight. Time will tell."

There's an aspect to Potter's vision of a successful future that is also long-term, though he considers it "a bit of blue sky."

"If industry could report information including quality metrics that is understood and trusted globally by regulators, then there is a potential to reduce the burden of multiple inspections by various inspectorates," said Potter. "There would be more reliance on companies to provide information than on inspectors turning up. It's not a stated goal of the FDA, but it could be at the back of the minds of senior quality leaders in the industry."

In keeping with that same longer term vision, Goetz believes the FDA's quality metrics program could, as a side effect, drive a lot more collaboration and benchmarking between firms. They might be willing to share metric structure and best practices about metric performance. For example, what is the difference between the quality system at a Tier 1 and a Tier 2 manufacturer?

"The conversations I see happening in executive boardrooms around quality system performance and continual improvement are compelling," Goetz said. "The needle has moved in the quality metrics dialogue." ■

By James Hale and Scott Fotheringham, PhD

References

1. US Food and Drug Administration. "Warning Letters 2015." http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/ucm432949.htm#OC.
2. ———. "Current and Resolved Drug Shortages and Discontinuations Reported to FDA." http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm.
3. ———. "Drug Recalls." http://www.fda.gov/Drugs/DrugSafety/DrugRecalls/default.htm.

4. ———. Food and Drug Administration Safety and Innovation Act. Sec. 705: Risk-based inspection frequency. http://www.fda.gov/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCAct/FDASIA/ucm366058.htm.
5. US Government Accountability Office. "Drug Safety: FDA Faces Challenges Overseeing the Foreign Drug Manufacturing Supply Chain." 14 September 2011. http://www.gao.gov/products/GAO-11-936T.
6. Medina, C., and F.J. Richmond. "Incentivizing Quality in the Manufacture of Pharmaceuticals: Industry Views on Quality Metrics and Ratings." *Therapeutic Innovation & Regulatory Science* 49, no. 5 (2015): 730–738.
7. "FDA Cites Data Integrity Issues in All 8 Warning Letters to API Makers." *FDA News*, 4 December 2015. www.fdanews.com/articles/174338-fda-cites-data-integrity-issues-in-all-8-warning-letters-to-api-makers.
8. Palmer, Eric. "Dr. Reddy's Blasted in Warning Letter for Hiding Existence of Testing Lab from FDA." 24 November 2015. http://www.fiercepharma.com/story/dr-reddys-blasted-warning-letter-hiding-existence-testing-lab-fda/2015-11-24?utm_medium=nl&utm_source=internal.
9. "Dr. Reddy's Laboratories Limited 11/5/15." www.fda.gov/ICECI/EnforcementActions/WarningLetters/2015/ucm473604.htm.
10. US Food and Drug Administration. Food and Drug Administration "Drug Shortages Task Force and Strategic Plan; Request for Comments." *Federal Register* 78, no. 29 (12 February 2013). https://www.gpo.gov/fdsys/pkg/FR-2013-02-12/html/2013-03198.htm.
11. US Food and Drug Administration. "Request for Quality Metrics." Guidance for Industry. July 2015. www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm455957.pdf.
12. US Food and Drug Administration. "Quality Metrics Public Meeting." 24 August 2015. http://www.fda.gov/Drugs/NewsEvents/ucm456083.htm.
13. ———. "Quality Metrics Public Meeting." Presentations. 24 August 2015. http://www.fda.gov/Drugs/NewsEvents/ucm456083.htm.
14. *International Pharmaceutical Quality*. "Update by CDER Director Janet Woodcock on FDA's 'Quality Revolution.'" http://www.ipqpubs.com/wp-content/uploads/2015/05/Woodcock-box-for-STOM.pdf.
15. *International Pharmaceutical Quality Monthly Update* 6, no. 3 (April/May 2015). www.ipqpubs.com/wp-content/uploads/2015/06/IPQ-Monthly-Update-April.May-2015.pdf.
16. ISPE. "Quality Metrics Program – Draft Guidance Comments to FDA." iSPEAK blog entry, 2 December 2015. http://blog.ispe.org/?p=2701.
17. ISPE. *ISPE Drug Shortages Prevention Plan*. October 2014. http://ispe.org/drugshortagespreventionplan.pdf.
18. Mezher, Michael. "Industry Calls for Clarity, Phased Approach for Quality Metrics." Regulatory Affairs Professionals Society, 4 December 2014. http://www.raps.org/Regulatory-Focus/News/2015/12/04/23718/Industry-Calls-for-Clarity-Phased-Approach-for-Quality-Metrics.
19. PhRMA. Response to Request for Draft Guidance. 24 November 2015. http://src.bna.com/bkT.
20. Generic Pharmaceutical Association. Response to Request for Draft Guidance. 25 November 2015. http://src.bna.com/bkQ.
21. Biotechnology Industry Organization. Response to Request for Draft Guidance. 24 November 2015. http://src.bna.com/bkP.

Looking at quality metrics in the auto industry

No matter how robust a quality metrics program is, it can't prevent cheating, as Volkswagen has shown. Since the carmaker was caught programming its diesel vehicles to evade emissions controls except during testing, it has been forced to recall 482,000 vehicles.[1] Given this, it may seem counterintuitive to look to the auto industry as a model for comparisons to the current discussions about quality metrics in pharma manufacturing. However, automotive manufacturing, like pharmaceuticals, is a must-not-fail enterprise that demands adherence to a complex combination of government regulation and internal quality control.

Pharmaceuticals manufacturing, is a must-not-fail enterprise that demands adherence to a complex combination of government regulation and internal quality control.

"This is a wonderful time for the auto industry to really forge forward in terms of quality," said Danica Kelso who teaches in the Automotive Business program at Georgian College in Barrie, Ontario. "As a result, technologies and practices will continue to change and evolve with the end result of a better product, better sales and content consumers."

As in drug making, automakers have dozens of quality metrics, measuring such things as parts-per-million defects, supplier improvement, customer satisfaction and severity incidents per billion.

"European, Asian and North American manufacturers share and use these metrics to improve their products and productivity," Kelso said. "It also allows manufacturers to better measure themselves, not only against their fellow competitors, but also to assess a manufacturer for possible future acquisitions or mergers."

A notable difference in the auto industry is that a supplier, with its own internal quality management system, may be producing dozens of different parts, for many automakers, each of which has its own quality and process standards. This contrasts with Big Pharma's outsourcing of drug production to suppliers that make one or, at most, a few different products for them.

To deal with this, the IATF, an ad hoc group of automakers and trade associations, developed a technical spec that functions industry wide. ISO/TS 16949 includes requirements such as the development of a supplier quality management system, specs for processes such as heat treating, plating, coating and soldering and measurement system analysis.[2] Certification is almost always a requirement of supplying parts or services to an original equipment manufacturer.[3]

Kelso noted that these standardized specs mean that manufacturers "can easily compare themselves not only to other manufacturers belonging to TS 16949, but can also compare plants and products within individual companies. This type of data could be used to determine which plant has the best quality to produce specific products."

In addition to the technical standard, suppliers of production materials, service parts and finishing services must refer to each automaker's customer-specific requirements (CSRs).[4] Although automakers strive to align these internal requirements to the technical specification,[5] the non-standardized nature of individual CSRs can result in a burden on the whole supply chain, adding a level of complexity without necessarily improving quality.[6]

A recent article comparing the current state of drug manufacturing to that of the US auto industry prior to the 2008 economic collapse, points to drugmakers' lack of attention on quality and quality metrics. Prabir Basu argues that this could be remediated if government and industry copied the auto industry and "encourage investment in fundamental science and engineering to design and manufacture pharmaceutical prod-

ucts. Greater savings can be easily achieved with innovative science and technology."[7] This, at a time when Big Pharma actually spends far more on marketing than it does on R&D.[8]

"The recent quality metrics guidance will not ultimately make a particularly large impact, as the metrics does not have any teeth, it does not reflect the quality culture," Basu wrote. "Manufacturing the metrics to look good is easy."

At times, too easy, as the scandal at Volkswagen shows. According to Lynne Frances Baxter, a researcher and senior lecturer in management systems at the University of York, manipulating metrics is a common problem. "There has long been a culture of gaming metrics in the automotive industry and other sectors do it too," she says.[9]

Despite the errors and deceit that does go on, the mix of external and internal regulation in automotive production provides useful insight for the current discussion of quality metrics in drug making. ■

By James Hale And Scott Fotheringham, PhD

1. The Economist – Can the Carmakers' New Boss Drive it out of Trouble? http://www.economist.com/news/21668232-its-deepening-crisis-volkswagen-has-stuck-tradition-has-not-served-it-well-can?zid=293&ah=e50f636873b42369614615ba3c16df4a
2. IATF – About the International Automotive Task Force. http://www.iatfglobaloversight.org/content.aspx?page=AboutIATF
3. IATF – PSA Peugeot Citroën Customer-Specific Requirements. http://www.iatfglobaloversight.org/docs/PSA_Peugeot_Citroen_CSR_v1_november_2013.pdf
4. IATF – OEM Customer-Specific Requirements. http://www.iatfglobaloversight.org/content.aspx?page=OEMCustomer-SpecificRequirements
5. IATF – Ford Motor Company Customer-Specific Requirements. http://www.iatfglobaloversight.org/docs/FordspecTS_Nov2015.pdf
6. *Customer-specific QM Systems Requirements*. Synopsis viewed at http://webshop.vda.de/QMC/product_info.php?cPath=23_24&products_id=168
7. CPhI – Looking Beyond the Global Pharma Horizon: Innovation – can Pharmaceutical Manufacturing Learn from the Lessons in Auto Manufacturing in the US? http://www.cphi.com/documents/129623/981416/CPhI+annual+rep+2015+v9f+part3.pdf/85eb60c0-7123-4b8b-b435-e7e9a362a231
8. The Washington Post – Big Pharmaceutical Companies are Spending Far More on Marketing than Research. https://www.washingtonpost.com/news/wonk/wp/2015/02/11/big-pharmaceutical-companies-are-spending-far-more-on-marketing-than-research/
9. The Conversation – VW is not alone: how metrics gaming is commonplace in companies. http://theconversation.com/vw-is-not-alone-how-metrics-gaming-is-commonplace-in-companies-48393

Look outside, not just inside

Quality benchmarking is vital to provide a stimulus for improving quality. However, benchmarks have often been scarce or hardly comparable. Now that benchmarking is becoming ubiquitous and also supported by industry-standard Quality Metrics, knowing where you stand is becoming the new standard. Furthermore, benchmarking reveals the large gaps that exist in process and product maturity between different sites and firms.

In the pharmaceutical industry, KPIs typically showcase large differences in quality performance between sites and between firms.

The pharmaceutical industry has long been and still is a bastion of science and science-based operations. Clearly, there is a desire to learn from the best scientific information. But in practice the learning is often limited. The first question that is often asked is whether quality is actually measurable and comparable? The work in quality benchmarking but also in ISPE Quality Metrics answers that question: most firms do measure quality. With effort, it is even possible to standardize definitions and to find reasonably comparable information. Enough to draw interesting learnings.

Secondly, regulation in the industry has grown around securing patient safety after incidents have happened. Therefore, much documentation in the industry is batch-based, incident-based or product-based. Useful learning actually comes from opening the aperture far wider. Interesting benchmarks can be found across value chains, not just along value chains. Many of the KPIs we have are lagging, rather than leading. Regulators have seen this and have been asking firms more and more for systematic root causes and systematic learning - but metrics have not caught up. Cross-company learning mechanisms are far and few between. Cross-company learning is actually much more common and even institutionalized in some other highly regulated industries, like nuclear power or aviation.

Benchmarking can play a useful role to stimulate that learning. In the pharmaceutical industry, KPIs typically showcase large differences in quality performance between sites and between firms. We see this whether we compare KPIs like first-time-right, the number of deviations per batch, yields, cost of quality or speed and productivity of the quality system. Differences of performance between sites from the median in the industry to best-of-best can be as large as a factor 4-10. The pharmaceutical quality system is set-up to correct any errors before they reach the market - but it is still an uncomfortable fact that there is so much room for improvement.

If the pharmaceutical industry were a commodity industry producing widgets, this kind of disparity in performance would be quite detrimental to lower-performing firms. Quality of pharmaceutical products however is not transparent to customers - and even only partially to regulators. Hence, we see the primary audience of this information as the pharmaceutical firms themselves, since they have the ability to understand this information and to act upon it.

What would best-of-best quality look like?

To get an idea of what a best-of-best site would look like in terms of quality performance, we consider some of today's benchmark sites out of McKinsey's POBOS Quality benchmark and combine their best-of-best performance across various dimensions (Exhibit 1). That hypothetical site would demonstrate quality performance unlike anything seen yet. Consider these possibilities:

- The site has zero recalls, no adverse events, and close to zero confirmed complaints.
- Shop-floor processes are incredibly reliable, with a right-first-time, end-to-end record of at least 99%.
- The site's quality systems operate effectively and fast, leading to less than 1 percent recurrence of deviations.
- This future site has only one quality assurance (QA) full-time equivalent (FTE) per 1,000 batches instead of the approximately ten common today.

In sum, the performance of this best-of-best site would be an order of magnitude closer to flawless performance compared with today's above-average performing sites—simultaneously hitting new heights not only with quality but also with productivity and speed.

So what would it be like to visit this "perfect" pharma site? We believe that if you spoke with any operator there, you would quickly sense that everyone considers quality his or her responsibility. You would realize that people shoulder this responsibility without expecting to depend on a large,

dedicated quality function focused on checks and controls. You would also see that the site's quality system runs less on detailed operating procedures and more on deep process knowledge, a strong quality culture, and clear values.

Moreover, your visit would show you that the paper burden on operators is very light. That's because the majority of critical-to-quality (CTQ) parameters are captured automatically, requiring little manual verification. This best-of-best site is also making extensive use of advanced analytics systems to make processes more reliable; its analytics tools have vastly improved the availability of data on true root causes of typical quality problems. It would also be apparent that the site's operators truly understand the science behind their products. Thanks to simplification, the processes they use are inherently robust. Operators can therefore devote the bulk of their time and energy to preventing future quality issues rather than having to deal with past problems.

Clearly, if we believe that we can achieve benchmark performance, pharmaceutical quality could look fundamentally different in 2030. Companies that could achieve the levels of performance described above could even gain strong competitive advantage. The ability to produce at much higher quality translates into significant cost savings, a stronger reputation, and better profit margins and thus could even alleviate pricing pressures as more products become generic.

The way forward

We think benchmarks also point to a different role that the Quality function should be playing, and how quality is perceived. Quality employees are frequently perceived as"police officers" who check and control adherence to standards and enforce bureaucratic requirements, or as "firefighters" who arrive on the scene to prevent issues from growing into catastrophic events. Quality procedures are seen as overly bureaucratic and too complex, perhaps better suited to meet regulators' increasing expectations but not to achieve the ultimate goal of improving patients' lives. These perceptions are a source of frustration for the entire industry because they place quality in a no-win situation.

Most executives are aware of quality's "inspiration gap" and acknowledge that closing it will require significant effort—but yield great benefits. As a first step to closing the gap, they will need to convince their organizations that inspiration and quality improvement are inextricably linked.

Inspiration is the starting point for each change a business organization seeks to make, whether to catch up to the industry average or to improve from "good" to "great." At companies that are lagging behind their industry peers, inspiring stories of success can open employees' eyes to the gap between their current performance and best practice and motivate them to start the journey toward greatness. For companies that are on par with their industry peers, inspiration is particularly important for dispelling employees' complacent beliefs that "everything is good" or "we are doing fine." Examples of what superior performance looks like can provide a case for action that motivates employees to overcome their complacency and pursue new avenues to success.

Externally, managers can first look to competitors within the pharma industry for inspiration. Understanding how these competitors advance quality can be best experienced through site visits. Engaging in real discussions with colleagues, consultants, and academics can help. Participation in industry benchmarking exercises can help to start to understand what best in class means. A benchmarking study will provide relevant insights into a company or site's quality performance relative to its competitors and highlight the corresponding best practices.

Inspiration is the starting point for each change a business organization seeks to make, whether to catch up to the industry average or to improve from "good" to "great."

External inspiration can also be found beyond pharma, from other industries that have faced similar challenges or are strong in certain functional or technical areas. For example, some automotive plants have used innovative approaches to foster quality awareness. Executives at one injection-molding plant, for instance, put defective parts on display in the plant's cafeteria. The "parade of ugly parts" raised awareness of the issues and motivated employees to discuss how to improve quality. Another automotive company sent all employees a package bearing the message, "See who's responsible for quality." Employees found a mirror when they opened the package. Other companies post this message next to the restroom mirrors. As another example, nuclear power companies have a mind-set of reporting and addressing every near miss—not only incidents that actually occur. They are also very adept at detecting low-likelihood but high-impact events - a much more leading rather than reactive way of managing quality. Subsequently, they share these issues in global forums so that their lessons.

We believe that there is a bright future for operations and quality leaders who know how to turn benchmarking into a true source of inspiration and learning. There is a world of performance improvement out there, starting with the first step of believing that you yourself can never be perfect - but that permanently striving for perfection is a worthy struggle. ■

About the authors

Paul Rutten is an Expert Principal at McKinsey & Company in Amsterdam. He joined McKinsey in 1998 and is leading the Quality, Compliance and Remediation practice of McKinsey with a focus on Europe. He is the sponsor of McKinsey's POBOS Quality benchmark and of McKinsey's involvement in the ISPE Quality Metrics initiative.

Vanya Telpis is a Director of Knowledge at McKinsey in New Jersey. She joined McKinsey in 2002 and is the Practice manager of the Quality, Compliance and Remediation Practice of McKinsey. She is the founder of McKinsey's POBOS Quality benchmark and is a team member of the ISPE Quality Metrics team.

Note: this article contains excerpts from "Flawless: From Measuring Failure to Building Quality Robustness in Pharma", McKinsey & Company, July 2014, edited by Paul Rutten, Vanya Telpis et al. The book contains further reading on Quality metrics, inspiration for quality and using site visits as a journey of inspiration. The book can be ordered via the McKinsey.com website.

Cultural Excellence: Ensuring that "Culture of Quality" is more than just a slogan

The ISPE Quality Culture team, operating under the auspices of the current ISPE Quality Metrics Initiative, launched their "Six Dimensions of Cultural Excellence" framework at the Quality Metrics Summit held in Baltimore in April 2015. In this article, Nuala Calnan, team co-lead, shares some insight on the subject of quality culture and outlines the work the team is undertaking to develop a series of practical tools, templates, and training for use by the industry to support the implementation of the cultural-excellence framework.

Since the February 2013 publication of the *US Food and Drug Administration [FDA] Drug Shortages Task Force and Strategic Plan; Request for Comments*, announcing the FDA's intention to explore the use of manufacturing quality metrics to assist in the evaluation of product quality, there has been much talk about the role that culture plays in an organization's manufacturing quality performance.

The FDA's recent draft guidance *Request for Quality Metrics Guidance for Industry* brought with it an acknowledgment of its ongoing quality concerns, noting that it has "not fully realized [its] 21st-century vision for manufacturing and quality—there continue to be indicators of serious product quality defects."

Culture remains on the agenda as a potential means to resolve these challenges with its inclusion as one of the topics singled out for "specific request for comments and information" by the FDA in the draft guidance. The FDA invited input on its proposed "optional" metrics related to quality culture and the extended commenting period closed on 27 November 2015. The dialogue with the industry continues, and the ISPE Quality Culture team has responded to the call.

Much of the talk about culture has emphasized the need for the pharmaceutical industry to engender a "culture of quality," but what does this mean, and what are we actually talking about when we talk about culture?

What are we talk about when we talk about culture?

"The way we do things around here..." – Marvin Bower (Bower, 1966)

The concept of corporate culture has been the subject of much debate over the past 50 years. Marvin Bower's well-used phrase, quoted above, so simple in construction and sentiment, belies the underlying complexities of culture. Edgar H. Schein, another noted expert on organizational culture, identifies culture as an abstract concept— difficult to describe and comprehend—yet the forces that derive from it are powerful, and he cautions that "if we don't understand the operation of these forces, we become victim to them." (Schein, 2004)

Schein's simple definition of culture, similar to Bower's, is "how we perceive, think about, and feel about things"; it formally links behavior and culture by indicating that behavior is a *derivative* of culture. It is this link to behavior that provides a concrete means to understand and interpret the operation of the powerful forces he warns of and offers a focus for action for those in the pharmaceutical industry seeking to improve their quality culture.

> Schein formally links behavior to culture by indicating that behavior is a derivative of culture.

Transforming the cultural DNA of the pharmaceutical industry

Schein also proposes that the prevailing cultural paradigm can be thought of as critical "genes" in the cultural "DNA" of an organization. To map these links between culture and behavior, he extends the analogy: If the total set of shared basic assumptions of a given organization's culture can be thought of as its DNA, then individual genes can be examined in terms of their potency in forcing growth in certain kinds of (desired) behaviors while other genes inhibit or prevent specific (undesired) behaviors.

This concept lends itself to envisioning a genetic reengineering of the cultural DNA of the pharmaceutical industry from a *compliance-led* culture to an *excellence-led* culture of quality. The author holds that the traditional culture of compliance is a fatal flaw ingrained in the DNA of the pharmaceutical industry. The evolution toward a culture of quality will require a reordering of the sequence to build a double helix, strengthened by a combination of *patient focus* and *excellence*. This concept is depicted in Figure 1:

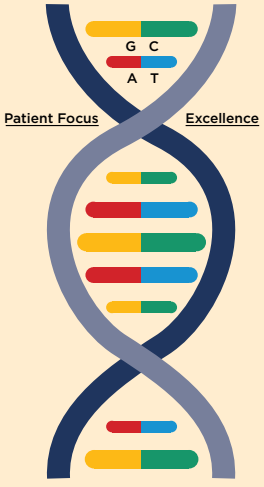


Figure 1: Transforming the cultural DNA of the pharmaceutical industry (Calnan, 2015b)

(Image reproduced with permission of the author)

This transformation of the genetic building blocks facilitates the identification and selection of the "desired" behaviors in order for them to be "hardwired into new habits so that employees can become assets to, and champions of, the transformation effort." (Morse, South, and Gideon, 2013)

Compliance versus quality: the transformation towards excellence

Let us imagine that a compliance-led approach to quality provides quality with a small "q," narrowly focused and limited in scope. Whereas, an excellence-led approach to quality provides quality with a big "Q," enabling protection for the patient and offering an integrated, holistic business excellence strategy.

In her plenary address at the September 2014 PDA/FDA Joint Regulatory Conference, Janet Woodcock, Director, Center for Drug Evaluation and Research, addressed this culture of compliance versus culture of quality head-on. She stated that in order for the industry to *own* quality, everyone from the "shop floor to the CEO must be fanatically committed to high quality—*not* to compliance."(Woodcock, 2014)

Explaining that a culture of compliance requires that you meet someone else's expectations, whereas a culture of quality means that you are trying to meet your own expectations, Woodcock acknowledged that it is a journey. She proposed that the FDA cannot mandate for this—it can only foster a culture of quality. Realistically, this desired state can only be achieved through the inclusive interaction between the pharmaceutical industry and the regulators, working together to deliver this outcome for the patient.

Leadership's role in delivering behavior-based quality

Critical to this transformation are *enabled leaders* who build a case for change and whose own behaviors accelerate the adoption of the new way at all stages of the transformation through an *engaged workforce* that is motivated and mobilized in the change effort. In order for employees to become passionate about eliminating mistakes, leadership and credibility of vision must be evident to motivate and sustain a culture of quality, and there is a growing awareness within the pharmaceutical industry about its impact. (Friedman, 2014; IPQ, 2014; ISPE, 2014; Paulson, 2013; Skibo, 2013)

Indeed, Woodcock has persistently provided both leadership and vision over the past decade as one of the most outspoken international regulators on the subject of product quality and, more specifically, manufacturing quality. She reminds us of how high the stakes are "because the consequences of quality problems such as sub-potency, lack of sterility, or product mix-ups can be so devastating." (Woodcock, 2012) The role of leadership in fostering and developing a vision for quality formed the starting point of the Six Dimensions of Cultural Excellence framework. (Calnan, 2015a)

The six dimensions of cultural excellence

The ISPE Quality Culture team, operating within the ISPE Quality Metrics Initiative, came together in July 2014 to develop a response to the question of whether it was possible to measure or quantify the impact of culture on the quality outcomes that matter to the patient.

The team, involving collaboration between industry and academia, shared insights gained from their experiences, programs, practices, and research. It soon became clear that no single tool or practice provided either a quantitative or qualitative "silver bullet" as a means to establish the current health of the quality culture within an organization.

This work led directly to the development of a cultural-excellence framework encompassing six different yet integrated dimensions of cultural excellence. (See Figure 2.) Taken together, these dimensions provide a pathway for an organization to foster and develop, monitor and measure, and learn and improve key areas that influence both culture and the underlying behaviors.

Work has now commenced on the development of tools, templates, and training resource materials within each of the individual dimensions.

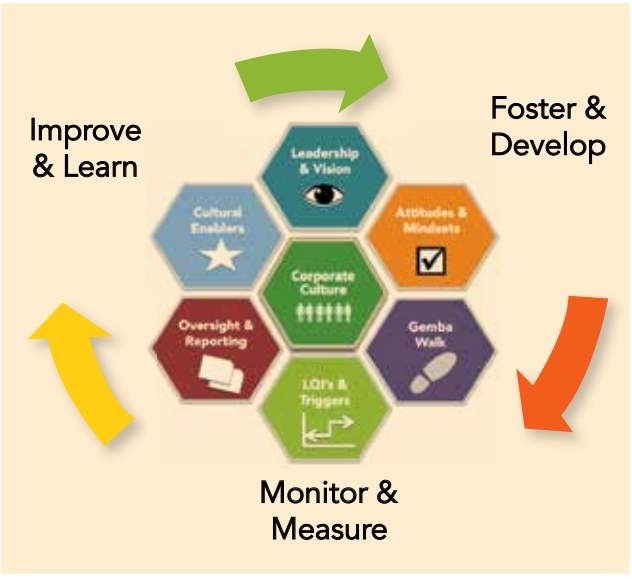


Figure 2 : The Six Dimensions of Cultural Excellence

Context is crucial

A key tenet of ISPE's position on quality culture lies in the acknowledgment that each organization will have a different context within which its quality culture exists. This may be based on an amalgamation of influences, including organizational ownership and history, supply-chain configuration, maturity, product mix, and regional influences. At an individual site level, this can be further impacted by ready access to qualified staff, language, and the influence and maturity of the local regulatory authority.

Knowledge of this context and its impacts is crucial when assessing, or planning to develop, the health of the culture at a given facility. The Six Dimensions of Cultural Excellence framework incorporates elements that enable the capture of this context, such as in its use of Gemba walks to enable open dialogue, coaching, and active listening.

An outline of the holistic framework

The cultural-excellence framework opens with the "Leadership and Vision" dimension, which focuses on establishing and engendering the quality vision through leader-led behavior. Resources in this area will incorporate the 5V concept (Visibility, Vigilance, Vision, Voice, and Values):

- Visibility: Leader's presence, Gemba, what he or she gives priority to/reacts to
- Vigilance: Leader's ability to drive accountability, grit, focus, follow-through
- Vision: Leader's strategy, game plan, unifying goals, mantra
- Voice: Leader's passion, credibility, authenticity, clarity, motivational ability
- Values: Leader's guiding principles, ethics, behavior, humility, empathy

The second dimension is understanding and influencing the "Attitudes and Mindsets" of the employees within the organization. This examines the relationship between the prevailing employee attitudes and mindsets and the actual behaviors practised in the day-to-day execution of tasks. Employee-engagement surveys, focus groups, and other mechanisms used to inform management of the current status of culture within their firm are under development, including best practices in closing the loop following the receipt of feedback from employees.

The third dimension is pivotal to the framework and involves assessing the behaviors through the use of "Gemba Walks." This is closely linked to the leadership elements described above and is a key engagement and communication tool. When used effectively, Gemba walks provide an opportunity to unify and motivate and facilitate accountability and recognition. They are a powerful operational excellence tool, and their role in cultural-excellence development is key.

The framework then moves to those elements related to the monitoring and surveillance of key "Triggers and Leading Indicators of Quality (LQI)." In acknowledgment of the Peter Drucker truism "What gets measured gets managed," the role of measurement in driving the desired behaviors is included in the model. These triggers and LQIs will not reflect the traditional quality performance metrics. Rather, they will focus on the selection of meaningful measures that target specific behaviors to promote prevention rather than a cure.

In closing the loop on the variety of surveys of attitudes, assessments of behaviors, and surveillance of targets and results, the fifth dimension explores tools to facilitate the proactive "Oversight, Reporting and Reviews by Leaders." This dimension focuses on how best to integrate and convey the outputs of the various assessments and measurement tools in order to provide "heat maps" of where the current strengths and weaknesses lie to facilitate action by leaders.

Finally, the framework is completed through reflection on the "Cultural Enablers" required to build competencies in areas such as:

- Learning organization development and the development of learning teams
- Influencing and recognizing change
- Proactive problem solving and getting to the true root cause

In summary, this cultural-excellence framework seeks to provide a comprehensive set of practical tools and principles to enable organizations to move beyond sloganeering and deliver real and sustainable improvements in the behaviors that matter to their patients.

I would like to acknowledge the commitment and dedication of the many volunteer team members who persist and inspire this work. We look forward to sharing the outputs with you in the coming year. ■

By Nuala Calnan, PhD, Dublin Institute of Technology, Ireland

Bower, M. (1966). *The Will to Manage: Corporate Success through Programmed Management* (p. 276). McGraw-Hill.

Calnan, N. (2015a). Culture of Quality: More than a Slogan. In ISPE (Ed.), *Quality Metrics Summit,* Baltimore.

Calnan, N. (2015b). *Protecting the Patient: Enhancing the Quality of Pharmaceutical Products,* Thesis.

FDA (July 2015) *Request for Quality Metrics Guidance for Industry*.

Friedman, R. L. (2014). Quality Systems and Lifecycle Compliance. In *ISPE Annual Meeting* 12–15 October 2014, *Las Vegas, Nevada* (pp. 1–11).

IPQ. (2014). New CMC Submission Approach Needed to Foster Transparency and Continuous Improvement, PhRMA Team Says; Embedding Control Strategy as Regulatory Commitment in QOS Proposed | IPQ Newsletter. Retrieved 5 October 2014.

ISPE. (2014). I*SPE Drug Shortages Prevention Plan*.

Morse, N., South, N., & Gideon, W. (2013). " Succeeding at the 'Harder' side of Change: The 'ABCs' of High-Performance Behavior" In *Leading Pharmaceutical Operational Excellence* (pp. 227–244).

Paulson, B. (2013). "FDA's Center for Drugs Redoubles Effort to Achieve 21st Century Quality and Foster Continuous Process Improvement" IPQ Newsletter. Retrieved 6 October 2014.

Schein, E. H. (2004). *Organizational Culture and Leadership* (3rd Ed., p. 437). John Wiley & Sons.

Skibo, A. R. (2013). "Outsourcing & Emerging Markets v's Quality and Drug Availability." *Creating, Implementing, and Sustaining a Culture of Quality: Putting the c into cGMP*. Baltimore, Maryland, USA: ISPE.

Woodcock, J. (2012). "Reliable Drug Quality: An Unresolved Problem." *PDA Journal of Pharmaceutical Science and Technology* / PDA, 66(3), 270–2. doi:10.5731/pdajpst.2012.00868

Woodcock, J. (2014). Culture of Quality: CDER Director Dr. Janet Woodcock's Plenary Address. In 2014 PDA/FDA Joint Regulatory Conference.

SAVE THE DATE!

ISPE 2016 Annual Meeting and Expo

Education Tracks:

- End-to-End Supply Chain Management
- Facilities and Equipment
- Information Systems
- Innovation Forum
- Product Development and Production Systems
- Regulatory Compliance and Quality Systems

Atlanta, Georgia

18–21 September | Marriott Marquis

www.ISPE.org

ISPE

Metrics for the Clinical Trial Material Supply Chain

Steven Yoder, Sandra Cook and Douglas Meyer

This article introduces the concept of clinical supply chain metrics and proposes a rationale and framework for standardization.

Metrics have become heavily embedded in the business culture of all top-performing organizations. As Peter Drucker once famously said, "What's measured improves." Companies that embrace the principles of "Plan, Do, Check, Act," however, understand clearly that while a robust set of metrics are central to the check step, the temptation to measure everything must be avoided.

While in some cases running the metrics is as simple as running a report; assembling the monthly metrics readout often means pulling data from several different sources, scrubbing and analyzing the data, and then ultimately putting them in presentation format along with the story the metrics are telling.

Metrics themselves typically cannot stand alone. They are most effective when incorporated into an established governance process. This typically involves regularly scheduled meetings and standard reporting mechanisms such as dashboards. Metrics should have established targets for acceptable and unacceptable limits, along with a clear path for escalation and action planning, should performance fall outside an acceptable range.

A solid operating system for running an enterprise typically includes both leading and lagging metrics. Leading metrics show trends that reveal problems as they begin to develop, allowing immediate action to avoid a bigger problem. Lagging metrics answer basic questions such as "Did we hit our deviation reduction target last month?" Both types are valuable.

Comprehensive supply chain metrics

While the objectives of supply chain metrics are applicable to multiple industries, the details of the metrics themselves may require customization, depending on the nature of the supply chain they are intended to manage. This article explores the customization of supply chain metrics for the clinical trial material (or investigational products) supply chain. In some cases, traditional supply chain metrics such as on-time delivery are directly applicable. The very nature of clinical supply chain management, however, includes unique but important elements that are worth measuring (such as accuracy of trial enrollment predictions and screen/failure rate of potential participants).

Many clinical supply organizations have developed their own key performance indicators (KPIs) and measure performance both in their own groups and in those closely linked in the supply chain. For example, the demand for investigational product is driven from the clinical side of the business; this means both the quality of information and the timeliness of communication are critical to a successful response. Furthermore, many companies outsource clinical supplies operational activities to service providers. As a result, these contract organizations receive their demand from the clinical supplies group of the sponsor company.

Given this complexity, leading and lagging metrics that ensure performance objectives are being met become even more important. The clinical team provides forecasting information to the clinical supplies team and has service-level expectations. The clinical supplies team depends on that forecast to provide requirements to the service provider, and has performance expectations as well. Finally, the service provider wants to meet these expectations, but part of their ability to execute successfully depends on input from their customer. Thus, the relationship between the clinical team and the clinical supplies team is not unlike the relationship between the clinical supplies team and the service provider. These intricate relationships indicate the need for a comprehensive and robust set of metrics to ensure the supply chain is performing optimally and efficiently.

While individual clinical supply organizations have developed their own metrics, the investigational products community has not yet homed in on the most relevant KPIs, conducted benchmarking, or targeted a common set of metrics with associated performance standards.

CoP task team

Recognizing the potential benefit in doing that, the ISPE Investigational Products Community of Practice (CoP) has assembled a task team to address this need. The team is comprised of global representatives with both sponsor and service-provider expertise who share over 100 years of industry experience. This article is intended to initiate awareness of the task team's efforts and to solicit feedback.

The team began its journey by simply brainstorming a list of clinical supply chain metrics. All team members shared the common experience of having measured KPIs that really did not seem to improve performance or efficiency. Because of this, the team's goal is to narrow the industry-wide metrics to those that yield the greatest benefit and eventually propose a common methodology for calculating each one. This will set the stage for industry-wide benchmarking in the future. The team has also identified the need for common definitions for the metrics and their associated concepts as a key challenge.

After their brainstorming exercise, the team took advantage of the November 2015 ISPE North American Annual Meeting to gather input on prioritization from attendees (see Figure 1). They will repeat this exercise at the 2016 European Annual Conference. The results of both sessions will be shared in

Figure 1 Brainstorming exercise at the ISPE North American Annual Meeting

an ISPE discussion paper scheduled to publish later in 2016. At this stage, members of the Investigational Products CoP are encouraged to provide input on the importance and prioritization of the metrics, how each metric should be calculated for purposes of standardization, and additional metrics that should be considered.

Metrics categories

The current list of brainstormed metrics, grouped by category, appears below:

Operational: These metrics provide the overall volume of activities during the measured period. They may also contain a year-to-date value and/or values from the same period in the previous year.

- Primary packs created
- Number of labels
- Secondary packs created
- Packaging jobs completed
- Number of lots released
- Cycle time for various activities:
  - Manufacturing
  - Packaging
  - Label creation
  - Complete to release

Conformance: These measure dates planned for specific activities (typically manufacturing/packaging activities) versus actual dates. The value of adhering to rigid dates vs. flexing to meet changing needs and situations and the effects of these changes should be considered when following these metrics:

- Manufacturing
- Packaging
- Label development/printing
- Product release
- Product available for first patient in (FPI)

Customer service response: Measurements that indicate the responsiveness of the vendor to requests from the sponsor.

- Time lapsed from request for quote to receipt of quote and/or plan

Availability of materials: These values track any instances when material required for the operation is not available, including:

- All components
- Drug product
- Label translations
- Label regulatory approvals

Release to distribution timeframe: Tracking time from when product is released until it is first shipped to clinical site. This could indicate accuracy of clinical in predicting FPI and/or indicate the amount of heroics required to bring in product just under the line.

Distribution: These help measure the activity, performance, effectiveness and monitor potential problem areas, including:

- Volume of shipments: site shipments by depot, depot-to-depot shipments
- On-time delivery: actual vs. expected
- Temperature excursions: total number, percent of total, amount of product lost
- Shipper capacity utilization: using correct shippers for amount of product
- Shipment optimization: number of shipments per site per period or other measure to determine optimal resupply parameters setup
- Number of expedited shipment**s**

Clinical: Capture the activities occurring at the clinical site:

- On-site temperature excursions: volume of excursions, product lost due to excursions, sites with high excursion volume
- Number of receipts by site
- Lead time to record receipts in interactive response technology (IRT)
- Number of patients screened in IRT
- Number of dispensings captured in IRT; IRT dispensing errors
- Returns recorded in IRT
- Accountability metrics per site
- Timely and accurate patient information recorded
- Timely and accurate drug needs from investigator-initiated trial sites

Forecast accuracy: Measures the accuracy of data received from the clinical team that drives supply activities. Generally these measures are actual vs. planned:

- Enrollment accuracy
- Study initiation date
- Number of centers
- Countries: numbers and specific countries
- Recruitment rate and last patient in
- Screen fail rate
- Dropout rate
- Open label extension plan

Number of changes: These values capture the number of times that manufacturing or packaging/labeling plans are changed within the locked window. These suggest the amount of "churn" due to last-minute changes in plan or changes due to revisions of inaccurate/incomplete documentation.

IRT: Measures the effectiveness of the IRT delivery team and the overall process:

- Time from specification completion to start of user acceptance testing (UAT)
- Number issues identified at UAT
- Number of UAT iterations (duration of UAT period)
- UAT completion to "Go Live"/IRT release
- If Go Live/IRT release did not include all initially requested elements (partial Go Live), time from initial Go Live to final Go Live of all elements

Training: Measures the group compliance in ensuring staff has received all mandatory training

Budget/resource: Measures the actual financial performance/resource requirement of the operation versus the plan

Quality: Captures and trends the total volume of issues as well as the lead times to process deviations:

- Number of quality issues
- Number deviations (normalized for volume)
- Time to raise deviation
- Time to close out deviations

One common objective in all industries is waste reduction. Equally important in investigational products is ensuring as tight a match as possible between demand and supply. Measured as "drug not consumed," the ability to reduce waste in clinical trials can be quite controversial. Many organizations have a zero tolerance for the ethical effect on patients should drug not be available, the lost investment in patient data, and the negative effect on company reputation. In these cases, reducing risk by building adequate overage may outweigh the drive for waste reduction.

Similar zero tolerance and risk reduction may also prompt the timing for availability of clinical supplies. While classic supply chain approaches target a sweet spot for inventory levels and their respective delivery timings, many clinical supply organizations build buffers or padding into their timelines to ensure that patient supply cannot possibly be interrupted. Striking a balance for the parameters of quantity and timing, therefore, may depend on the culture of individual companies.

Conclusion

The use of metrics in the clinical supply chain has thus far not been standardized across the industry. With this article and subsequent discussion paper, the Investigational Products CoP Metrics Task Team is reaching out to the community to gain input about the most relevant KPIs, how data capture can be standardized, and input on performance targets. The task team welcomes comments on this article, and encourages readers to contact any of the authors by email (see "About the Authors"). Readers are also encouraged to watch for the discussion paper scheduled to publish on the ISPE website in 2016, which will include instructions for providing further comment and input.

The task team welcomes your contribution to this important initiative. ■

About the authors

Steven Yoder is the Global Director of Clinical Supply Optimization at Fisher Clinical Services. Steve has over 20 years of supply chain experience and leadership in the pharmaceutical industry, with the last 9 years focused specifically on investigational products. His career spans experiences in finance and leadership in manufacturing, distribution, outsourcing, and global logistics. He earned a bachelor's degree in management and finance from Purdue University and a master's degree in business administration (MBA) with an operations focus from Indiana University. He is APICS certified in production and inventory management (CPIM), and served as a member (and past chair) of the ISPE Investigational Products North America Steering Committee. He may be reached via email at Steven.Yoder@ThermoFisher.com

Sandra Cook, PhD, Founder and President of Cook Consulting, LLC, is a results-oriented project management and training consultant with 28 years' experience in the pharmaceutical industry. The past two decades have been focused on investigational products, where she has held both line management and senior-level project management roles facilitating high-performing teams in the delivery of worldwide clinical supplies, including materials supporting key priority blockbuster products for large pharma. Additionally, Dr. Cook has been instrumental in the design, development, and implementation of several global process-improvement projects for the R&D supply chain. An active member of the ISPE and coauthor of the 2014 ISPE Pharmaceutical Engineering publication "The Blinding of Material in Clinical Trials: Essential Processes for Ensuring the Integrity of Clinical Study Data," she also serves as program coordinator and co-meetings facilitator for the intercompany Equal Partners in Clinical Supplies forum. Dr. Cook is a frequently invited speaker, facilitator, and trainer and is recognized for her ability to communicate technical concepts while motivating audiences. She can be contacted at sc@scookconsulting.com.

Douglas Meyer is Associate Director of Clinical Drug Supply for Biogen, Inc. in Cambridge, Massachusetts, US. Meyer has more than 21 years of pharmaceutical supply chain experience with a focus on investigational product planning and logistics, development and implementation of clinical supply chain systems and leading continuous process improvement projects. In his current role he is responsible for managing the business process and applications for the Clinical Drug Supply group including planning and IRT systems. He holds a BS degree in pharmacy and an MBA degree, both from the University of Connecticut. He is a certified project management professional (PMP) and is an APICS certified supply chain professional (CSCP). He is a former member of ISPE Investigational Products North America Steering Committee. He can be contacted by email at douglas.meyer@biogen.com.

Predictable.

We honor your schedule.

Delayed departures, late arrivals, change of plans - we have all experienced how frustrating it is when we have important meetings and deadlines to keep!

In our industry it's vital to keep schedules – to get your new pharmaceutical manufacturing facility up and running on time, to ensure your critical process systems perform as specified and you are able to satisfy your commitment to the patients dependent on life saving therapies.

Pharmadule delivers solutions, from concept design through start-up and qualification. Our predictable and well-proven delivery model, based on our modular concept and off-site construction, will ensure the success of your project – meeting the market demand and maximizing your return on investment.

For us it's a matter of honoring deadlines – continuing to deliver the values that Pharmadule has been recognized for over the last 25 years.

On Time , On Budget - The Modular Way

pharmadule

www.pharmadule.com

Cleaning Buffer Preparation Tank Air–Liquid Interface Rings

Paul Lopolito, Dijana Hadziselimovic, Amanda Deal and Amy Thanavaro

Buffers are routinely used in biopharmaceutical manufacturing operations to adjust pH, salinity, or nutrient levels; equilibrate and flush columns and filter membranes; and for in-process and final product formulations. While buffers are easily cleaned with water (with a few exceptions due to high water solubility), the industry continues to struggle with visible residue at the air–liquid interface on buffer preparation and storage tanks. The residue can adhere tightly to the surface, appearing as distinct bands or rings at the air–liquid interface. Articles and presentations have been published that define the residue as hydrophobic in nature and due to trace polymers from the packaging, handling, raw materials, or manufacturing processes found in buffer components.[1–3] These trace components, such as slip agents, are used to help the flow of dry ingredients, manipulation of plastic packaging, and storage of the components. Hydrophobic contaminants can also be derived from worn or chemically incompatible gaskets, valve diaphragms, and tubing materials.

This article will review the different types of buffers, provide approaches to investigate the best cleaning procedure using laboratory testing, and detail strategies for cleaning air–liquid interface residues within buffer preparation and storage tanks.

Buffer types

Buffers are solutions whose pH is altered not to any great extent by the addition of small quantities of strong acid or strong base. Buffer solutions are divided into two types:

1. Acidic buffers are a mixture of a salt of a weak acid and a strong base, for example: acetic acid (CH_3COOH) and sodium acetate (CH_3COONa). A solution containing equal quantities of acetic acid and sodium acetate maintains a pH value around 4.75.

   $pH = pK_a + \log (salt/acid)$

where K_a is the acid dissociation constant of the weak acid.

2. Basic buffers are a mixture of a salt of a weak base and a strong acid, such as ammonium hydroxide (NH_4OH) and ammonium chloride (NH_4Cl). A solution containing equal quantities of ammonium hydroxide and ammonium chloride maintains its pH value around 9.25.

   $pOH = pK_b + \log (salt/base)$

where K_b is the base dissociation constant of the weak base. These equations are called Henderson–Hasselbalch equations.

Buffers can be further divided:

- Single-substances solutions, which represent the solution of the salt of a weak acid and weak base.
- Mixture solutions, which represent any acid buffer or basic buffer.
- Natural buffer solutions, which maintain their pH in a variety of conditions. Human blood, for example maintains a pH value around 7.35 in spite of the wide variety of foods we consume.

Buffer solubility

Buffers are generally cleaned with water (with some exceptions, such as human blood), based on their solubility in water. Table A lists buffers and their solubility in water.[4–5]

Nonroutine cleaning challenges

Common challenges with cleaning buffer preparation tanks are the bands of residue found along air–liquid interfaces. These can occur after a single production batch or after multiple batches of the same or differing buffers. As reported in the 2013 CIP Summit[9] benchmarking survey, 89% of the participating companies that use water for cleaning reported that their buffer preparation tanks were cleaned with purified water. Buffer salt solubility supports the use of "water-only" cleaning, but companies continue to be challenged with visible residue on the preparation tanks concentrated as bands or rings.

Common approaches to cleaning air–liquid interface rings:[2,6]

- Increased spray impingement by using rotating spray devices focused on the air–liquid interface
- Increased time of the initial rinse, which typically removes gross residue
- Use of oxidizing agent with an alkaline cleaning solution
- Increased temperature (75–85°C)
- Use of a formulated cleaning agent containing surfactants and chelants
- Increased cleaning agent concentration
- Clean first with an acid, followed by an alkaline cleaning agent

Laboratory testing model

Laboratory testing has been effective at defining critical cleaning parameters for removing process residues.[7–8] Laboratory testing involves applying the residue on a surface that is representative of the preparation and storage tank. The test continues by conditioning the applied residue on a surface to simulate the "real-world" process, and finally cleaning the surface in a manner that is representative of how the equipment is normally

Table A Solubility of select buffers in water

Buffers	Solubility in water
Acetic acid	Miscible with water
Ammonium formate	Soluble in water
Bicine (2-(Bis(2-hydroxyethyl)amino) acetic acid)	Soluble in water
CAPS (N-cyclohexyl-3-aminopropanesulfonic acid)	Soluble in water: 10 g/100 g at 20°C
Ches (2-(Cyclohexylamino)ethanesulfonic acid)	Soluble in water: 10.4 g/100 g at 20°C
Citric acid	Soluble* in water: 54 g/100 g 10°C to 78.8 g/100 g at 80°C
Glycine	Soluble in water: 25 g/100 g
Guanidine HCl	Freely soluble* in water
HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid)	Soluble in water: 40 g/100 g at 25°C
L Histidine HCl	Soluble in water: 4.1 g/100 g at 25°C
Mes (2-(N-morpholino)ethanesulfonic acid)	Highly soluble* in water
Phosphoric acid	Soluble in water
Polysorbate 20 trehalose dehydrate	Soluble in water: 68.9 g/100 g at 20°C
Sodium chloride	Soluble in water: 35 g/100 g at 25°C
Sodium citrate	Soluble in water: 92 g/100 g at 25°C
Sodium sulfate, anhydrous	Soluble in water: 4.76 g/100 g at 0°C and 42.7 g/100 g at 100°C
Sodium sulfate, heptahydrate	Soluble in water: 19.5 g/100 g at 0°C and 44 g/100 g at 20°C
Sucrose	Soluble in water: 200 g/100 g at 25°C
Tetramethyl ammonium chloride	Soluble in water
TRIS (tris(hydroxymethyl)aminomethane)	Soluble in water: 40 g/100 g at 25°C

* Highly or very soluble: < 1 part solvent to 1 part solute
Freely soluble: 1–10 parts solvent to 1 part solute
Soluble: 10–30 parts solvent to 1 part solute
Source: US Pharmacopoeia.

cleaned within the facility. The various cleaning factors to monitor during the laboratory testing include cleaning agent, temperature, time, action, water quality, surface material, rinsing method, and environmental factors.

Purified water is commonly used as the cleaning agent to remove buffer residue between batches of the same buffer as well as different buffers. Water-only cleaning utilizes water solubility at the temperature cleaned as the cleaning mechanism.

When a formulated cleaning agent is used, the cleaning mechanisms include solubility in an aqueous solution, wetting, emulsification, dispersion, chelation, and hydrolysis. These additional cleaning mechanisms are important in removing water-insoluble residue from the surface.

Procedure and results

Some of the buffers evaluated include:

- Acetate, pH 5
- Acetate, pH 8
- Acetic acid, 1M
- Glucose buffer
- HEPES, 25mM
- Sodium acetate, 20mM
- Sodium chloride, 0.15M
- Sodium chloride, 3M
- Sodium chloride, 2.5M, pH 7
- Sodium chloride, 2M, pH 5.6
- Sodium chloride, 1M / acetic acid, 1M
- Sodium hydroxide, 0.1M
- Sodium hydroxide, 1M
- Sodium phosphate, 60mM
- TRIS buffer
- and more ...

Table B outlines the laboratory test procedure.

A coupon was considered to be clean if it was visually clean, water break free, and its precoating and postcleaning weights were equal (< 0.1 mg residue per 7.5 × 15 cm coupon).[8]

Under these conditions, the buffers evaluated were easily cleaned in 5 minutes using deionized water at ambient temperature. Unfortunately, these cleaning parameters are not always effective in preventing visible residue in buffer preparation tanks.

Table B Laboratory test procedure

Step	Procedure
1	Dry, clean 304 stainless steel coupons (7.5 × 15 cm size) were weighed on an analytical balance (±0.1 mg) to obtain the pre-coating weight
2	Coupons were then coated with 3–5 ml of the sample. The amount of residue per surface area was controlled and recorded; it varied by the application form (dry powder, compressed powder, and slurry)
3	The samples were air-dried at ambient temperature for 72 hours
4	The conditioned coupon was weighed on an analytical balance for a determination of pre-cleaning weight
5	Each coupon was cleaned by agitated immersion, spray wash, or by cascading flow
6	Each coupon was removed and visually observed for cleanliness
7	Each side of the coupon was rinsed with tap water for 10 seconds at a flow rate of 2 L/min
8	Each side of coupon was rinsed with deionized water and examined for a water break-free surface
9	Coupons were dried and then weighed on an analytical balance to determine the post-cleaning weight

Coupon conditions

One of the difficulties with providing effective cleaning recommendations for removing air–liquid interface rings is in generating laboratory coupons representative of what is seen on the tank walls. A number of factors can contribute to this:

- Trace elements are normally in parts per billion levels within the buffer solution.
- Trace elements are normally hydrophobic in nature and migrate to the air–liquid interface.
- High mixing speeds migrate the trace components to the air–liquid interface, which increases residue adherence to the tank side walls.
- Large liquid volume increases the amount of trace residues present.
- Small surface area at the air–liquid interface allows greater residue concentration.
- Repetitive hot water rinses can heat the surfaces and bake residues onto the side walls. Contaminants in the water can also have an impact. Characteristics of the hot water, such as its source before heating, should be considered.

In a mammalian cell culture performed by a large multinational biopharmaceutical company, for example, floats similar to fishing bobs were added to the bioreactor during production, and then sectioned for cleaning evaluation. This model was effective in identifying two distinct residue types at the air–liquid interface.

- A whitish residue more consistent with salts and antifoam in the media (Figure 1)
- A brownish residue consisting of proteins, lipids, and cellular debris used in the culture process (Figure 2)

Laboratory testing using agitated immersion proved that the whitish residue band required 4× the concentration of the formulated alkaline cleaning agent used to remove than the brown residue.

Unfortunately, due to the high mixing rates used in media and buffer preparation tanks, 316L stainless steel floats are not a practical option because they can damage tank side walls.

A different model is required—one that will generate a residue or change in the surface property of the coupon representative of the air–liquid interface residue along the side wall. Partially submerging the coupon into a beaker of media or buffer for a period of time will generate a visible residue at the air–liquid interface (Figure 3). But this residue is normally easy to clean, and may not be representative of the residue on the tank surface.

Residue conditioning techniques can increase the difficulty of cleaning the residue from the coupon, making it more representative of the actual interface residue in media and buffer tanks. Several conditioning techniques are listed below:

- Air dried at ambient temperature (Figure 4)
- Baked on the surface
- Coupon partially submerged and then air dried at ambient temperature
- Coupon partially submerged and then baked on the surface
- Coupon preheated, coated with the buffer, and then baked on the surface

Identifying the major component(s) in the air–liquid interface residue helps determine the cleaning parameters. This allows the analyst to spike the buffer solution with high levels of trace residue found in the buffer and at the air–liquid interface. Increasing soil levels can also decrease the time required to condition coupons and produce visible residue with tenacity similar to that observed in the production area.

In our laboratory tests, we spiked buffer samples with slip agents to generate residue on stainless steel surfaces similar to what we have seen in the field. We tested several of the most common slip agents, wetting agents, and packaging materials used in the industry: erucamide, oleamide, stearamide, talc, polyisoprene, and polyethylene.

Erucamide, oleamide, (Figure 5) and stearamide are the most commonly used slip agents in the pharmaceutical industry and life sciences industries. Because they are insoluble in water and buffers, they tend to float at the liquid surface, aggregate at the air–liquid interface, and adhere to the tank side wall.

Coupons were prepared under several different conditions:

- Slip agent mixed with the buffer
- Melted slip agent mixed with buffer
- Slip agent dissolved in methanol or ethanol and mixed with buffer

The coating process consisted of dispensing approximately 4 ml of samples onto the coupon with a plastic transfer pipette, and then spreading the sample over an approximately 100 cm^2 area with the pipette. The amount

Figure 1 Mammalian cell bioreactor air–liquid interface residue, thin white film

Left: Thin white film.
Right: After cleaning with formulated alkaline cleaning agent

Figure 2 Mammalian cell bioreactor air–liquid interface residue, heavy brown residue

Left: Heavy brown residue.
Right: After cleaning with formulated alkaline cleaning agent

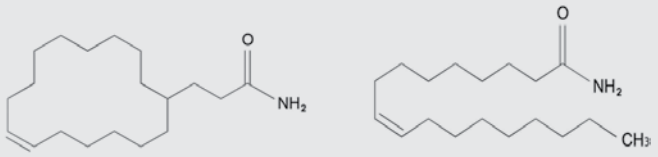
Figure 3 Air-dried buffer residue on 304 stainless steel coupons

Note: Coupons are not proportional but representative of the description

Figure 4 Partially submerged 304 stainless steel coupons create a visible air–liquid interface

Note: Coupons are not proportional but representative of the description

Figure 5 Chemical structure of erucamide and oleamide



Left: erucamide. **Right:** oleamide

of residue by weight and surface area coated were recorded to provide the amount of residue in mg/cm^2 per sample.

The hardest-to-clean condition was when the slip agent was dissolved in methanol or ethanol and then mixed with the buffer.

Coated coupons were conditioned five ways:

1. Air-dried at ambient temperature for 16 hours
2. Baked in a drying oven at 121°C for 16 hours
3. Autoclaved at 121°C for 1 hour
4. Partially submerged in the cleaning solution and baked in a drying oven at 121°C for 16 hours
5. Preheated in a drying oven at 121°C before coating and then baked in a drying oven at 121°C for 1 hour

Because condition 5 was hardest to clean, we chose it as our test model. We evaluated the following cleaning agents to determine the most suitable chemistry for removing erucamide, oelamide, and stearamide residues from the air–liquid interface (Table C):

- Deionized water
- 5% w/v sodium hydroxide or potassium hydroxide
- 5% v/v formulated alkaline cleaner containing sodium hydroxide or potassium hydroxide as well as surfactants and other components
- 2% v/v formulated alkaline cleaner containing potassium hydroxide + 2% v/v detergent additive containing hydrogen peroxide

Oxidative chemistry effectiveness

Cleaners formulated with sodium hypochlorite or hydrogen peroxide use oxidation as the cleaning mechanism. Oxidation cleaves high-molecular-weight molecules into smaller molecules, which are more susceptible to removal by other cleaning mechanisms, such as emulsion, solubility, and hydrolysis. Repeated use of oxidative cleaning agents at high concentration and temperature may discolor stainless steel, so these are generally used for periodic cleaning.

Risk assessment

When assessing the effect of the air–liquid interface residue on the quality of the next product or batch, one should ask the questions shown in Table D:

Case study 1

A pharmaceutical drug manufacturer was observing air–liquid interface "rings" in several blend tanks (Figure 6). The rings appeared at multiple levels in the tank and were black in color. The blended product was water soluble, so purified water was used to clean the tank between product batches.

After visual inspection of the tank, the air–liquid interface rings were wiped and scraped, and the residue was submitted for material analysis; a wipe sample of a black gasket was also submitted (Figure 7). The results of the scraped material were somewhat inconclusive as to its source, due to the opacity of the black particulates. However, Fourier transform infrared spectroscopy (FTIR) results from the gasket and tank ring wipes appeared similar.

Procedure

The gasket, scraping material, and wipe samples of the gasket and tank ring were analyzed using a Digilab Excalibur Series FTIR FTS 4000 (SSR: 734) Fourier transform infrared spectrometer. Infrared spectroscopic data were collected between 4,000 cm^{-1} and 600 cm^{-1} (neat). A background spectrum was collected using the blank ATR diamond cell.

Results

The FTIR gasket spectra (carbon black filled) and the black scraping material produced skewed baselines. Carbon black filled types of materials are difficult to analyze by spectroscopic methods because of their very high absorption rates and their propensity to scatter infrared light. Figure 8 shows the spectrum of the gasket; Figure 9 shows the spectrum of the black scraping from the ring in the tank. Note that although the spectra are not exactly the same, there are similarities in some absorbance bands and the baseline slope.

Spectra of the wipe material (clean spot) and black residue on the wipe were collected independently. Spectral subtraction was used to determine the black residue on the wiping material. The spectra from gasket and tank ring wipes (Figure 10) appear to be fairly similar after subtraction of the wipe material.

The tank rings contained residue from the black EPDM gaskets. Water-only cleaning was not sufficient to remove the hydrophobic residue, which allowed it to build up on the tank as visible residue. The solution was filtered into a storage tank where there were no observed rings. Further testing should be done to identify the residue and assess its effect on the product.

Gaskets were replaced and the tanks were cleaned with a combination of manual cleaning (brush from the manway) and automated cleaning using

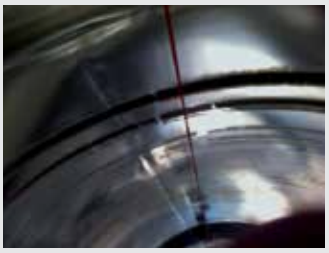
Table C Laboratory cleaning trials

°C	% v/v	Cleaner	Minutes*	Residue	Water Break Free
Euracamide, agitated immersion					
60	N/A	Deionized water	120	Heavy	No
	5	Sodium hydroxide	120	Moderate	No
	5	Potassium hydroxide	120	Moderate	No
	5	Formulated cleaner containing sodium hydroxide	120	Light	No
	5	Formulated cleaner containing potassium hydroxide	120	Light	No
	1 + 1	Formulated cleaner containing potassium hydroxide + detergent additive	60	Trace	No
	2 + 2	Formulated cleaner containing potassium hydroxide + detergent additive	30	Visually Clean	Yes
80	5	Formulated cleaner containing potassium hydroxide	120	Trace	No
Oleamide, agitated immersion					
60	N/A	Deionized water	120	Heavy	No
	5	Sodium hydroxide	120	Moderate	No
	5	Potassium hydroxide	120	Moderate	No
70	5	Formulated cleaner containing sodium hydroxide	120	Light	No
60	5	Formulated cleaner containing potassium hydroxide	120	Trace	No
	1 + 1	Formulated cleaner containing potassium hydroxide + detergent additive	60	Visually Clean	No
	2 + 2	Formulated cleaner containing potassium hydroxide + detergent additive	60	Visually Clean	Yes
Stearamide, agitated immersion					
80	N/A	Deionized water	120	Heavy	No
	5	Sodium hydroxide	120	Light	No
	5	Potassium hydroxide	120	Moderate	No
70	5	Formulated cleaner containing sodium hydroxide	120	Trace	No
60	5	Formulated cleaner containing potassium hydroxide	120	Trace	No
80	4	Formulated cleaner containing potassium hydroxide	120	Trace	No
	5	Formulated cleaner containing potassium hydroxide	45	Visually Clean	Yes

* Tested at 15 minutes intervals

Note: Polyethylene and talc were easier to clean, requiring 1% v/v formulated alkaline cleaner containing surfactants at 60°C for 5 minutes. The residue could not be cleaned at ambient temperature or with hot (45°–60°C) water.

Figure 6 Visible rings in tank.



Note: The red line is an artifact of the picture-taking process, possibly due to the red-eye reduction setting or use of a red laser pointer during inspection.

Figure 7 (left to right): Scraping from the tank ring, a used gasket, and a wiping of the tank side

a spray device with a formulated alkaline cleaning agent containing surfactants. The tanks and gaskets were also monitored more closely to determine if the gaskets should be replaced more frequently.

Case study 2

A biopharmaceutical manufacturer was observing air–liquid interface rings in its sodium chloride buffer tanks.

The sodium chloride arrives as large clumps in polyethylene containers with a polyethylene bag liner (Figure 11). The clumps are broken up by the operators while in the container prior to preparing a sodium chloride solution. The buffer tanks are cleaned with water between batches. Laboratory studies to investigate residue ring cleaning and prevention were conducted in parallel with field trials and analytical residue testing.

Procedure

Laboratory testing consisted of two parts:

1. The 304 stainless steel coupons were partially submerged in a beaker with 3M sodium chloride solution or a saturated sodium chloride solution for 30 minutes while mixing on a stir plate. The soiled coupons were then air dried at ambient temperature overnight (> 16 hours) prior to washing with 80°C deionized water by agitated immersion for 5 minutes. The soiling and cleaning process was repeated up to 10 times.

   The clean coupons were visually inspected, and then rinsed with tap water for 10 seconds at 2 gallons per minute per foot bandwidth. The coupons were rinsed on each side with de-ionized water and examined for a water break-free surface. The coupons were then air dried at ambient temperature and visually observed for cleanliness. Gravimetric analysis and FTIR analysis was also performed on select samples.

Table D Five questions to help assess risk

What might go wrong?

A visible air–liquid interface residue ring may appear in the buffer tank after one or more batches. This can lead to increased cleaning challenges, microbial excursion, and corrosion.

What is the likelihood it will occur?

Air–liquid residue rings depend on the type, volume, mixing rate, and raw material of the buffers manufactured. The age and wear of gaskets, tubing, and diaphragm pumps are additional contributing factors.

What is the likelihood it will be detected?

Air–liquid residues within a buffer tank have a low probability of detection by routine operators. Most buffer tanks are not routinely visually inspected, therefore residue can go unnoticed for a long time. The probability of detection during visual inspection increases if a high-lumen light source is used, operators are adequately trained, and the surface is dry, since residue can be difficult to observe on a wet surface.

What are the consequences?

Visible residue on a vessel surface of could adversely affect cleaning, microbial control, and stainless steel maintenance.
A product and patient risk assessment should be performed to evaluate the effect of the residue on the next batch or product,
as well as the patient.

What are some mitigating actions?

- Raw material selection should include a sourcing questionnaire and screening.
- Implement a routine low-concentration formulated alkaline cleaning agent with surfactants instead of water-only cleaning.
- Ask subject matter experts to inspect tank surfaces periodically, and implement remediation procedures as required.
- Remediation procedures could include manual cleaning or incorporating a detergent additive with hydrogen peroxide to be used with a formulated alkaline cleaning agent with surfactants.
- Filter the buffer from the blend tank to the buffer storage tank.
- Validate or verify that the filtration process removes trace components identified in the air–liquid interface ring.

Figure 8 Gasket spectrum

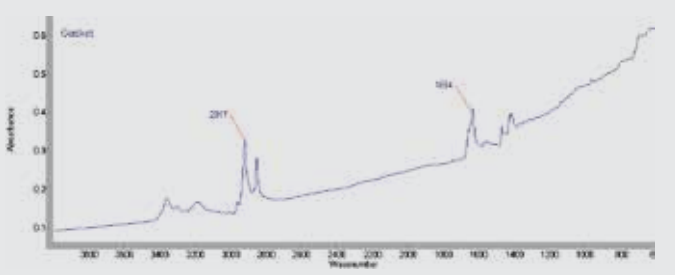


Figure 9 Black scraping from tank ring

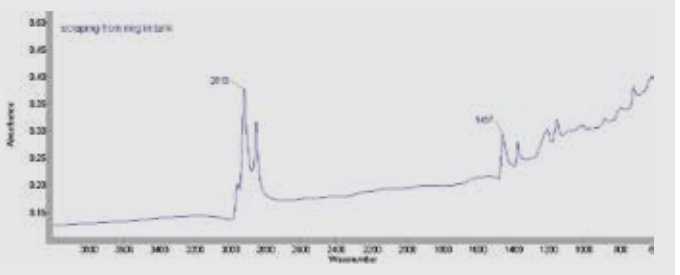
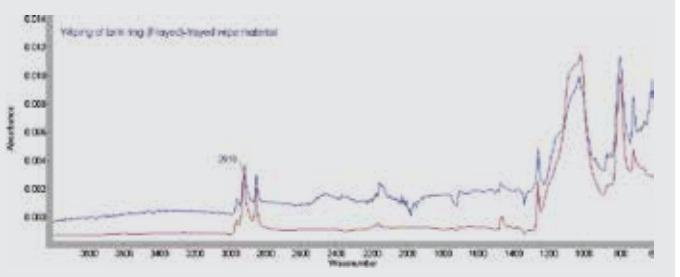


Figure 10 Gasket and tank ring wipe



Bottom (red) spectrum: gasket wipe; **top (blue) spectrum:** tank wipe

Figure 11 Sodium chloride raw material

Figure 12 Coupon conditions after 10 cleaning cycles

Left: Coupon 1 after 10 applications of 3M NaCl and 10 cleanings with 0.25% v/v CIP 100 at 80°C for 5 minutes.
Right: Coupon 2 after 10 applications of 3M NaCl and 10 cleanings with deionized water at 80°C for 5 minutes.

2. Part 2 testing compared repeated soiling and cleaning as detailed above, but coupons were washed with a 0.25% v/v formulated alkaline CIP detergent at 80°C for 5 minutes by agitated immersion instead of 80°C deionized water by agitated immersion for 5 minutes.

Results

While the coupons were visually clean, those cleaned only with water failed the water break free test after only one soiling and cleaning cycle (Figure 12). The water break free failure was not produced on stainless steel when cleaned with 0.25% v/v formulated alkaline CIP detergent by agitated immersion at 80°C for 5 minutes, even after 10 soiling and cleaning cycles.

Analytical testing of the air–liquid interface rings demonstrated trace polyethylene residue, most likely from the raw material packaging.

The results did not confirm conclusively that the residue observed in the laboratory studies was polyethylene, however.

These laboratory studies demonstrated that the sodium chloride contained a water-insoluble hydrophobic residue that remained on the surface when cleaned only with water. This residue could continue to build up on the surface and result in a visual failure or reduce the efficiency of subsequent cleaning, sanitization, or stainless steel maintenance. A low-concentration alkaline cleaning agent with surfactants appeared to remove this hydrophobic residue when used after each cleaning. Periodic cleaning of the surface with a low-concentration alkaline cleaning agent after the residue develops to a visual failure was not evaluated during this study.

Conclusions

This article reviewed common buffers used in pharmaceutical and biopharmaceutical manufacturing processes. Based on solubility and benchtop cleaning trials, water should be effective at removing theses residue. However, trace components from the packaging, raw materials, gaskets, diaphragms, tubing, etc., can migrate to the tank surface during blending and adhere to the side walls, creating air–liquid interface rings after one or more batches.

Identifying the ring components is the first step in determining whether the residue is intrinsic (e.g., residue from a minor component in a raw material, such as starch or a wetting agent in calcium carbonate) or extrinsic (e.g., residue from packaging material or a worn gasket) to the buffer. Laboratory studies have been effective at providing a course of action in some cases, but simulating the air–liquid interface residue without having identified the residue remains a challenge. Identifying the residue allows analysts to spike the buffer sample, which improves the visibility and tenaciousness of the residue on test coupons. Cleaning procedures could also be modified to better remove extrinsic particulates, or at least implement a maintenance cleaning procedure proven to clean the equipment and prevent the ring from forming or remove it once it is visible.

If the residue is inherent to the process, the cleaning procedure should be modified to consistently clean the buffer residue; at minimum, a maintenance cleaning procedure should be defined to clean the equipment prior to the residue being visible. An alternative would be to identify the source of trace material and try to eliminate it from the raw material through a corrective and preventive action plan.

If the air–liquid interface ring is due to a maintenance issue, then the source of the residue should be identified, the equipment repaired or replaced, and cleaned. Common cleaning approaches include the use of a formulated alkaline cleaning agent at elevated temperatures, often with a detergent additive to increase the surfactant level with or without hydrogen peroxide. If this is not successful then a manual cleaning of the air–liquid interface may be warranted. ■

References

1. Sharnez, R., C. Flint, M. Monk, and A. Tholudur. "Cleaning Validation Challenges for Bioprocesses Strategies for Eliminating Tenacious Residues." Presented at the PDA Annual Meeting, Phoenix, Arizona, US, 16–18 April 2012.
2. Lopolito, P. "Case Study: Cleaning and Passivation of Buffer Preparation Tanks." Presented at the Cleaning Validation and Critical Cleaning Processes Conference, Philadelphia, Pennsylvania, US, 19–21 August 2013.
3. Carlson, J. (2014) "Design a Cleaning and Passivation Program for Buffer Preparation Tanks." Presented at the Cleaning Validation and Critical Cleaning Processes Conference, San Diego, CA, 20 August 2014.
4. Merck. The Merck Index, 12th ed. CRC Press: Whitehouse Station, New Jersey, US, 1996.
5. Stevens, L. "Buffers," chapter 3 in *Proteins Lab Fax*, edited by N.C. Price. Academic Press, 1996.
6. Carlson, J. "Biotech Residues and Cleaning," chapter 17 in *Cleaning and Cleaning Validation*, Volume 1, edited by P.L. Pluta. Parenteral Drug Association and Davis Healthcare International Publishing, 2009, pp. 383–413.
7. Rathore, N., W. Qi, C. Chen, and W. Ji. "Bench-Scale Characterization of Cleaning Process Design Space for Biopharmaceuticals." *Biopharm International* 22, no. 3 (1 March 2009): 32–44.
8. Hadziselimovic, D., and P Lopolito." Critical Cleaning of Carbomer Containing Products." *Journal of GXP Compliance* 16, no. 3 (2012): 32–38.
9. 2013 CIP Technology and Industry Benchmarking Summit. Seventh Annual CIP Technology & Industry Benchmarking Summit. Benchmarking Sessions at Amgen in Longmont, Colorado, US, 23 April 2013.

About the authors

Paul Lopolito is a technical services manager for the Life Sciences Division of STERIS Corporation (Mentor, Ohio, US). He currently provides global technical support related to process cleaning and contamination control, which includes field support, site audits, training presentations and educational seminars. Paul has more than 15 years of industry experience and has held positions as a technical services manager, manufacturing manager and laboratory manager. He has authored and published numerous articles on cleaning and contamination control. He earned a B.A. in Biological Sciences from Goucher College in Towson, Maryland, US.

Dijana Hadziselimovic is a senior technical services associate for the Life Sciences Division of STERIS Corporation (Mentor, Ohio, US). She provides technical support in the area of process and research detergents and conducts laboratory experiments to recommend cleaning procedures. Dijana has over 13 years of laboratory experience in the pharmaceutical and biotech industries. She holds a BA degree in chemistry from the University of Missouri, St. Louis (Missouri, US).

Amanda Deal is a senior technical services associate for the Life Sciences Division of STERIS Corporation (Mentor, Ohio). She provides technical support in the area of process research detergents and conducts laboratory experiments to recommend cleaning procedures. Amanda has over nine years of laboratory experience in the pharmaceutical and biotech industries. She holds a Bachelor's of Science degree in Biology from the University of Missouri-Kansas City.

Amy Thanavaro, Ph.D. is a Senior Scientist, Analytical Services & Development, STERIS Corporation. Her current responsibilities include scientific leadership of new product development and developing analytical analyses to support Product Development, Manufacturing and cross-site functional projects. She led the chemistry team and coordinated with multiple teams that resulted in the 510(k) Clearance for the Reliance Endoscope Processing System (Cleaning Claim). Dr. Thanavaro received her B.S. degree in chemistry from Chulalongkorn University, Bangkok, Thailand, in 1996 and her Ph.D. in chemistry from University of Missouri – St. Louis in 2003.

ISPE 2016 TRAINING

Industry's Trusted Source of Knowledge

A well-trained staff is critical to meeting cGMP regulations. Training can also be the difference between successful operations and regulatory violations.

Since 1998, ISPE has been delivering and developing high quality globally-vetted, topic-specific, in-depth skill development and knowledge. Our 2-to-3 day training courses provide measurable learning objectives that provide an in-depth understanding of "how" and "why". Our courses use lectures, group exercises, case studies, and ISPE's Guidance documents to provide tangible "take-a-ways" for immediate application on the job.

Training Options

ISPE Training Institute:

Housed in the ISPE Headquarters in Tampa, FL, the ISPE Training Institute provides over 2,200 square feet of classroom space, easy access to a world-class airport and an adjacent hotel.

Online Courses and Webinars:

Online courses and webinars can help you expand your skills and knowledge from the comfort of your desk. Visit www.ISPE.org/Elearning.

Onsite:

Prevent performance lapses and stretch your training budget by bringing our courses to you. Contact Training@ispe.org to request a quote.

Classroom Training:

Small classroom settings offered in many locations around the globe. Work side-by-side with like-minded professionals to solve your common problems.

2016 ISPE Training Schedule

JANUARY

ISPE Training Institute, Tampa, FL

- GAMP® 5 Data Integrity (T50)
- Basic GAMP, Annex 11 / Part 11 (T45)

FEBRUARY

ISPE Training Institute, Tampa, FL

- Auditing (G07)
- Bio Manufacturing (T31)
- Bio Process Validation (T32)
- C&Q (T40)
- GAMP® 5 Process Control (T21)
- HVAC (T14)
- Process Validation (T46)
- Technology Transfer (T19)

MARCH

ISPE Training Institute, Tampa, FL

- Application of GAMP® 5 (T11)
- Cleaning Validation (T17)
- Facilities, Systems and Equipment Workshop (T48)
- QRM (T42)

APRIL

California

- Basic GAMP® 5, Annex 11 / Part 11 (T45)
- Bio Manufacturing Processes (T24)
- Facility Project Management* (T26)
- OSD (T10)
- Water Generation, Storage, Delivery and Qualification (T04 and T23)

Case Study: Implementation of Catalytic Technology to Improve the Aeration Process for a Syringe-Filling Line Isolator

Donald Eddington, John Lanier, Michael Walsh, Jerry Shrake and Stefan Kleinmann

This article presents a process improvement effort that drastically reduced the aeration time on a production isolator.

Aseptic filling lines utilize many technologies to protect the finished product from contamination from microbes or nonviable particles. The syringe filler shown in Figure 1 is completely enclosed by an isolator. The system includes an e-beam tunnel for sterilizing the outer surfaces of tubs that contain nested syringes as they are transported into the filling line and a material transfer chamber (MTC) for introducing and removing items aseptically.

It has been scientifically proven that humans are usually the main source of microbial contamination in cleanrooms. Filling lines that are enclosed by restricted access barrier systems (RABS) or isolators reduce the risk of product microbial contamination by physically separating the operators from the filling equipment during the filling process. Any required manual interventions must be conducted using fixed glove ports.

The EudraLex Volume 4, Annex 1[7] divides cleanrooms into four grades: A, B, C, and D, with Grade A having the least amount of microbial contamination. The ISO 14644-1[8] standard divides cleanrooms into categories based on the amount of allowable particles per volume ranging from ISO 1 to ISO 9, with ISO 1 being the purest. The air quality inside a RABS or isolator used for filling is designed to be Grade A (ISO 5), and normally requires unidirectional air flow (UAF) with a typical air velocity of 0.45 m/sec, although lower air velocities are considered to be acceptable in isolators.

Isolators are sealed during operation, except for openings such as interfaces to tunnels for feeding sterilized vials or syringes and a "mouse hole" for transporting the filled sealed product containers for downstream inspection, labeling, etc. A RABS air supply usually comes from the cleanroom; air passing through the enclosure is vented directly back to the room. Because of the increased physical separation, aseptic isolators are usually installed in a Grade C cleanroom (ISO 8, in operation), while RABS are usually installed in a Grade B cleanroom (ISO 7, in operation). The operational costs for RABS are higher, due to increased energy consumption required for the higher-level cleanroom[1] as well as increased gowning and environmental monitoring requirements.

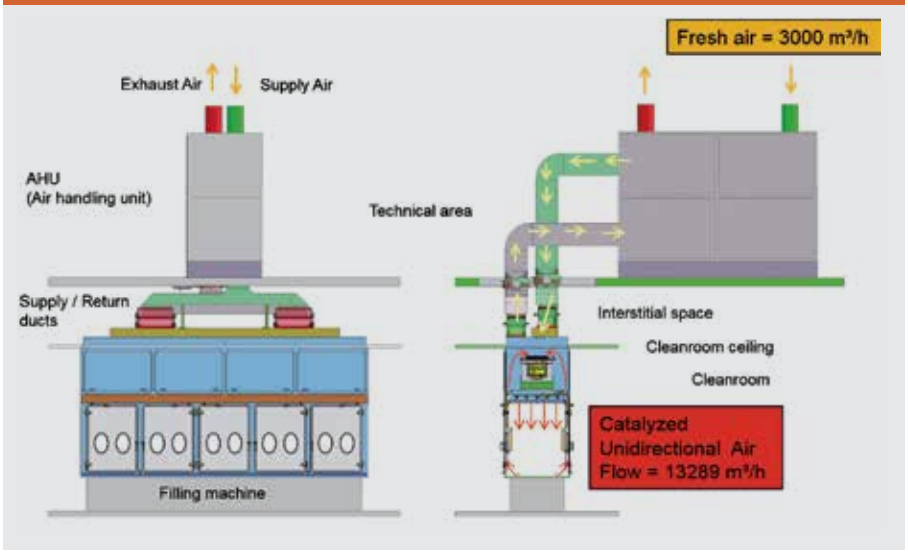
Another advantage of isolators is that because they can be completely sealed prior to initiating the filling process, they can be fumigated with a sporicidal agent before the actual aseptic manufacturing begins. In the early days of isolation technology, formaldehyde was used as a fumigant. It has since fallen out of favor, because it is now recognized as a carcinogen. Oxidizing chemicals such as ozone, chlorine dioxide, hydrogen peroxide, and hydrogen peroxide/peracetic acid mixtures have also been used for isolator decontamination. Since the 1990s vapor phase hydrogen peroxide (VPHP) has been the predominant method for isolator decontamination[2] because it has a desirable combination of efficacy, material compatibility, and safety. Hydrogen peroxide is also desirable for environmental reasons because it ultimately breaks down into water and oxygen.

An isolator must be aerated to reach a safe residual level after using VPHP for decontamination. In the United States, the National Institute for Occupational Safety and Health has a recommended respiratory 8-hour time-weighted average exposure limit of 1.0 parts per million (ppm) for hydrogen peroxide.[3] For this reason, most isolators are aerated to at least ≤ 1.0 ppm of hydrogen peroxide. The recommended time-weighted exposure limit in Germany is 0.5 ppm; the European Union is also considering recommending this lower limit. Many new isolator installations use this lower limit as their aeration target.

Potential damage to protein-based drug products by oxidation from low levels of hydrogen peroxide has been evaluated in recent years as more biotechnology drugs come to market and the use of filling line isolators has increased.[4] Related studies have been conducted to quantify the sources

Figure 1: Nested syringe filler with isolator and e-beam tunnel

Figure 2: Catalytic aeration



of low-level hydrogen peroxide in barrier systems.[5] Although this topic has most often been associated with isolators, there is risk of product oxidation during the filling process in traditional cleanrooms, because liquid chemical agents (such as hydrogen peroxide/peracetic acid mixtures) are commonly used for manual wipe-downs and mopping. Residual vapors from sodium hypochlorite (bleach), a commonly used cleanroom sanitizing agent, were found to cause oxidation in protein even faster than hydrogen peroxide/peracetic acid mixtures.[6]

Catalytic aeration concept

Catalytic converters are sometimes used for isolator exhaust systems to reduce hydrogen peroxide emissions to the atmosphere. Catalyst technology has also been used to reduce aeration time in isolators. This usually involves adding a recirculation loop to create a different airflow path during decontamination or aeration.

Production isolators that have unidirectional air flow (UAF) for filling applications generally have multiple recirculation blowers to provide the large amount of airflow required in the working area. These blowers also generate a lot of heat, so fresh air from the isolator HVAC system is introduced to cool the isolator to the desired set point during normal operation, and in some cases to control the humidity level as well.

The fresh air supply for a UAF production isolator is typically over 150 air exchanges per hour. The amount of air recirculating within the isolator is much higher. For example, the isolator shown in Figure 1 has a total volume of 18.4 cubic meters (m^3) and a fresh air supply of 3,000 m^3/hour, which yields an air exchange rate of 163 air exchanges per hour. The UAF volume can be calculated based on the 8.2-square-meter footprint of the filling line and the UAF set point of 0.45 m/sec which yields an airflow rate of 13,290 m^3/hour.

The isolator shown in Figure 1 uses a single-pass design for the flow of VPHP during the decontamination process. The VPHP-laden air flows through piping, where it is introduced in the space in between the recirculation HEPA filters and the diffuser membrane. Most of the VPHP flows downward through the diffuser membrane into the isolator workspace and back up through the double-walled air returns to the isolator exhaust. The recirculation blowers are not turned on during the decontamination phase, so some of the VPHP flows back through the HEPA filters to the isolator exhaust. Since the VPHP does not recirculate during the decontamination process, it is referred to as a single-pass design.

In most isolators, the fresh air supply rate is the main factor affecting aeration. The fresh air dilutes the outgassing hydrogen peroxide until the desired low-level concentration is reached. Using single-pass decontamination piping allows catalytic panels to be inserted above the recirculation HEPA filters without compromising the decontamination process. The recirculation blowers are not turned on during the decontamination process. During the aeration process and normal operation, these blowers are turned on and recirculate a substantial amount of air through the working space of the isolator as described above. The catalytic panels in the recirculation loops destroy a significant amount of the VPHP residue, while at the same time the fresh air exchange also reduces the concentration via dilution. The concept is shown schematically in Figure 2.

Feasibility study

Method

The catalytic aeration process described above was tested on the syringe-filling isolator shown in Figure 1. Prototype catalytic panels, constructed of stainless steel frames and wire mesh to contain commercially available catalyst pellets, were implemented for feasibility testing. The pellets have an activated alumina substrate that is coated with catalytic rare metal oxides. The frames were made in the same rectangular shapes as the five HEPA filters in the isolators so they could be slipped above them and fastened with existing hardware. Besides the addition of the catalytic panels, no other mechanical modifications were made to the isolator.

Hydrogen peroxide absorbs into some materials and can desorb slowly. Temperature also plays a key role in the aeration process. At the beginning of the aeration process, the air inside the isolator has a high concentration of VPHP, which is flushed out relatively quickly. Hydrogen peroxide outgassing from materials inside the system prolongs the time required to reach the low concentration target.[5] Warm temperatures increase outgassing rates for absorbed hydrogen peroxide, which helps eliminate hydrogen peroxide residues faster. Conversely, cool temperatures decrease outgassing rates and typically lead to longer aeration times. Efficient aeration processes use an initial warm phase to drive off the majority of the residue, followed by a cooling-off phase to bring the concentration down to the desired level.

The syringe-filling isolator uses a three-phase aeration process:

Aeration 1: Introduces fresh air from the HVAC without turning on the recirculation blowers. This purges some of the high VPHP concentration from the isolator.

Aeration 2: A heated phase that turns on the recirculation blowers. The temperature is controlled by a sensor downstream from the heater. The set point for the heater was 40°C during the feasibility tests. Heat from the recirculation blowers increased the isolator temperature to approximately 45°C during Aeration 2.

Aeration 3: Cools the isolator down to the normal operating temperature of 19°C, which is measured by a temperature sensor in the isolator. At the end of programmed phase time, the isolator control system activates measurement with Dräger Polytron 7000 low-level hydrogen peroxide sensors that measure VPHP outgassing from the isolator, e-beam, and MTC. The software will allow the isolator to transition out of the Aeration 3 phases if the hydrogen peroxide concentration is lower than 1.0 ppm in all three sections of the system.

Dräger Polytron 7000 low-level hydrogen peroxide sensors have a measurement range of 0.0 to 5.0 ppm with a detection limit of 0.1 ppm, and are widely used for aeration process control for set points as low as 0.5 ppm.
Isolators that are used for filling oxidation-sensitive products may require a VPHP aeration target as low as 50 or 30 parts per billion (ppb), depending upon the actual sensitivity of the product. Dräger Polytron 7000 units are not sensitive enough to measure at these low levels. An Aero-Laser AL2021 automated wet chemistry system with a VPHP measurement range of 0.05 to ±2,000 ppb (gaseous) was also used for some of the feasibility test studies.

Results

Five tests were conducted on the syringe-filling isolator with the prototype catalytic panels installed above the recirculation HEPA filters on the syringe-filling isolator. Two trials were run using the Dräger Polytron sensors with a VPHP target of ≤ 1.0 ppm. Prior to the catalytic panel installation, total aeration time to reach ≤ 1.0 ppm was 3:30 (h:min). Following catalytic panel installation, the first test with Dräger sensors used a total aeration time of 2:00, with the aeration time chosen without any prior experience with the catalytic panels. The VPHP level at the end of 2:00 aeration was less than the Dräger instrument's detection limit (< 0.1 ppm). A second test run using 1:30 reached the VPHP target of ≤ 0.5 ppm, as measured by the Dräger instrument.

A second series of tests studied aeration down to low ppb levels of residual hydrogen peroxide vapor in the isolator using the Aero-Laser instrument. The first test in this series used a total aeration time of 9:00, as before, a time chosen without any prior experience. The Aero-Laser system sampled near the base of the isolator between doors 1 and 2, which are to the left the operator shown in Figure 1. The VPHP level after 9:00 aeration was 18 ppb. Two more tests were run using the Aero-Laser system. After 8 hours of aeration, the VPHP level reached 38 ppb; after 11 hours of aeration it reached 9.4 ppb. The results are summarized in Table A.

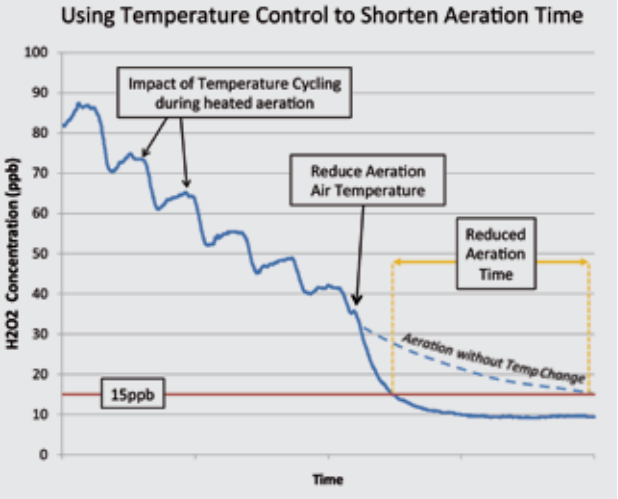
The effect of the transition from the heated Aeration 2 phase to the cooled Aeration 3 phase was noticeable during all of the tests. VPHP concentration drops much faster when the isolator starts cooling down during Aeration 3; this is caused by a reduction in outgassing rate of the VPHP from materials in the isolator. The heated Aeration 2 phase speeds up outgassing; this is a major factor in how low the VPHP concentration will be when the isolator cools to the temperature used for production.

The effect of temperature was clearly observable during the final test using the Aero-Laser device. The isolator was cycling from 43.9° to 45.2C with a cycle taking about 24 minutes. The VPHP level in the isolator was gradually decaying, but small oscillations in the readings followed the same cyclic pattern as the isolator temperature as shown in Figure 3. Figure 3 also shows an example of the potential aeration time saving from reducing the temperature at the end of the aeration cycle for an arbitrary 15 ppb aeration endpoint.

Table A VPHP levels during aeration testing

Parameter	Test				
	1	2	3	4	5
Total aeration time at end reading (h:min)	1:30	2:00	8:00	9:00	11:00
Aeration 1 (min.)	1	1	1	1	1
Aeration 2 (min.)	59	89	300	360	480
Elapsed aeration 3 at end reading (min.)	30	30	179	179	179
H2O2 end reading	0.5 ppm	< 0.1 ppm	38 ppb	18 ppb	9.4 ppb
Measurement device	Dräger	Dräger	Aero-Laser	Aero-Laser	Aero-Laser

Figure 3 Influence of temperature on low-concentration VPHP levels



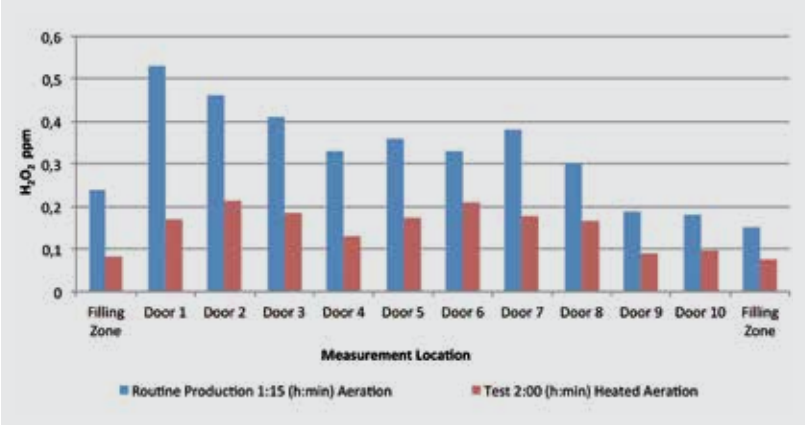
Data Provided Courtesy of Metall + Plastic (Don Eddington) and Cook Pharmica (John Lanier)

Final catalytic panel design

Feasibility results were encouraging, based on residual VPHP levels measured by both systems. The prototype catalytic panels broke down the hydrogen peroxide efficiently; they added too much restriction to the airflow, however. Due to the increased pressure drop added by the prototype panels, the desired unidirectional airflow rate was not being maintained. The commercially available catalyst pellets used to build the prototype panels were not well suited for this application.

A test isolator was used to evaluate different types of catalytic material and panel thicknesses. An updated design for the catalytic panels was implemented using a porous 316L stainless steel substrate that could be coated with a proprietary selection of catalytic metallic oxides. This updated de-

Figure 4 Comparison of routine production and longer heated aeration phases



sign was identified as a promising substitute for the catalytic pellets. The new material had roughly the same catalytic efficiency as the pellets. For a given thickness, panels made from the new material created about half the pressure drop as panels made with the pellet material. Panels ranging from 20 mm to 50 mm thick were tested with isolator UAF velocities ranging from 0.25 to 0.75 m/sec. All panel thicknesses tested exhibited good catalytic activity, with the thickest panels working only slightly better at the highest air velocity tested. The panel design was finalized using catalyst substrate thicknesses as thin as 20 mm.

Isolator retrofit

Isolator retrofit implementation

After the new catalytic panel design was finalized and fully tested, a retrofit was planned for the syringe-filling isolator shown in Figure 1. The goal was to implement the upgrade during a scheduled 3-week shut-down period. The implementation plan included the following steps:

- Preinstallation media fill
- Install catalyst panels
- Update asset and maintenance management systems
- Recertify HEPA filters
- Test for air velocity uniformity
- Perform airflow visualization (smoke) study
- Development study to establish new aeration parameters
- Verify that all other performance requirements work normally, i.e., temperature and humidity control.
- Performance qualification (PQ) with biological indicators (BIs): three replicates
- Post-installation media fill – 3 replicates

Thin (20-mm) catalytic panels were installed above each of the five recirculation HEPA filters. No moving parts were required for the installation. The hydrogen peroxide aeration target for the isolator was 1.0 ppm. Although a heated aeration phase of 40°C was used during the feasibility tests, the setpoint had been increased to 55°C for the most recent production parameters, based on the results of a process improvement study. An extensive heated aeration phase was not required to reach the 1.0 ppm target after the catalytic panel upgrade. The temperature setpoint for the heated aeration phase was dropped from 55 to 30 ºC.

The system has built-in low-level VPHP Dräger Polytron 7000 sensors in the e-beam tunnel, isolator, and material transfer chamber (MTC). The hydrogen peroxide concentration sensors must be ≤ 1.0 ppm in all three sections of the system to allow the transition from aeration to the production mode. Studies conducted after the retrofit determined that a 1:15 aeration process was sufficient to reach VPHP levels of 0.5 ppm in the isolator and MTC and 0.9 ppm in the e-beam tunnel.

A new production VPHP cycle was validated using the 1:15 aeration phase. The decontamination phase maintained a robust theoretical 6+ spore log reduction validated using triplicate BIs and a three-replicate PQ. The maximum load items were used for the decontamination and aeration portions of the PQ. The total cycle time starting with leak test and ending with the aeration concentration check was reduced from 5:30 to 2:45. Preparation for a new production lot—which includes glove leak testing, decontamination, aeration, fluid path setup, and transferring stoppers to the isolators—can easily be done during one work shift; this facilitates staffing and scheduling. Experience gained from the syringe line was utilized during similar catalytic panel retrofits that were performed on a vial-filling isolator and lyophilizer loading and unloading at the same facility.

Isolator retrofit residual concentration study

After the syringe-filling isolator retrofit work plan was completed, studies were conducted to benchmark the residual concentration of VPHP in the isolator using a more sensitive measurement system than the built-in Dräger Polytron sensors. This information can be useful for filling oxidation-sensitive products. The new production 1:15 aeration phase was evaluated using a Picarro G1114 cavity ringdown spectrophotometer that has a VPHP measurement range of 100 ppm to 10 ppb.

In addition to the new production aeration phase, a second test using a longer heated 2:00 aeration phase that used a heating setpoint of 50°C was also conducted. Sampling tubes were installed near the filling zone and near the air-return entrances at the bottom of each of the 10 isolator doors. Both test cycles used a 19°C cooling setpoint for the Aeration 3 phase. After the programmed aeration finished, an initial sample was taken from the filling zone. Readings were taken from the other locations at 5-minute intervals. A final reading was taken from the filling zone. The results are shown in Figure 4. The 2:00 heated aeration reduced the residual VPHP concentration roughly by half when compared to the new routine production 1:15 aeration phase. The measurement locations at the air returns tended to have substantially higher VPHP readings than the readings from the filling zone.

Conclusions

The effort to reduce aeration time in the syringe-filling isolator was a cooperative project that started with a conceptual design and ended with a successful installation and qualification. Total decontamination cycle time from leak test to the completion of aeration was reduced from 5:30 to 2:45. After the addition of the catalytic panels, a prolonged heated aeration phase was not necessary to reach a VPHP target of ≤ 1.0 ppm. Prior to the upgrade the production aeration phase heated the isolator to 55°C. The new routine production aeration phase uses a 30°C setpoint for the heating phase, which lowers energy consumption and reduces stress on the filling machinery. A heated aeration phase is beneficial when trying to reach very low VPHP target levels when required for production of oxidation sensitive products. Cooling down the isolator at the end of the aeration process is also important for reaching the desired low level of VPHP. The implementation of the final design took a highly coordinated effort to perform the work plan during a shutdown period. The investment in time and resources were considerable, but the payback will come from the increased production time that will be available. ■

References

1. Hoffman B., K. Frank, and J. Rauschnabel, "Comparing Energy Consumption of RABS and Isola-tor Configurations," *Pharmaceutical Engineering* 33, no. 6 (2013): 70–78, www.pharmaceuticalengineering.org.
2. Imai K., S. Watanabe, Y. Oshima, M. Kokubo, and J. Akers, "A New Approach to Vapor Hydrogen Peroxide Decontamination of Isolators and Cleanrooms," *Pharmaceutical Engineering* 26, no. 2 (2006): 96–103, www.pharmaceuticalengineering.org.
3. National Institute for Occupational Safety and Health. *NIOSH Pocket Guide to Chemical Hazards*, 3rd printing. NIOSH Publication No. 97-140. Washington, DC: US Government Printing Office, January 2003, p.168.
4. Yin, F., E.A. Vance, P.M. Kovach, G. Troyer, and C. Grothen, "Compatibility Study of Vapor-Phase Hydrogen Peroxide (VPHP) and Biotech Products in Isolators." Presented at the ISPE Washington Conference, June 2007.
5. Walsh, M. and J. Shrake, "Adsorption and Desorption of Vapor Phase Hydrogen Peroxide (VPHP): Implications for Use in Barrier Systems," Presented at the ISPE Tampa Conference, February 2011.
6. Wang, W., T-Y Cui, J. Wang, and S. Martin-Moe, "Oxidation of Protein by Vaporized Sanitizing Agents," *PDA Journal of Pharmaceutical Science and Technology* 58, no. 3 (2004): 121–129.
7. European Commission. Health and Consumers Directorate-General. "Complaints, Quality Defects and Product Recalls." EudraLex Volume 4, *Good Manufacturing Practice* (GMP) Guidelines. 13 August 2014. http://ec.europa.eu/health/files/eudralex/vol-4/2014-08_gmp_chap8.pdf
8. International Organization for Standardization. ISO 14644-1:1999. "Cleanrooms and Associated Controlled Environments—Part 1: Classification of Air Cleanliness." http://www.iso.org/iso/catalogue_detail.htm?csnumber=25052.

About the authors

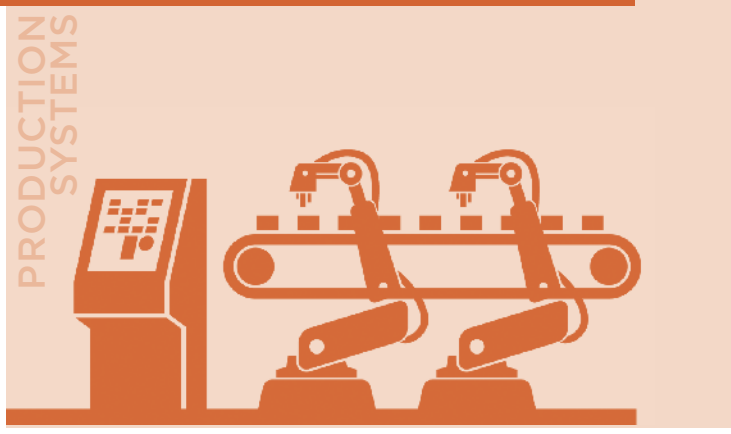
Donald Eddington, PhD, is a Technical Consultant with Eddington and Bond Associates. His prior employment was with METALL+PLASTIC as director of R&D, where he focused on isolators, aseptic processing and hydrogen peroxide decontamination. Prior to M+P, he held various positions at STERIS/AMSCO starting in 1991 as a senior engineer and rising to director of process engineering. His responsibilities included the development and application of hydrogen peroxide sterilization machinery. Eddington received his BS and ME from the University of Florida and his PhD degree from North Carolina State University. Prior to joining the pharmaceutical equipment industry, Eddington held university positions, where his work involved plant disease control, agricultural chemical research and applications of electronics and control systems for agricultural production. Eddington is a long time member of ISPE, the Parenteral Drug Association, and the American Biological Safety Association.

John Lanier is a Process Development Engineer at Tolmar, Inc., in Fort Collins, Colorado. Prior to joining Tolmar, John was a senior process engineer and SME for barrier isolator technology at Cook Pharmica LLC, in Bloomington, Indiana. He has over 27 years' experience in biopharmaceutical process development and large scale manufacturing. His experience ranges from drug substance purification process design and scale-up to drug product formulation and filling. John has a BS degree from Butler University and engineering studies from Rose Hulman Institute of Technology. John is a longtime member of ISPE.

Michael Walsh, PhD, is a chemist in the Process Analytical Technology group at Eli Lilly and Company. Prior to joining Lilly in 2004 he worked at the Dow Chemical Company as a process analytical systems specialist and has also served as a nuclear power engineer in the US Navy. Dr. Walsh has worked in the field of process analytical technology for more than 20 years and has led projects developing new process analytical technologies as well as implementing instruments into production plants including measurement systems for ultra-low VPHP measurements. Dr. Walsh received a Ph.D. degree in analytical chemistry at the University of Illinois at Urbana–Champaign and a BA degree in chemistry at Vanderbilt University.

Jerry Shrake is a chemist at Eli Lilly and Company in Indianapolis, Indiana. His contributions include the design, installation, validation, and support of process analytics systems in pharmaceutical development and manufacturing sites over the past thirty years. These installations include hundreds of online/in-line instrumentation systems such as: pH, conductivity, RI, NIR, UV, VIS, HPLC, electrochemical, and mass-spec based systems. His current role is with the global product protection technical team supporting anti-counterfeiting initiatives.

Stefan Kleinmann, PhD, is the Chief Executive Officer at METALL+PLASTIC GmbH in Radolfzell-Stahringen, Germany, and has served in this position since February 2014. Prior to that, Mr. Kleinmann held global leading positions in the fluid handling, pharmaceutical and process industry. He received his PhD degree in mechanical engineering.



Managing Computer System Retrofit Risks in a GMP Manufacturing Facility

Richard Parapar

This article presents a range of risks that were encountered in successfully retrofitting an advanced but aging distributed control system in a modern pharmaceutical manufacturing facility.

Since the introduction of the first digital process control systems in the 1970s, vendors and integrators of industrial control systems have developed broad experience and expertise implementing sophisticated manufacturing automation systems. In addition to the many advances in computing technologies and process instrumentation, established software modeling and methodologies such as the ANSI/ISA S88 batch control[1] and S95 integration of enterprise and control systems[2] standards and ISPE Good Automated Manufacturing Practices (GAMP)[3] have helped provide solid foundations for successful design and implementation of manufacturing automation systems.

However, as the number and complexity of such systems has grown over time, manufacturers are increasingly faced with significant risks and challenges by their aging systems. There are many factors that can drive a well-functioning manufacturing automation system toward obsolescence:

- Industry shifts away from once-prevalent computing technologies. Transitioning from the UNIX operating system to Microsoft Windows, for example, or even from Windows XP to more current Windows versions will also necessitate replacement of the hardware on which the new software runs.
- Increasing scarcity of critical spare parts. Basic hardware components crucial to once-common system architectures, such as control network interface cards may no longer be manufactured in the physical form factors required by legacy computer hardware platforms.
- Mergers and acquisitions constantly change the vendor landscape with little guarantee that customers will be able to obtain key system components and technical support.
- Loss of key technical resources. Many manufacturers depend on the expertise and institutional knowledge gained by staff members over years of operating and supporting increasingly antiquated systems. As these employees retire, finding experienced engineers and recent graduates to support "ancient" technologies becomes more problematic.

Plant engineering groups are increasingly tasked with updating or replacing systems that are expected to run continuously. While such retrofits must frequently be performed without seriously interrupting or degrading manufacturing operations, delaying a system retrofit for too long can have profound consequences on the profitability and even, in extreme cases, continued existence of the business entity.

Retrofitting manufacturing automation systems in good manufacturing practice (GMP) facilities introduce additional sets of risks and constraints compared with the original system implementations:

- Can the business afford the retrofit? In the life sciences industry, it is not unusual for the cost of lost production to dwarf actual project costs by a factor of 10 or more. In some cases, businesses have chosen to run aging facilities until no longer practical and sell them rather than face the costs and challenges of retrofitting.
- What is the minimum plant downtime needed for system cutover? When can the production schedule afford such an interruption? Can production be shifted to other facilities, or inventories boosted in advance to allow sufficient time for the deployment of replacement systems?
- How much of the plant will be affected by the retrofit? Must the entire facility be impacted at once or can different areas be updated separately? Will unforeseen issues cause prolonged delays in resumption of GMP operations?
- How will standard operating procedures (SOPs) be affected? Will large numbers of SOPs need extensive review, updating, and coordinated release?
- How should training programs for operators and support staff be adjusted? Timing the delivery of training on the replacement system is critical—too early and the training fades before it can be applied, too late and the training is not effective for meeting site performance and quality requirements.
- What's the best way to ensure all regulatory licensing requirements continue to be satisfied? How will critical historical manufacturing data in legacy databases remain secure and accessible over long retention periods, as required by regulatory agencies?

This article discusses many of the risks identified and mitigated in retrofitting an advanced but aging distributed control system (DCS) in the most profitable and productive GMP manufacturing facility in the Roche/Genentech manufacturing network.

Author's note: This article is based on personal experience executing a major control system retrofit project as system architect and technical lead. Except where otherwise noted, all information presented is my own.

CCP1 system landscape

Genentech's first large-scale cell culture production facility (CCP1), located in Vacaville, California, US, is a high-volume active pharmaceutical ingredient manufacturer and global supplier of critical life-extending medications. Initial construction of the facility began in 1995 and licensure was granted by the U.S Food and Drug Administration in April 2000.

The CCP1 facility was Genentech's first highly integrated manufacturing environment, in which major process operations are conducted by a central DCS with relatively little operator interaction. In addition to the DCS, the facility employs an enterprise resource planning (ERP) system, manufacturing execution system (MES), laboratory information management system, and quality assurance (QA) electronic batch record review application to perform many of the activities that are essential for GMP operations. Figure 1 illustrates the major computer systems and software applications that make up the CCP1 manufacturing system environment, using the Purdue "Reference Model for Computer Integrated Manufacturing (CIM)."[4]

Each of the systems in CCP1 provide sophisticated functionality in their own right, but their capabilities and realized value grow exponentially when the systems are integrated to share manufacturing data and work together. While beneficial, such integrations also introduce interdependencies that increase the risk and complexity of performing system retrofits.

Of course, the effort and expense to implement and integrate manufacturing systems does not end with deployment. Validated automation systems in GMP environments must be maintained carefully to ensure they continue to operate consistently and reliably. Unfortunately, even the best-cared-for systems will eventually require replacement as they approach obsolescence.

Following a series of acquisitions, the original CCP1 DCS vendor looked very different in 2007 than when the system was purchased 11 years earlier. Approximately 60% of the DCS components were no longer available for purchase, including the UNIX-based computer servers that ran the supervisory control and data acquisition (SCADA) and batch management applications; the remaining supported components were also approaching end of life.

The most critical DCS component for automated plant operation—the Direktor batch management application—had been declared obsolete by the vendor in 2005 and technical support was becoming increasingly difficult to obtain. While the site maintained a capable engineering and technical support staff, reliance on internal expertise alone was not realistically sustainable for the expected life of the plant.

In late 2007 Genentech became concerned about the effect that possible system failures could have on the facility's ability to deliver the quantities of medications necessary to treat current and projected patient levels. The company conducted a risk assessment to determine the criticality of all major CCP1 systems. For each system component, the assessment identified possible failure modes, likely causes, possibility of occurrence, and probability of detection. Also evaluated were the potential impacts in terms of plant downtime, lost inventory, and of course costs that would continue accruing until return to GMP operation.

The risk assessment showed that both the CCP1 MES and DCS systems were already at or near obsolescence. Most importantly, risk prioritization indicated that a serious DCS server failure that halted the SCADA graphical user interface and batch management applications would have the largest impact on manufacturing operations. It was estimated that the fully burdened cost of an unplanned facility shutdown due to such a failure would exceed $10 million per week.

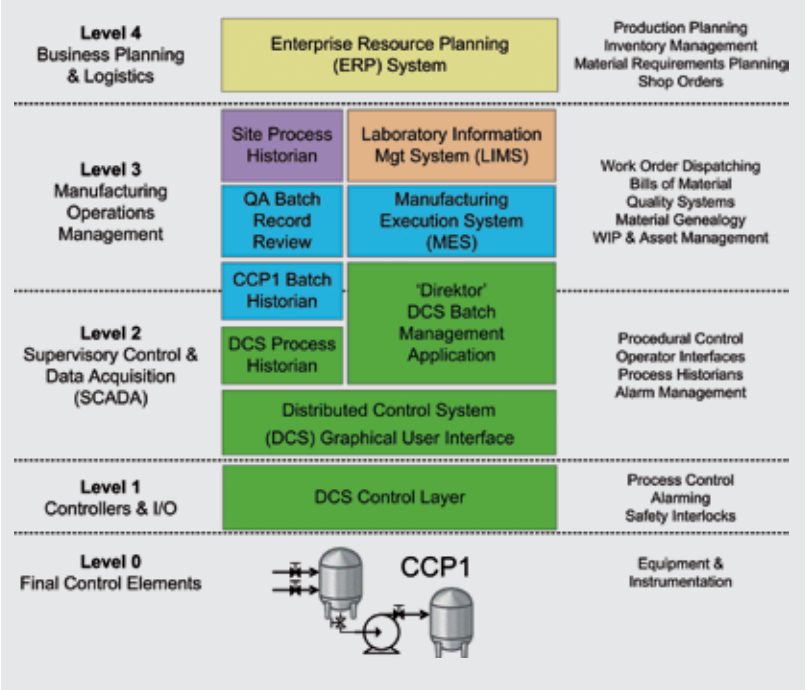
Based on these conclusions, the site initiated a CCP1 DCS retrofit project. The project was tasked with identifying viable risk mitigation strategies, determining technically feasible approaches for their execution, and estimating the associated costs and added risks that each approach would incur. The primary objectives of the project were to:

- Eliminate failure modes that would have multibatch impact and/or result in significant plant downtime
- Extend the support of legacy system components not subject to immediate upgrade through stockpiling of spare parts to buy time for an eventual complete upgrade
- Ensure timely resumption of GMP operation and continued regulatory compliance
- Minimize anticipated project and total system life cycle costs
- Avoid affecting global supply chain by maintaining current production capabilities.

System retrofit risks and considerations

Many kinds of risk must be considered in planning a system retrofit. The most obvious is technical risk—e.g., the possibility that the new or updated system may not function reliably as intended. When the preferred approach

Figure 1 CCP1 system landscape



is to reimplement equivalent legacy capability using modern technologies, the technical risk is relatively low, since the current functionality is already well documented in user requirements and technical specifications. Still, every effort should be made to ensure the updated system environment will operate in a predictable manner and continue to be supported by established vendors with long-term product road maps and upgrade strategies.

Technical risk also aligns with overall project complexity. Replacing several major hardware and software components at the same time greatly increases the project's reliance on effective project management, sound design and engineering standards, and effective inter- and intrateam communications. Upon startup, the new and legacy system components must work together correctly and consistently, or risk incurring frequent production interruptions, product quality deviations, and excessive technical support costs.

Another important consideration is the risk to business continuity: Will the facility resume full production in a timely manner as planned? The business enterprise depends on operational plants to generate inventory and revenue. Vacaville's CCP1 has the capacity to produce almost $1 billion in marketable product each year; every week the plant is offline can cost upward of $10 million. Obviously, minimizing plant downtime for system cutover should be a key consideration in determining the overall magnitude of any retrofit project.

When updating GMP systems and databases, the requirement to manage and retain historical data securely introduces another strategic risk. Regulatory and company quality standards dictate that a product's manufacturing data remain accessible for extended periods, typically greater than 10 years. Major changes in database technologies and application data structures make it difficult, if not impossible, to transfer all the necessary information reliably from legacy to new databases. The potential risk of corrupting or losing GMP data should be thoroughly assessed, as a data migration failure could have serious implications for the facility's continued right to operate.

Production scheduling is another factor in planning major system retrofits, as the master production schedule will inevitably be affected. Many aspects of deployment timing should be considered, such as:

- When does the production schedule present the best window for taking the facility offline to perform the cutover?
- What is the maximum allowable downtime that can be tolerated?
- Can product inventory be increased in advance of the shutdown, or production transferred to other facilities?
- From the project's perspective, will there be sufficient time prior to the optimum shutdown window to complete system development and testing?

Of course, the greater the overall scope of work, the more upfront time will be required to evaluate, implement, and validate new systems and interfaces.

There are also various costs to be estimated. Again, the most obvious are the up-front capital material and labor costs for purchasing, engineering, and commissioning new systems. In a GMP environment, there are the additional costs for system installation qualification (IQ), operational qualification (OQ) and process qualification (PQ), which can often exceed 30% of

the total project budget. Following deployment, there will also be ongoing support and maintenance costs. These all contribute to the system's total cost of ownership.

Different strategies for extending a manufacturing facility's productive life span will incur different levels of risk, costs, and schedule impact. The simplest and most straightforward strategy is to stockpile as many critical spares as possible from the original vendor and other suppliers. Even e-commerce sites such as eBay should be explored. If sufficient quantities can be secured, such a strategy can help keep the plant operational for a few more years and, most importantly, buy valuable time for to plan and implement additional, more extensive retrofit efforts.

Two more complex strategies are "transformational" and "like-for-like" system retrofits. In a transformational retrofit, the implementation of new applications and technologies will also entail making changes to established business processes and workflows, organizational responsibilities, and perhaps even familiar terminology. Transformational retrofits are often appealing because they promise greater capabilities and higher efficiencies when compared with current legacy systems. However, transformational retrofits introduce their own risks and costs, in many cases exceeding those of a greenfield installation, because of extensive shutdown requirements and potential impact to existing operations.

In like-for-like retrofits, legacy system hardware and software components are replaced with newer applications and technologies that maintain consistency with the current system functionality. While such retrofits depend on commercial availability of compatible products, or possibly custom development based on newer technologies, they have the advantage of being significantly less disruptive to proven business processes and manufacturing operations. In many situations, a like-for-like retrofit may be the only viable solution due to low business tolerance for extended cutover downtime.

Clearly, there are several important and interrelated considerations when planning a system retrofit, such as: overall scope; technical, data migration and business continuity risks; impact to production schedules; and system implementation and total life cycle costs. All should be carefully assessed prior to embarking on a major system retrofit project.

CCP1 DCS system retrofit

Initially, Genentech management preferred a transformational approach to retrofitting the legacy DCS system to better align CCP1 systems with current corporate automation standards and global vendors. The industrial controls vendor responsible for implementing automation systems in greenfield Genentech manufacturing facilities was asked to perform an engineering study for a total DCS replacement in CCP1.

After a year-long evaluation of current CCP1 system functionality, retrofit project requirements, and their own product capabilities, the vendor estimated that an entirely new DCS, including reimplementation of all interfaces with external systems, would necessitate a 6-to-8 month production shutdown, with total costs exceeding $125 million. Unfortunately, the potential value in standardizing systems and technical support across sites would be offset by the disruption to CCP1 operations arising from incompatibilities between the vendor's product and rest of the manufacturing system environment.

The CCP1 DCS retrofit project team was then challenged with finding a more practical and cost-effective upgrade strategy. The team chose a like-for-like approach and began to explore ways to implement equivalent (or slightly improved) current functionality. Clearly, replacing the legacy DCS would have to be done in multiple phases for the project to be economically feasible. A "vertical" area-by-area retrofit of individual plant sections was first considered (Figure 2), but rejected due to the additional complexities such an approach would incur, including:

- Needing to maintain and support both legacy and new DCS systems concurrently
- Integrating common process operations across both systems, particularly clean-in-place (CIP), sterilization-in-place (SIP), and utility subsystems that support wide areas of the plant
- Ensuring proper handling of GMP data from both legacy and new DCS platforms in the MES, process and batch historians, and QA batch review systems
- Requirements for operators to be trained and qualified on both systems

The project team found that the best way to minimize risk, deployment downtime, and overall cost was to perform the DCS retrofit in two "horizontal" layered phases (Figure 3). The first phase would replace the legacy DCS SCADA user interface, batch management application, and embedded process historian. In addition, all DCS interfaces to other manufacturing and quality systems would need to be reestablished. A subsequent project phase would address replacement of the DCS control layer, i.e., the control network, process controllers and input/output (I/O) modules that monitor field instrumentation and manipulate plant equipment such as motors, pumps, and valves.

The major benefit of this approach would be to address the most critical DCS risks identified in the risk assessment quickly, while buying additional time to plan later replacement of the DCS control layer. Limiting project scope in this way would also help better focus constrained internal engineering resources and reduce the risk of hurried and/or poor design decisions.

Replacing the legacy UNIX computer servers with new Microsoft Windows–based platforms would fundamentally change the DCS system architecture, particularly in the number of server platforms that would be needed. Figure 4 contrasts the size and complexity of the legacy and new CCP1 DCS server architectures. Finding sufficient space to install the new equipment in a computer room already filled with equipment racks, power cables, and network wiring without disturbing the existing systems was going to be a major challenge.

Figure 2 "Vertical" area-by-area retrofit approach

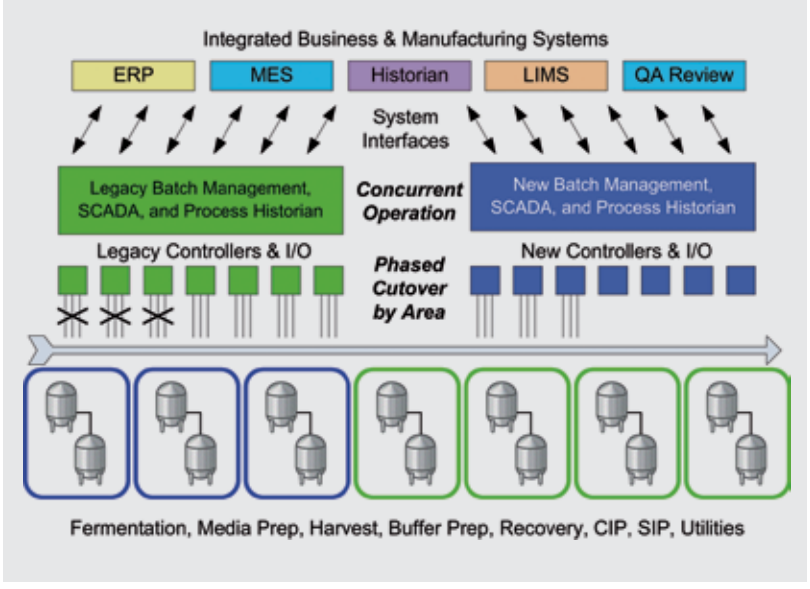
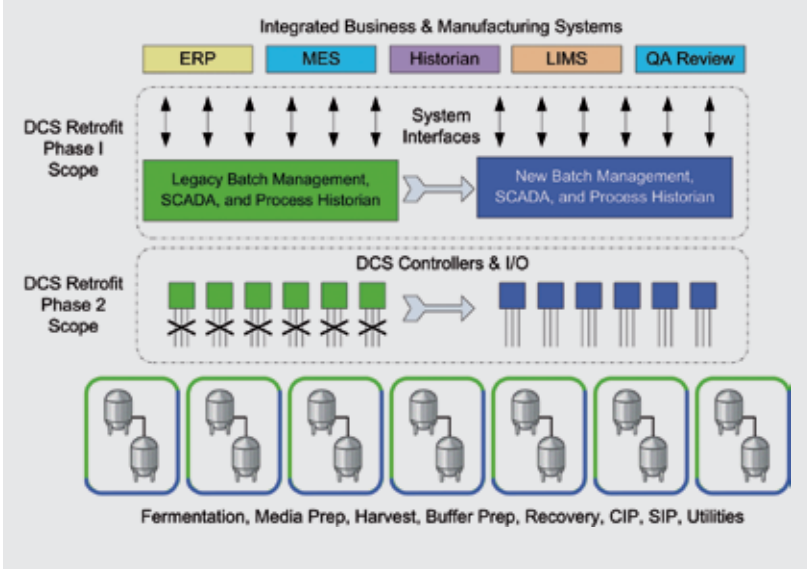


Figure 3 "Horizontal" layered retrofit approach



To minimize physical impact to the computer room and operational risk to running systems, computing virtualization technologies were employed that allow dozens of different operating systems and software applications to run on high capacity blade servers residing in a single redundant pair of physical chassis. With virtualization, the project was able to deploy over 122 new computing platforms to create three separate development, validation, and production system environments without affecting the legacy DCS servers, computer equipment racks, and associated infrastructure (e.g., power distribution, system networking, and environmental controls).

Automated batch database migration

Although the UNIX-based Direktor batch management application was obsolete and unsupported, the Microsoft Windows–based InBatch application (from Wonderware) had evolved from Direktor and still maintained broad compatibility with the user interface and batch functionality. Another carryover from Direktor to InBatch was the application program interface (API) library of software functions for customizing batch management functionality and interfaces to external systems. Because the two APIs were so similar, updating the DCS integrations with other systems would not require redesign or changes to current functionality.

Given the amount of process and equipment automation invested in the Direktor application, there was a worry that manually reentering over 1,000 validated recipes and associated information into InBatch would

put this valuable intellectual property at risk. Extensive requalification of the entire InBatch configuration (much of it occurring during the plant shutdown) would also be necessary to ensure the complete and accurate transfer of the configuration data.

Jointly, Genentech and Wonderware evaluated creating a software program to migrate the recipe, equipment, and material information automatically from Direktor to InBatch. They found that developing and validating an automated migration program would require significantly less time than manual transfer and requalification of the information. And notably, the entire migration process could be repeated many times for extensive testing and qualification prior to cutover. In the end, the automated migration solution delivered a much more reliable and cost effective result than manual data entry.

Like-for-like user interface and graphics

Choosing a compatible batch management application that permitted automated migration of the CCP1 batch configuration was an important step. But the project still needed to minimize the operational impact the new DCS user interface and process graphics would have in terms of operator retraining and changes to SOPs. Budgeting estimates held that, on average, revising a "typical" SOP required 80 man-hours at a cost of $10,000. In the case of CCP1, hundreds of SOPs would need to be reviewed and, if affected, updated, approved, and released in a well-coordinated manner. These concerns drove the decision to reimplement the entire set of existing DCS user interface and process graphic displays as nearly as possible to their original design (Figure 5).

Application of S88-based modeling in the original implementation had encouraged extensive use of template-driven process equipment classes and associated graphic displays. Still, the CCP1 DCS user interface contained almost 2,000 individual control module faceplates, process graphics, and user navigation displays that would need to be reimplemented and qualified. Accordingly, the current display design specifications were extensively reviewed against the actual system to ensure their completeness and accuracy. These specifications formed the basis of design for subsequent development and testing of the recreated displays.

There were drawbacks to the like-for-like approach, such as not being able to leverage newer human-machine interface (HMI) design standards. The original DCS process graphics were piping and instrumentation diagram–centric, a style that was popular in the 1990s. They employed black backgrounds with bright and flashing colors to represent process parameters, tank levels, and equipment status. Studies have since shown that process displays are more effective with subtle grey backgrounds and colors employed only to annunciate alarms and operating conditions outside normal boundaries. While it would have been preferable for implementation of the new CCP1 DCS user interface to leverage current HMI design standards, the resulting operational disruptions, as well as additional training and associated costs, would have been unacceptable.

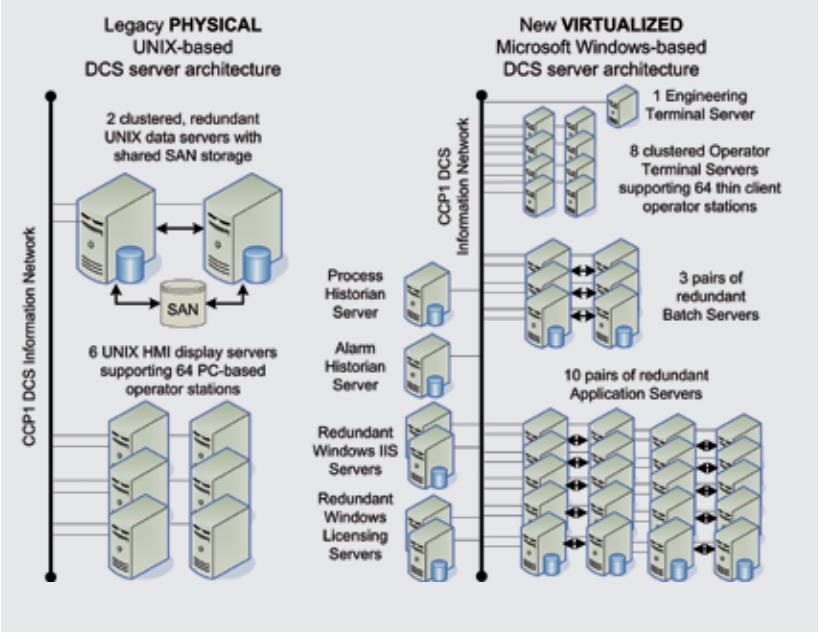
Performance benchmarking

Ensuring that the retrofitted DCS would allow the plant to resume and hopefully exceed its historical operating performance was an important objective. As the facility had already been in GMP operation for over a decade, there was a wealth of key performance metrics that could be used to benchmark target performance levels. These included average and maximum numbers of recipe procedures running at the same time, numbers of open batch clients, and active DCS operator terminals in concurrent use. Also quantified where the number of open displays per terminal, complexity of process graphic displays in terms of controller tag quantities and refresh rates, and transaction volumes between the DCS SCADA and control layer, as well as between the DCS and external systems.

As development of major DCS components neared completion, they were staged in a performance test environment that included a full recreation of the DCS control network with actual controllers running communications simulation logic. Performance testing first conducted on the legacy DCS was repeated on the new DCS to collect equivalent metrics. This verified acceptable performance levels prior to cutover.

In addition to demonstrating before and after performance, establishing an accurate characterization of DCS performance targets early in the project also helped to determine the best system configuration for the new DCS implementation, including number of required computing platforms and optimum OPC data groupings and exchange rates between the SCADA and process control layers. With this information, key adjustments to the underlying infrastructure were made before they could affect downstream development activities and the project schedule.

Figure 4 CCP1 legacy and virtualized DCS server architectures



Offline qualification

Separating the CCP1 DCS retrofit project into the two horizontal phases also changed the fundamental nature of the initial effort from a control system retrofit to an information technology (IT) retrofit. This yielded a major benefit: the ability to perform offline qualification testing of the new DCS functionality.

By their nature, control systems are tied closely to instrumentation and process equipment. Consequently, the bulk of control system testing must typically be performed using the actual equipment, as replicating or simulating the process environment can be not only expensive but difficult to achieve with sufficient levels of completeness and accuracy.

Adapting an IT-centric perspective meant that all of the new DCS computing hardware, software, and networking components could be staged and qualified outside of the process environment and far in advance of their actual deployment. Spare controllers were set up with sufficient simulation logic to replicate the communications load between SCADA/batch and process control layers. This permitted extensive testing and full qualification of recipe migration procedures, new user interface and process graphic displays, and DCS interfaces to the external systems.

Because the majority of IQ and OQ activities were conducted offline far in advance of cutover, the testing was not subject to high time-pressure constraints. This allowed more comprehensive and thorough testing than would have been possible given the time constraints for online testing during cutover. In addition to minimizing plant downtime, another advantage of offline testing was to shorten the overall project duration. The majority of testing was conducted in parallel with design and development activities. This revealed functional and performance issues early, allowing them to be resolved while still in development. Careful planning and coordination of software development and testing activities reduced need to retest due to late-stage design changes.

While offline IQ and OQ testing of the new DCS greatly reduced the time required for cutover, it did incur additional configuration management overhead for the project. Once initial IQ was complete, the new DCS hardware platforms had to be maintained under formal change control to avoid degrading their validated status. Updating operating systems, applying vendor application patches, and keeping security and anti-virus software up to date still had to be performed regularly. Similarly, strict change management and version control was maintained for all new software components as each completed qualification and was installed into the validated environment.

When time came to halt CCP1 production and shut down the legacy DCS, all OQ testing had been completed successfully. The transition from old to new DCS platforms was performed in 8 hours. Cutover entailed switching network cables, starting up computer processes and system interfaces in the proper sequence, and completing IQ testing and documentation. CCP1 operators spent the next 9 days exercising the new DCS functionality by executing the automated CIP and SIP procedures necessary to return the plant to GMP operation following a shutdown.

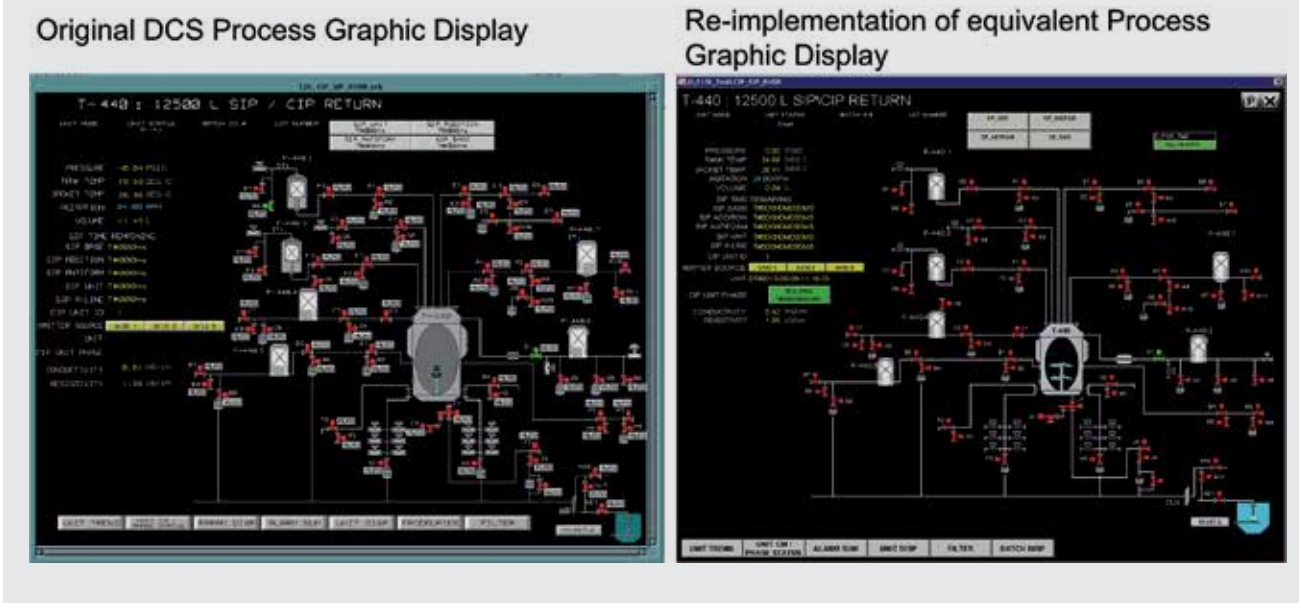
Subsequent PQ testing included a 3-month GMP campaign to manufacture a product with which the site already had extensive experience. This eliminated the possibility of introducing process-related issues associated with a new product transfer. The campaign was conducted at full production run rates with no system discrepancies or product deviations due to the new DCS. Successful completion of all PQ testing provided final verification that full GMP operation of the facility had been restored.

Results and next steps

Phase 1 of the CCP1 DCS retrofit project completed in August 2013 with all business and technical objectives met or exceeded. Total project duration from initial pilot study to PQ completion spanned 40 months. To date, unplanned downtime has been reduced 95% since the plant's return to GMP operation in May 2013. Total project costs were in the $30 million range and were easily justified by the extended DCS lifespan and continued productivity of the plant.

Additional projects to retrofit the remaining legacy DCS control layer and CCP1 MES are currently in planning stages and will likely apply the lessons learned on this project. Both projects will employ a like-for-like system replacement strategy. The MES retrofit project, also being IT-centric, will benefit from significant offline qualification testing, resulting in minimal disruption to plant operations.

Figure 5 CCP1 process graphic comparison



On the other hand, phase 2 of the DCS retrofit to replace the legacy control layer will present new challenges as the project team evaluates how best to minimize cutover downtime and resulting loss of production. The first of two promising technical solutions being evaluated is an automated control logic migration program (similar to the batch database migration) that would help minimize online testing requirements. The other eliminates the need to revalidate field wiring by installing new DCS I/O cards that are physically and functionally identical to the legacy cards. It is anticipated that utilization of these technologies will help deliver acceptable cutover durations and total project costs.

Conclusion

The CCP1 facility was Genentech's first implementation of a fully integrated manufacturing system environment. Not surprisingly, CCP1 was also the first to face critical system obsolescence issues. Most, if not all of the major pharmaceutical manufacturing facilities in the life sciences industry will eventually encounter similar issues.

Pharmaceutical manufacturers must rely upon their system automation technologies to deliver quality products that improve patient care, while meeting strict regulatory requirements and ensuring business efficiency. Retrofit projects to apply vital technology updates will be necessary to extend the productive life spans of aging manufacturing systems.

Engineers tasked with replacing legacy systems in GMP environments should understand the many challenges associated with retrofit projects so that they can successfully manage the risks involved. Continued profitability of pharmaceutical manufacturing operations will hinge on the proper planning and execution of these efforts. ■

References

1. International Society of Automation. Standard ISA88, "Batch Control." https://www.isa.org/isa88.
2. International Society of Automation. Standard ISA95, "Enterprise-Control System Integration." https://www.isa.org/isa95.
3. International Society for Pharmaceutical Engineering. "GAMP Resources." http://www.ispe.org/gamp-resources.
4. Purdue Research Foundation. "A Reference Model for Computer Integrated Manufacturing (CIM)," edited by Theodore J. Williams. Research Triangle Park, North Carolina, US: Instrument Society of America, 1989.

About the authors

Richard Parapar has almost 35 years' experience developing advanced automation solutions for the life sciences, petrochemical refining, high-purity gas production, and consumer food processing industries. Richard recently retired after 21+ years at Genentech/Roche as a Senior Principal Engineer and Technical Lead for Automation Engineering. In this role he was responsible for delivery of major strategic information management and manufacturing automation projects and shaping the long-term direction of manufacturing execution systems and process control systems for Genentech. Richard graduated from Rensselaer Polytechnic Institute with a BS degree in computer and systems engineering. He is an ISPE member and formerly served on the World Batch Forum board of directors as host committee chairman (1999–2000).

Advertisers' index

Alfa Laval Lund AB	Back cover
Azzur Group LLC	Inside back cover
Brookfield Engineering Laboratories, Inc.	82
Burkert	29
Camfil Air Pollution Control	Inside front cover
Commissioning Agents	21
Computational Dynamics, Ltd	81
CRB	1
EI Associates	77
Electro-Steam	87
Elettracqua Srl	47
Fristam Pumps USA	7
Ing. Punzenberger COPA-DATA GmbH	26
Intelligen Inc	39
Letzner Pharmawasseraufbereitung GmbH	5
Mar Cor Purification	48
Novo Nordisk	25
Pharmadule Morimatsu AB	65
ProPharma Group	3
Watson Marlow	43

Classified advertising

Please see the ads for each of our advertisers in this issue.

API Manufacturing

Novo Nordisk
800 Scudders Mill Road
Plainsboro, NJ 08536

Architects, Engineers, Constructors

CRB
7410 N.W. Tiffany Springs Parkway, Suite 100
Kansas City, MO 64153 USA
Tel: +1 816-880-9800

EI Associates
8 Ridgedale Avenue
Cedar Knolls, NJ 07927 USA
Tel: +1 973-775-7777

Pharmadule Morimatsu AB
DanvikCenter 28
SE-13130 Nacka, Sweden
Tel: +46 (0)8 587 42 000

Dust Collection Systems and Equipment

Camfil Air Pollution Control
3505 S. Airport Drive
Jonesboro, AR 72401 USA
Tel: +1 870-933-8048

Electric Dry Steam Generators

Information Technology

Ing. Punzenberger COPA-DATA GmbH
Karolingerstrasse 7b
Salzburg, Austria 5020
Tel: +43 662 43 10 02-0

Instrumentation

Bürkert Werke GmbH
Christian-Bürkert-Strasse 13-17
D-74653 Ingelfingen, Germany
Tel: +49 (0)7940 10 0

Instruments and Controls

Brookfield Engineering Laboratories, Inc.
11 Commerce Boulevard
Middleboro, MA 02346
Tel: +1 508- 946-6200

Pumps

Alfa Laval, Inc.
5400 International Trade Drive
Richmond, VA 23231 USA
Tel: +1 804-222-5300

Fristam Pumps USA
2410 Parview Road
Middleton, WI 53562 USA
Tel: +1 800-841-5001

Watson Marlow Fluid Technology Group
37 Upton Technology Park
Wilmington, MA 01887 USA
Tel: +1 800-282-8823

Software/Hardware Products

Computational Dynamics, Ltd.,
60 Broadhollow Road
Melville, NY 11747 USA
Tel: +1 631-549-2300

Software Simulation and Processing Systems

Intelligen, Inc.
2326 Morse Avenue
Scotch Plains, NJ 07076 USA
Tel: +1 908-654-0088

Validation Services

Azzur Group, LLC
726 Fitzwatertown Road, Suite 6
Willow Grove, PA 19090 USA
Tel: +1 215-322-8322

Commissioning Agents, Inc.
652 N. Girls School Road
Indianapolis, IN 46214 USA
Tel: +1 317-271-6082

ProPharma Group, Inc.
10975 Benson Drive., Suite 330
Corporate Woods Bldg. 12
Overland Park, KS 66210 USA
Tel: +1 913-661-1662

Water/Steam Systems

Letzner Pharmawasseraufbereitung GmbH
Robert Koch Str. 1
42499 Hückeswagen, Germany
Tel: +492192/92170

Water Treatment and Purification

ELETTRACQUA Srl
Via Adamoli 513
16165 Genoa, Italy
Tel: +39 010 8300014

Mar Cor Purification
160 Stedman Street
Lowell, MA 01851 USA
Tel: +1 978-453-9600

The Future of Brand Names

Anyone who has gone through the process of naming a child—a few days of brainstorming, head scratching, and compromise—might believe that branding a new drug is no more difficult. But considering that the process begins with a list of as many as a thousand invented candidates, is whittled that down to a handful, requires approval from exacting third parties with veto power, can take more than a year to complete, and has a bill that runs upward of $250,000, [1] that person would be wrong.

The long road to US Food and Drug Administration (FDA) approval becomes more twisted with each approved name. Besides legal and trademark concerns, the ultimate goal is to clear regulatory hurdles aimed at preventing prescription errors and avoiding inherent claims about efficacy.

The process starts during Phase II trials with a long list of invented names, most of which are eliminated through a series of filters:

- Has the name already been taken?
- Does it sound like another drug?
- Can it be pronounced and distinguished orthographically and verbally from all existing medications?
- Does it mean something negative or offensive in any common language?

Drug makers have turned to brand consultants to help navigate these complexities. By the time the consultancy hands off its short list to the client, fewer than a dozen names remain. The company then submits a primary name and one or two backups to regulators.

"There are so many hurdles, you can understand why it's becoming more challenging to get a name cleared," says Suzanne Martinez, Associate Creative Director at InterbrandHealth. This might explain the recent spate of difficult-to-pronounce names that have more letters, more syllables, and awkward letter strings. Though her company had home run success naming Prozac and Viagra in the 1980s and 1990s, she admits that those names would never be approved today.

Every drug has at least three names: chemical, brand, and generic. The latter two must be approved by bodies such as the FDA and the European Medicines Agency, which strive to ensure that names are constructed to avoid medication errors. The name must look unique when handwritten, since scrawled scrips are still common, and many states do not require physicians to type them. [2]

Take Brilinta (a blood thinner approved in 2011) and Brintellix (an antidepressant approved in 2013). The FDA's Division of Medication Error had received 50 reports of medication errors involving these two drugs by June 2015. [3]

"The future of naming will be tricky," says Martinez. "We can make the name longer, which nobody wants to do for pronunciation and translation purposes, or continue to look for awkward letter combinations, specifically at the beginning of the name. The trend is to create surprising new names that can get clearance from regulatory"—hence names such as Addyi, Xifaxan, Nuwiq, and Avycaz, all approved by the FDA in 2015. [4]

Scott Piergrossi, Vice President, Creative at Brand Institute, which came up with Lipitor, Lunesta, and Gardasil, agrees: "As the name-review process gets more conservative, is there a point at which the 'spell-ability' and intuitive pronunciation of a name becomes a significant consideration in determining its approvability?" he asks. "Currently, that's a conversation I don't see on the horizon."

While companies have historically created memorable names, many are turning to broader branding strategies as names become more difficult to spell. Consultancies are also considering the emotional response of consumers, who are now more involved in treatment decisions. "The entire approach to marketing a new drug has changed," says Martinez. "We need other elements that inform a campaign for a new product that describe what makes it special."

The focus has turned to visual identity, involving the brand logo, color palette, photography, and imagery. One powerful branding opportunity is the color of a drug, which is reflected in Addyi, the pink Viagra for women, or Nexium's focus on its purple pill.

Although the brand name game is tighter, home runs are still possible.

"The name I'm most proud of is Bexsero," says Martinez, about the serogroup B meningitis vaccine. "It's a scientific and descriptive name that's memorable. But we've got away from the expected letter strings that are associated with other meningitis drugs."

Piergrossi points to the hematology product Alprolix. "It signifies prolonged half-life, a more stable product and includes 'ix,' which refers to [coagulant] factor IX."

"Companies can't rely on short, memorable, easy-to-pronounce names anymore," says Martinez. "The name is becoming almost a throwaway, so they are spending more time developing other assets of their brand." ■

By James Hale and Scott Fotheringham, PhD

1. "Making Drug Names Easy to Swallow." *Wall Street Journal*, 30 June 2010. http://www.brandinstitute.com/wallstreet2010.asp.
2. Nordrum, Amy. "Why do Prescription Drugs Have Such Weird Names?" International Business Times, 24 June 2015. www.ibtimes.com/why-do-prescription-drugs-have-such-weird-names-blame-branding-consultants-fda-1981819.
3. Mezher, Micnael. "FDA: Brand Name Confusion Led to Dozens of Medication Errors." Regulatory Affairs Professionals Society, 31 July 2015. www.raps.org/Regulatory-Focus/News/2015/07/31/22951/FDA-Brand-Name-Confusion-Led-to-Dozens-of-Medication-Errors.
4. Center Watch. "2015 FDA Approved Drugs." www.centerwatch.com/drug-information/fda-approved-drugs.

ACTIONS SPEAK LOUDER

Some companies say they can do it all, but we've taken the steps to ensure that we actually can.
We build partnerships, foster employee growth, and value good old-fashioned hard work.
Whatever you need, we're ready to provide...from Discovery to Delivery™.

AZZUR GROUP

AZZUR CONSULTING
HEADQUARTERS
Ryan Ott: Ext. 517
Kevin Martin: Ext. 509

MID-ATLANTIC
Nate Roman: Ext. 519

SOUTHEAST
Shelley Preslar: Ext. 512

NEW ENGLAND
Chris Mansur: Ext. 520
Ravi Samavedam: Ext. 201

CALIFORNIA
Brad Lozan: Ext. 30

AZZUR ENGINEERING
Dave Manku: Ext. 103

AZZUR WORKFORCE
Thomas O'Donnell: Ext. 514
Shaleen Parekh: Ext. 101

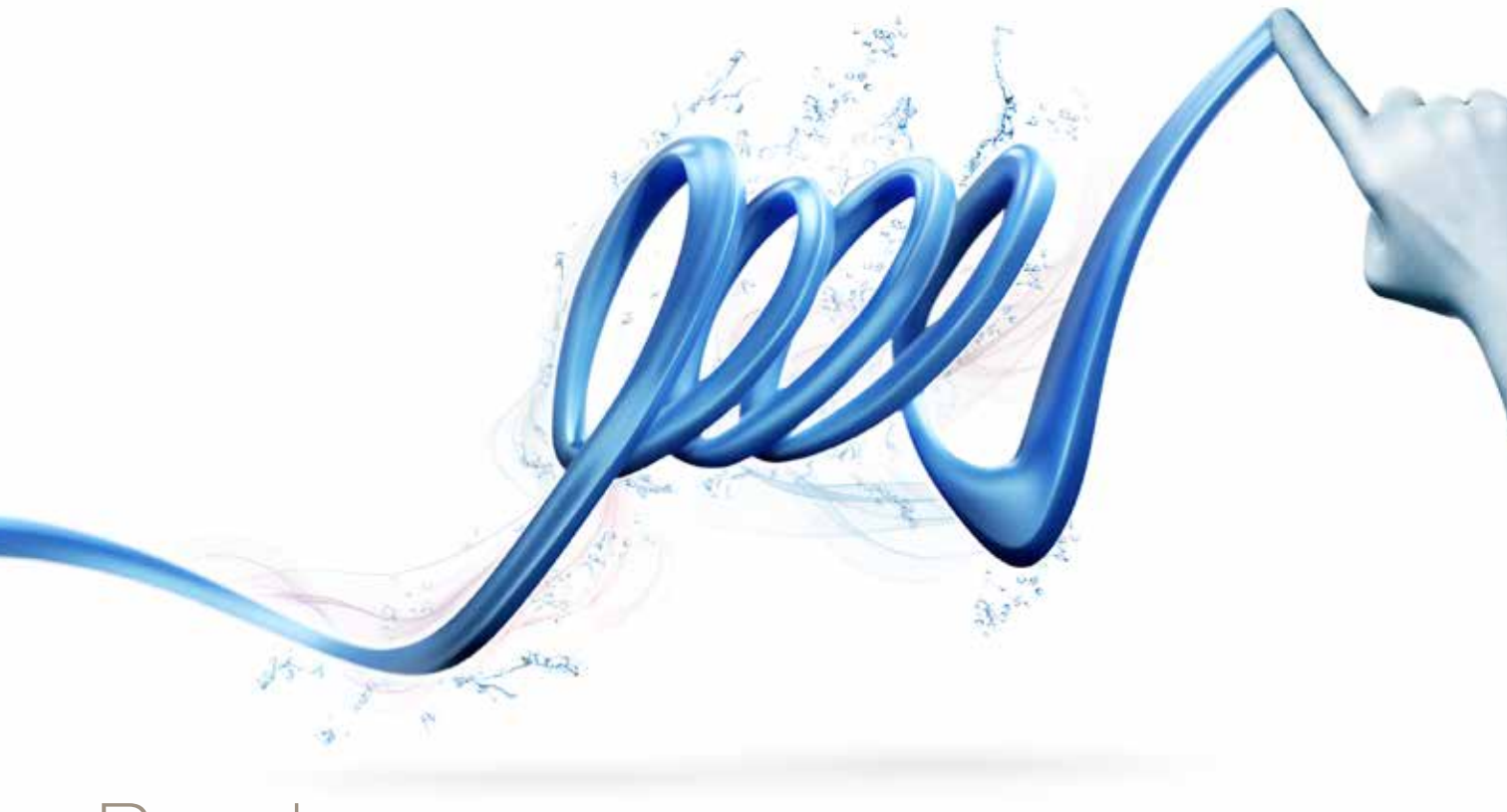
AZZUR LABS
Kym Faylor: Ext. 521

AZZUR TECHNICAL SERVICES
Mark O'Donnell: Ext. 513
Kym Faylor: Ext. 512

AZZUR IT
Doug Shaw: Ext. 650

Inc. 5000

AZZUR.COM | 1.800.726.0331



Premium goes Prime

Introducing the self-priming pump developed for the pharmaceutical industry: the Alfa Laval LKH Prime UltraPure

The premium Alfa Laval UltraPure range of centrifugal pumps just gained a new family member, the Alfa Laval LKH Prime UltraPure. This energy-efficient, self-priming pump supplied with Q-doc documentation package is designed to meet the most stringent demands of the pharmaceuticals industry.
Designed primarily for Cleaning-in-Place duties and with the ability to pump product, this versatile, reliable, prime-performing pump delivers safe and hygienic production and increased uptime.

It's time to go Prime. Learn how at alfalaval.com/lkhprimeup

Alfa Laval
LKH Prime UltraPure

Alfa Laval
LKH Prime

Alfa Laval
LKH

Alfa Laval
LKH UltraPure

Alfa Laval
LKHPF

Alfa Laval
LKH Multistage

Alfa Laval
LKH Evap

Alfa Laval
LKH Ex