PHARMACEUTICAL ENGINEERING®

THE OFFICIAL TECHNICAL MAGAZINE OF ISPE

SEPTEMBER/OCTOBER 2014 VOLUME 34, NUMBER 5

Pharmaceutical Product Quality

Single Use, Disposable Technology

User Centric Batch Operations

Lean Pharmaceutical Lab Design

Legacy Products and Process Validation

Common Regulatory Misunderstandings

Cloud Computing

Interview with Chi-Wan Chen, Pfizer

ISPE's Drug Shortages Prevention Plan
Interview with François Sallans,
Chair of Drug Shortages Initiative Team

Pharma EXPO Preview

Connecting a World of Pharmaceutical Knowledge

ISPE®

www.PharmaceuticalEngineering.org

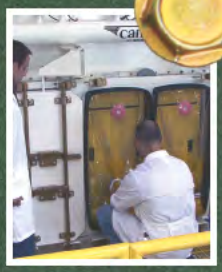
GENERAL VENTILATION TABLET PRESSES GRANULATING
TABLET COATING FILLING & PACKAGING
MIXING & BLENDING LOCAL EXHAUST
DRYING CENTRAL VACUUM
AND MORE

DUST PROBLEMS SOLVED

Farr Gold Series® Industrial Dust Collector

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.

S LIKE A SAFE BECAUSE IT'S

BUILT LIKE A SAFE™

877-749-8664 www.camfilapc.com

camfil
AIR POLLUTION CONTROL

PHARMA EXPO™

JOINT VENTURE

PMMI ISPE

Processing & Packaging Conference and Tradeshow

November 2–5, 2014 • Chicago, Illinois USA

Smart Solutions for Lifecycle Innovation

Where Innovators Learn To Stay Ahead.

At Pharma EXPO, you'll get up to speed on trends you need to know. Each day of the robust 33-session conference program focuses on a specific manufacturing, compliance and packaging topic critical to the success of the pharmaceutical lifecycle.

Visit **pharmaexpo.com** for complete conference program information.

Learn about the industry's most advanced solutions.

Add to Your Tradeshow Experience
Attend an ISPE Education Session

Step Up to the ISPE Knowledge Bar
BOOTH #W-330

CONNECT, SHARE AND NETWORK

Show Hours

Sunday – Tuesday
9:00 am – 5:00 pm
Wednesday
9:00 am – 3:00 pm

Co-located with:

PACK EXPO ADVANCING PROCESSING AND PACKAGING

Register at pharmaexpo.com today.

BENEFIT FROM 33 WORLD-CLASS EDUCATION SESSIONS.



Overview of the sessions:

DAY 1: MONDAY, NOVEMBER 3
MANUFACTURING OPERATIONS TRACK

- Managing the Design of a Single-Use Facility
- Convergence: The Connected Machine
- Automation Project Ishikawa

KEYNOTE

- ASTM E2500 Approach to Quality Risk Management: Part I
- Application in Additive Manufacturing/3D Printing
- Chemical and Media-Free Pretreatment for Biopharma RO
- EBR Deployment: Part I

- ASTM E2500 Approach to Quality Risk Management: Part II
- Excellence in Quality
- Improving the Compounding Process
- EBR Deployment: Part II

DAY 2: TUESDAY, NOVEMBER 4
COMPLIANCE TRENDS TRACK

- New Options in Anti-Counterfeiting
- Global Approach to Serialization
- Eliminating 483's Based on Regulatory Observations

KEYNOTE

- Managing and Assuring Quality: Part I
- The Next Big Thing for Nutraceuticals
- Tools for Successful Serialization Implementation
- Global Serialization Deployment

- Serialization: A Comprehensive Overview: Part II
- Managing and Assuring Quality: Part II
- Using Technology to Meet FDA Serialization Requirements
- ISPE Drug Shortages—A Special ISPE Report

DAY 3: WEDNESDAY, NOVEMBER 5
PHARMACEUTICAL PACKAGING TRACK

- Identification Using 2D Barcode Technology
- Thermal Imaging Inspection & Detection on High-Speed Production Lines
- Package Component Specifications of Consent Decree

KEYNOTE

- Package Prototyping and Implementing 3D Printing
- Transforming the Pharmaceutical Supply Chain
- Flexible-Isolator-Filling-Line
- Maximizing Your Productivity and Protecting Vial Integrity

- The Evolution of Visual and Automated Inspection
- Improving Packaging Line Efficiency with Simulation
- Single-Use Final Fill Assembly Implementation
- "Predictive" Condition Monitoring Using Machine Learning

A Sample of Sessions Offered:

MONDAY

Automation Project Ishikawa

Using Ishikawa diagrams, the goal is to provide a working knowledge of factors, which if not addressed early, could jeopardize any Automation project.

Applications in Additive Manufacturing/3D Printing

An introduction to the world of Additive Manufacturing/3D Printing technologies and how they are applied in health care.

TUESDAY

Managing and Assuring Quality: Part I

Hear how to develop and implement programs and systems to effectively and efficiently manage product quality, and the tools to enable a fundamental science and risk-based controlling processes.

Drug Shortages—A Special ISPE Report

This session will present recommendations from the ISPE Drug Shortages Prevention Plan for managing the multiple internal activities required when facing shortage situation.

WEDNESDAY

Thermal Imaging Inspection & Detection on High-Speed Production Lines

A 100% real time inspection system that is totally non-invasive and not limited by line speed is needed to provide continuous serialized control of individual packages.

Improving Packaging Line Efficiency with Simulation

A process model can be used to increase throughput and improve efficiency, helping attendees to understand the role of simulation in driving process improvements and lowering costs.

Visit pharmaexpo.com to register and for complete conference details.

PHARMA EXPO™

Keynote sessions are free and open to all registered attendees

DAY 1: 9:00 am – 9:45 am
KEYNOTE SPEAKER:
Michael James, Site Leader, SAFC Biosciences, Division of Sigma Aldrich

DAY 2: 9:00 am – 9:45 am
KEYNOTE SPEAKER:
TJ Cristl, FDA, Invited

DAY 3: 9:00 am – 9:45 am
KEYNOTE SPEAKER:
Dan Balan, President, Fastraqq Inc.

CHALLENGING
INEVITABLE
CONSTANT

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.

CONSULTING
DESIGN
CONSTRUCTION
COMMISSIONING
QUALIFICATION

Celebrating 30 years 1984-2014

THE RELENTLESS PURSUIT OF SUCCESS. YOURS.™

crbusa.com | 877.4CRBUSA

editorial staff

PHARMACEUTICAL ENGINEERING®
(ISSN: 0273-8139) is published bimonthly by ISPE, 600 N. Westshore Blvd., Suite 900, Tampa, Florida 33609, USA. Telephone +1-813-960-2105. Fax +1-813-264-2816. Periodicals postage paid at Tampa, Florida, USA.

subscriptions

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

Canada Postmaster:
Send change of address information and blocks of undeliverable copies to PO Box 122, Niagara Falls, ON L2E 6S8. Canada Post Agreement Number 40012899.

www.PharmaceuticalEngineering.org

ISPE Global Headquarters
600 N. Westshore Blvd.
Suite 900
Tampa, Florida 33609 USA
Tel +1-813-960-2105
Fax +1-813-264-2816
ask@ispe.org

www.ISPE.org

Pure Fristam.

FKL
Positive
Displacement
Pump

For decades, Fristam has set the standard for reliable, efficient, high-purity centrifugal pumps. Our FKL PD pump is built with that same Fristam quality, to provide gentle product handling and consistent flow.

As with all our pumps, it comes with the best service and most comprehensive documentation in the industry. Let the proven performance of Fristam ensure the security of your process. There is a reason you've trusted us for so long.

Fristam PUMPS®

Engineered For Lasting Performance®

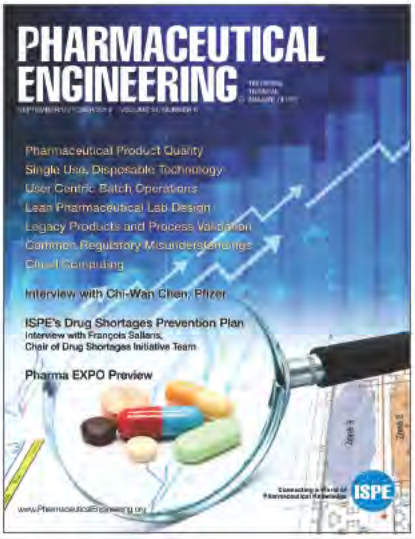
www.fristam.com/fkl

table of contents

PHARMACEUTICAL ENGINEERING®

THE OFFICIAL TECHNICAL MAGAZINE OF ISPE

SEPTEMBER/OCTOBER 2014
VOLUME 34, NUMBER 5



also inside

Insight to Operation

People | Process | Product

CAGO

commissioningagents.com

Contact:		
USA Northeast	e: Stella.Lanphear@cagents.com	c: +1 203 482 2757
USA Southeast	e: Jennifer.Clark@cagents.com	c: +1 919 696 2335
USA Midwest	e: David.Shenberger@cagents.com	c: +1 317 721 9847
USA Mountain	e: Tony.Thompson@cagents.com	c: +1 970 978 0485
USA Pacific	e: Nicki.Lange@cagents.com	c: +1 215 237 5127
Canada	e: Reid.Jenner@cagents.com	c: +1 403 809 8078
Puerto Rico	e: Vimarie.Vega@cagents.com	c: +1 787 410 4682
Europe	e: Alice.Redmond@cagents.com	c: +353 86 838 5088
Asia	e: Damian.Thornton@cagents.com	c: +353 86 407 2551
China	e: Lissa.Ji@cagents.com	c: +86 13817128872

USA | Canada | Puerto Rico | Europe | Asia

This issue of *Pharmaceutical Engineering* focuses on product quality and process capability - and how to measure them, in addition to a preview of the ISPE Pharma EXPO Conference (page 92) and *Pharmaceutical Engineering* Article of the Year Finalists (page 93).

In the lead article, Peng, et al, presents a summary report of the main points from the 28th IFPAC Annual Meeting Process Capability Symposium. Pharmaceutical scientists from both the innovator and generic pharmaceutical industries and the FDA presented their perspectives on the potential applications of process capability to monitor pharmaceutical product quality, and a panel discussion provided interesting information on process capability indices.

In a separate article, Garcia, Nosal and Vukovinsky respond to the symposium summary report, constructively commenting on areas requiring further clarification and discussion, including the impact of process capability on specification limits, the relationship between QbD and process capability, and the desire for regulatory flexibility.

The use of metrics to track quality is one of the "six dimensions" identified in the framework of the *ISPE Drug Shortages Prevention Plan*. This plan is aimed at guiding the pharmaceutical and biopharmaceutical industry in establishing reliable, robust, and resilient supply chains that can, without interruption, provide quality medicines to patients.

Under the discussion of the dimension of metrics, the plan examines parameters for measuring and tracking performance and offers metrics for discovering any weaknesses that may be in process or product.

This issue includes an Introductory Summary of the plan, aimed at highlighting important areas of the Team's work. The full ISPE Drug Shortages Prevention Plan will be published in October 2014.

Two candid interviews are featured; the first with Francois Sallans, the Vice President and Chief Quality Officer for Johnson & Johnson, (Janssen) in Belgium, and Chair of ISPE's Drug Shortages Initiative Team and the second with Chi-Wan Chen, Executive Director Global CMC, Pfizer, who discusses possible regulatory changes in China, the impact of these changes on various guidance documents, and the evolution of CFDA's draft comment process.

Dockery, et al, present a case study based on an international workshop hosted by Novartis Vaccines to prepare guidelines for incorporating lean principles into pharmaceutical quality control laboratory design, while Chatterjee and Wong describe a method to account for missing information associated with legacy products, and provide recommendations on how to apply the three stages of the latest process validation guidance to satisfy the FDA and other regulatory agencies.

Technological advances in manufacturing are also discussed in this issue, with Ladoski and Klees presenting guided wave radar level measurement as an acceptable, less expensive alternate to load cell systems, while Harrison presents how technology has advanced electronic batch records into solutions which compete one-to-one with paper flexibility. Also in the field of IT, Streit and Vidstrup representing the GAMP Cloud Computing Special Interest Group (SIG), explain the key items that must be addressed to successfully adopt a Cloud Computing model within a regulated company.

Finally, Churchward, Ogilvie, and Wright present a timely reminder that there are many GMP-related "myths" circulating throughout the industry. In their article, several myths are "busted" and better communication with regulators is recommended to prevent future myths from rising.

As always, I welcome your feedback – email me at ghall@ispe.org.

Gloria Hall
Editor, *Pharmaceutical Engineering*

ISPE Publications

You Have Questions. We Have Answers.

3 NEW Good Practice Guides

What You Need to Know and How to Apply It.

Technology Transfer

This Good Practice Guide has been revised to align with industry concepts, terminology and regulatory developments, including:

- ICH Q8, Q9,Q10 and Q11
- Alignment with the FDA Process Validation Guidance, Jan 2011
- The transfer of knowledge as a key part of technology transfer and of the overall lifecycle knowledge management process

MEMBER PRICE: **$145**
NONMEMBER: **$435**

Commissioning and Qualification of Pharmaceutical Water and Steam Systems

Revised to include the most up-to-date industry concepts and terminology, this Good Practice Guide includes:

- Information to bring the Guide in line with the final release and institution of the FDA's 21st Century initiatives
- PAT, risk-based management and ASTM-2500
- Methods to conform and comply to current practices and documentation

MEMBER PRICE: **$145**
NONMEMBER: **$435**

Clinical Supply Systems

This Good Practice Guide contains:

- Proposed standard data terminology, and frequently-used equivalent terms, data term definitions and data formatting standards
- Detailed discussion of important areas of clinical supply system functionality
- Key business requirements to help develop customized clinical supply applications and/or assess COTS systems for implementation

MEMBER PRICE: **$145**
NONMEMBER: **$435**

Order Today! www.ISPE.org/Guidance-Documents

Symposium Summary Report: The Use of Process Capability to Ensure Pharmaceutical Product Quality

by Daniel Y. Peng,* Richard Lostritto, Dafni Bika, Jean-Marie Geoffroy, Thomas Shepard, Brian Eden, Kenneth Coté, Alpesh Patel, Michael Choi, and Lawrence X. Yu*

**The views presented in this article by the authors do not necessarily reflect those of the Food and Drug Administration.*

This article presents summary report of the main points from the 28th IFPAC Annual Meeting Process Capability Symposium.

The symposium, "*Use of Process Capability to Ensure Pharmaceutical Product Quality*," was held on 23 January 2014, in Arlington, Virginia (USA) during the 28th International Forum on Process Analytical Chemistry (IFPAC) annual meeting.[1] More than 75 participants from worldwide innovator and generic pharmaceutical companies, academia, regulatory agencies, and professional societies attended this symposium. Pharmaceutical scientists from both the innovator and generic pharmaceutical industries and the Food and Drug Administration (FDA) presented their perspectives on the potential applications of process capability to monitor pharmaceutical product quality. The panel discussion provided an excellent source of information regarding the challenges and opportunities when using process capability indices. This summary report documents the main points from the symposium and intended to stimulate further discussion on the use of process capability.

Opening Remarks

On behalf of symposium chair Dr. Lawrence Yu (Acting Director, Office of Pharmaceutical Science, Center for Drug Evaluation and Research (CDER)/FDA), Dr. Daniel Peng delivered opening remarks. Dr. Peng began with a quotation from H. Thomas Johnson: "*What you measure is what you get. More likely, what you measure is all you'll get. What you don't (or can't) measure is lost.*"[2] This highlights the importance of measuring the right things and measuring them correctly. Dr. Peng emphasized that, in the past, it was usual and customary to set acceptance criteria based on process capability (the variability observed in the data). However, this practice unintentionally allows manufacturers with poor manufacturing and process controls to have products with relatively wider acceptance criteria compared to good manufacturing and controls with tight specifications. This also could be one of the fundamental reasons why the pharmaceutical industry only gets 2-3 sigma since, the specification is set based on process capability.[3] To break the vicious cycle, our view may need to be fundamentally changed so that the role of specifications is to confirm (control) product quality rather than process robustness. Therefore, prior to

Not unified by chance. Unified to enhance.

We are a partnership of companies, a team of talented professionals, an alliance of like-minded individuals; all strategically unified to better suit the needs of our customers. By combining our vast skillsets with our superior expertise, we have the power to change the way you think about service. Together, anything is possible.

Azzur Group LLC
AZZURGROUP.COM

Azzur Labs LLC
AZZURLABS.COM

BIOMaintenance SERVICES
BIOMAINTENANCESERVICES.COM

BioSPEQ
An AZZUR GROUP Company
BIOSPEQ.COM

Azzur Engineering LLC
AZZURENGINEERING.COM

Visit us at the ISPE Annual Meeting October 12–15 in Las Vegas

Find out more at:

CHANGEISCOMING.CO

726 Fitzwatertown Rd. • Suite 6 • Willow Grove, PA 19090 | 610.363.0422 | www.azzurgroup.com

Inc. 5000

PINNACLE GLOBAL ISPE PROGRAMME SPONSOR 2014

further discussion on process capability, it is important for all of us to understand that acceptance criteria should be independently established based on product safety and efficacy (patient's needs), not process capability.

Clinically Relevant Specifications: A Regulatory Perspective

Dr. Richard Lostritto (Acting Deputy Director for Science and Policy and Acting Biopharmaceutics Lead, Office of New Drug Quality Assessment (ONDQA), CDER/FDA) discussed the regulatory perspective on Clinically Relevant Specifications (CRSs).

Dr. Lostritto first introduced the working definitions of some vocabulary related to CRSs:

- **CRS:** *in vitro* test methods that reject batches that are likely to exhibit inadequate clinical performance.
- **Adequate Clinical Drug Product Performance:** appropriate pharmacological action and safety for a given drug, indication, route of administration, and patient population.
- **Equivalent Quality:** equivalence between test and reference drug products based on *in vitro* specifications and bridging studies.
- **Bioequivalence:** equivalence between test and reference drug products based on drug independent pharmacokinetic criteria (e.g., Cmax, Tmax, AUC).
- **Clinical Equivalence:** equivalence between test and reference drug products based on drug dependent criteria of safety and efficacy.

The longstanding problem is that end product testing is asked to fulfill two conditions: to serve as a quality control tool (precise and accurate manufacture) and to serve as a predictor of *in vivo* performance. In the current state, there is often not enough focused data and knowledge on this issue to be sure that both of these conditions are met at the time of initial approval. Dr. Lostritto stated that "This is just an observation, not a limitation," and he suggested that with some thoughtful modification of development programs with CRSs in mind, this may be achievable earlier on without a huge increase in total work.

Today, we have additional tools to help us address this situation, such as *In Vitro/In Vivo* Correlation (IVIVC), *In Vitro/In Vivo* Relationship (IVIVR), Biopharmaceutics Classification System (BCS), guidance documents, modeling/prediction software, and published research findings. The time is right to use these tools of greater mutual benefit in developing and implementing CRSs. There are also industry, regulatory, and professional standards, as well as societal expectations of quality, purity, and potency, to consider that may reasonably transcend other less sensitive factors (e.g., a very wide therapeutic index).

Benefits of CRSs include: 1. reject batches with likely inadequate *in vivo* performance would be rejected, 2. follow up actions after a reject are better clarified to be patient relevant, 3. related *in vitro* quality standards are more likely to have clinical relevance, and encourages meaningful innovation, and 4. post-approval changes are better linked to meaningful product performance requirements.

Challenges to developing and implementing CRSs include: 1. an organic and multicultural resistance to change, 2. to be there at initial approval may require some shift in development focus, and 3. uncertainty in the balance of opportunity costs to gains.

Dr. Lostritto presented four case studies to illustrate the benefits of and challenges to setting up clinically relevant dissolution specifications for immediate release and extended release products. He closed with a view of future developments in CRSs: 1. CRSs are needed in the modern world, 2. the benefits of CRSs are worth investing in, 3. compartmentalizing the problem on a risk basis can facilitate progress, 4. CRSs will exploit and in turn further stimulate other advances such as quality by design (QbD), and 5. consider more supportive data to support CRSs at initial submission.

Use Process Capability to Ensure Pharmaceutical Product Quality

Dr. Daniel Peng (Senior Product Quality Reviewer/QbD Liaison, Office of Pharmaceutical Science, CDER/FDA) gave an overview on how to use process capability to ensure pharmaceutical product quality. Dr. Peng first introduced the definition and calculation formula of the four process capability indices according to the ASTM E2281 standard guide.[4] Dr. Peng then discussed the difference between process capability indices (Cp and Cpk) and process performance indices (Pp and Ppk). Process performance indices (Pp and Ppk) account for the overall variability in the system and do not require the process to be in a state of statistical control. Hence, process performance indices address how the process **has performed** and cannot be used to forecast future batch failure rate. On the other hand, process capability indices (Cp and Cpk) only account for the inherent variability (noise) due to common cause of a stable process. It represents the potential (theoretical) capability (i.e., how well a given process **could perform** when all special causes have been eliminated). In order to evaluate if the process reaches a statistical control state and estimate the inherent variability, Shewhart control charts and the eight Western electric rules are often used.[5,6] Dr. Peng then further discussed different types of control charts and used examples to illustrate their uses in the pharmaceutical industry.

To facilitate the discussion and collect industry feedback, Dr. Peng used questions to ask the audience's opinion on the potential applications of these process capability indices during the product development stage, process scale up/

"Off-the-shelf solutions? No thank you. After all, our customers are something special."

Daniel Drossel
Mechanical Engineering Technician
(Design department)

Each customer has its very own special requirements. That's why we, at Optima, manufacture filling lines that are fine-tuned to our clients' particular needs while offering the benefits of an integrated and complete line: The complete machine package including high-precision functionalities, backed by consistent documentation and supported by an optimized and tailored software solution – in addition to a central point of contact who is passionate about your every concern… We are experts in special solutions, after all.

ISPE Annual Meeting, Las Vegas | October 12 – 15, 2014
PHARMA EXPO Chicago | November 02 – 05, 2014 | Hall West Booth # 921

OPTIMA

EXCELLENCE IN PHARMA

OPTIMA pharma GmbH | 74523 Schwaebisch Hall | Germany | www.optima-pharma.com
OPTIMA Machinery Corporation | Green Bay, WI, 54304 | USA | www.optima-usa.com

Member of
PACKAGING VALLEY Germany

technology transfer/process qualification stage, and routine commercial manufacture stage. The general consensus is that process capability indices can be a powerful tool during late stage commercialization (e.g., technology transfer, process qualification, and routine commercial manufacture). During the development stage, the preliminary index has its limitations due to limited batches and equipment scale. Dr. Peng also shared a case study in which the Agency performed a process capability analysis of eight generic products and their Reference List Drug (RLD) of an anti-epilepsy drug product. The batch release data of the annual stability batches (ranged between 10 and 18 batches based on data availability) were collected. All generic products and the RLD met current USP quality standards. However, process capability indices provided quantitative metrics by which to rank manufacturing process performance and help FDA focus its surveillance efforts on the manufacture sites that had the lowest performance (especially when the Ppk 95% confidence bound was below 1). Dr. Peng also proposed a vision that it may be possible to use these indicators as "Real-Time Quality Surveillance" tools to monitor process performance—similar to how credit card companies monitor abnormal transactions nowadays—in the future with advances in IT infrastructure.

Finally, Dr. Peng summarized the advantages of the process capability indices: 1. it considers not only the process mean and variability, but also considers these in relation to the specification that is established based on patient needs (safety and efficacy), 2. it is quantitative and action enabling, 3. it can apply to cross sectors (brand, generic, OTC, and biotech products), and 4. no additional testing is required since the commercial batch release data are available at the manufacture site per current regulations. Hence, Dr. Peng believes process capability indices provide a simple and powerful tool by which to ensure product quality and process robustness while not adding too much burden to industry to implement the tool.

Product Robustness: Reducing Variability and Ensuring Delivery of Superior Quality Products to Patients

Dr. Dafni Bika (Vice President, Global Manufacturing Science and Technology, Bristol-Myers Squibb) provided an innovator pharmaceutical company perspective on how to use process capability indices as a tool by which to drive operational excellence at Bristol-Myers Squibb (BMS).

Dr. Bika started the presentation by describing that *"process robustness is the ability of a process to demonstrate* ***acceptable*** *quality and performance while* ***tolerating input variability.***" Then, Dr. Bika discussed that product robustness is a holistic and comprehensive strategy at BMS that is used to ensure product quality, compliance, and uninterrupted supply. The process capability concept is therefore applied across the value chain from raw materials to manufacturing processes and distribution to reduce variability from different sources (materials, equipment, methods, processes, etc). Process robustness monitoring plans are applied to many new, growth, and mature products. This is supported by automated data gathering and analysis at the growth and launch manufacturing sites with future technology implementation planned for most sites. Product robustness and process capability analyses also have been extended to analytical methods, equipment, distribution, and selected external manufacturers. BMS has updated its business processes and quality systems and engaged employees in developing the required skills and setting the expectations.

The symposium, *"Use of Process Capability to Ensure Pharmaceutical Product Quality,"* was held on 23 January 2014, in Arlington, Virginia (USA) during the 28th International Forum on Process Analytical Chemistry (IFPAC) annual meeting. This symposium provided an opportunity for pharmaceutical scientists to discuss the potential applications of process capability indices to ensure product quality. Various presentations from both the innovator and generic pharmaceutical industries and the Food and Drug Administration (FDA) were included. The panel discussion provided an excellent source of information regarding the challenges and opportunities when using process capability indices. This summary report documents the main points from this symposium: 1. clinically relevant specifications (CRSs) are needed in the modern world, and are worth investing in because of their benefits, 2. process capability indices can be a powerful tool by which to ensure drug product quality and process robustness, 3. case studies from both the innovator and generic pharmaceutical industries demonstrated that process capability indices can be an useful tool by which to drive operational excellence and ensure delivery of superior product quality, 4. use of process capability indices should always go hand-in-hand with enhanced scientific understanding, and 5. some technical and culture challenges in implementing these tools still exist. Hence, further discussion and broadly engaging industry and other stakeholders on details of the implementation are still needed.

Introducing the New AstroCel® I H

- HEPA filtration for critical dry heat sterilization processes
- High temperature resistance up to a peak of 752 °F (400 °C)
- Robust structure for superior durability during heating and cooling
- Free of silicone to safeguard air quality during the various drying process steps
- Handles high airflow rates up to 1236 CFM for speedy temperature control

www.aafintl.com

AAF® INTERNATIONAL

BETTER AIR IS OUR BUSINESS®

Dr. Bika then discussed the application of process monitoring plans and data analysis (including process capability) across all stages of validation lifecycle, with emphasis on early and routine commercial manufacturing (Stage 3).[7] Product performance across the network is tracked by leading indicators (e.g., process capability) and resulting business outcomes such as reduction of product recalls, batch rejections, and investigations. Dr. Bika also presented specific process monitoring examples, robustness improvement cases, and future applications.

Dr. Bika concluded that even with some challenges that exist, the return on investment is evident and manifests itself every day across BMS's manufacturing network in savings from yield and cycle time improvements, avoidance of rejects, write offs, and time lost on investigations. It also continues to building an engaging and proactive culture where monitoring data and related metrics are used to anticipate and prevent manufacturing issues.

Control Charting Drives Value Creation by Identifying Opportunities for Reducing Product Defects and Confirming Enhanced Performance*

**Dr. Jean-Marie Geoffroy and Thomas Shepard from Hospira were not in attendance to deliver their presentation due to unforeseen conflicts.*

Dr. Jean-Marie Geoffroy (Vice President Quality, Pharmaceutical Engineering and Analytical Services, Hospira) and Thomas Shepard (Director of Manufacturing Science and Technology, Hospira) prepared a case study on how control charting drives value creation by identifying opportunities for reducing product defects and confirming enhanced performance.

Control plan strategies for parenteral drugs and their containment are evolving with the industry's regulatory environment. The ability to use leading indicators to predict field performance remains our industry's best option for reducing customer and patient risk. This case study is one example of how mature product control plans can be developed using the concepts of QbD and how overall quality can be improved.

The overall strategy for controls is structured to progressively monitor critical response variables that indicate the performance and quality of the IV container. Control is obtained by identifying critical parameters that correlate to the overall quality of the product, then monitoring the parameters, and finally acting on changes in parameters. Each phase of product maturity requires control planning and is part of an overall control strategy. The phases of product maturity are raw components, in-process preassemblies, pre-sterile product, and finally released product. The historical performance of each phase is used to generate baseline control parameters and limits.

The control plan for mature products starts with the lagging variable and moves upstream to define design Critical Quality Attributes (CQA) for the product, and progresses to Critical Control Parameters (CPP) for the manufacture and incorporates the component CQA. Component CPP was not included in this study.

Phase 1: identify primary areas of field performance and monitor for variance over time with Pareto analysis and control charting.

Phase 2: online process inspection is trended by lot to indicate overall capability of the process to produce defect-free containers. Defects at the form fill seal pre-sterile inspection were identified as a leading indicator for field performance.

Phase 3: identify if average performance or product consistency is the primary driver for pre-sterile defects. Average performance of the container is defined by the design of the device, while the degree of variability in the container is dependent upon the overall compounded variability of the process as measured by temperature, equipment alignment, pressure, and component performance variability. Compounded variability was identified as a leading indicator for pre-sterile defects.

Phase 4: identify areas of contribution to compounded variability. Unscheduled process interruption (equipment failure, intermittent operator intervention, process readjustment, etc.) and component dimensional variability were identified as primary contributors to process variability. The interrelationship between component and unscheduled process interruption was observed when the process steady state was disturbed by a disruption in component supply or placement.

A continual improvement project was initiated to standardize component placement and add upstream component dimensional monitoring at the component supplier. Implementation of the project resulted in a reduction of unscheduled process interruption. Effectiveness of the improvement was then monitored and was substantiated by a significant improvement in field performance. By using an integrated control plan of leading performance variables to provide indicators for field performance productivity, overall quality was improved.

Process Capability Applications: Mylan's Perspective

Brian Eden (Vice President, Global Operational Excellence, Mylan Inc. (absent due to business travel)) and Kenneth Coté (Operational Excellence Leader, North America Technical Operations, Mylan Inc.) described the applications of

process capability indices to drive operation excellence in Mylan.

Coté first gave a brief summary on what industry is hearing about process capability (Cpk/Ppk) as a tool from worldwide regulatory guidances.[7,8,9,10] Then, Coté discussed their current status. Even though the commercial batch manufacture data, in-process control data, and batch release data are collected in the Annual Product Review (APR) at the manufacture site in accordance with Current Good Manufacturing Practices (CGMPs), the raw data tend to be tabular without statistical analysis and the full potential of the dataset is not best utilized. Hence, Coté believes it can be greatly beneficial for industry to use statistical process control tools, control charts, monitor and trending, and Cpk/Ppk calculations to improve drug product quality. These tools can provide a more detailed understanding of product trends and transform from the reactive trouble shooting paradigm to a proactive failure reduction or prevention paradigm. Cot also emphasized that it is important to monitor not only the output measures (e.g., product critical quality attributes), but also the high-risk input material attributes and process parameters.

Coté then discussed the practical procedure of process capability analysis in Mylan:

- Collect raw data – data source (Laboratory Information Management System (LIMS) and manual collection)
- Refine data – filter/sort/pool with Microsoft Excel®
- Perform statistical analysis – verify assumptions and perform process capability analysis using Minitab®[16]
- Prepare report – annotate and provide commentary analysis for business decisions to be made using Microsoft PowerPoint®

Coté then shared an oral solid dosage form Content Uniformity (CU) example to illustrate the procedures and how these tools were used to quantitatively evaluate product quality and identify continual improvement opportunities. Due to non-normal distribution of the CU data, data transformation was discussed. Coté also shared process capability analysis results of an injectable product assay (18 commercial batches between January 2011 and June 2012).

Coté closed with suggestions on how to make these initiatives more sustainable:

- Standardize documentation through global directives and annual product review templates and Standard Operating Procedures (SOPs)
- Provide education to employees and stakeholders, for example via workshops on basic statistics, statistic software, Statistical Process Control (SPC) tools, and lean/six sigma black belt trainings.

Process Capabilities – Cp and Cpk – Generic Industry Perspective

Dr. Alpesh Patel (Vice President, Global Regulatory Affairs, Amneal Pharmaceuticals of NY LLC) described Amneal's generic industry perspective on the current status and practices of using process capability indices to improve drug product quality over product lifecycle.

Dr. Patel started his presentation by quoting from Socrates, **"The unexamined life is not worth living."** He modified the quotation to be ***"An unexamined manufacturing process is not worth implementing"*** to remind the audience how important it is to control the process to the target with minimum variation. Then, Dr. Patel discussed the definition in process capability indices in layman language by using the parable of **parking a car (mean and variability)** into a **garage (fixed specifications)** to help the audience understand the concept. Further, Dr. Patel discussed a process capability roadmap based on Amneal's current practice. To illustrate the roadmap, Dr. Patel first shared a case study for a transdermal patch process understanding of the coating step: 1. perform initial risk assessment to select potential high-risk process parameters, 2. conduct multivariate studies using formal experimental design to identify critical process parameters (CPPs), 3. optimize CPP ranges to achieve the desired product performance with minimum variability, and 4. demonstrate process robustness by using the statistical process control tools (individual control charts, Xbar-Range charts) and process capability analysis (Cp and Cpk). Then, Dr. Patel shared another case study for an oral tablet compression unit operation process understanding and control by using batch-to-batch tablet weight data as part of continual improvement to demonstrate process capabilities during product lifecycle management. Dr. Patel concluded that "Process Capability indices (Cp/Cpk, Pp/Ppk) are excellent tools that can be used during development and throughout product lifecycle to ensure the drug product quality."

Process Capability: Understanding the Science and the Statistics

Dr. Michael Choi (General Manager, Johnson & Johnson HyangNam Pharmaceutical Plant, Korea) gave a presentation on how to link QbD to process capability using science and statistic tools (e.g., process capability indices).

First, Dr. Choi gave a brief introduction on process capability and discussed the benefits and limitations of using process capability indices in manufacturing process control. Then, Dr. Choi shared an example case study for tablet drug-layering process understanding and how science and process capability tools can be used to improve process robustness.[11] A process capability equation is derived from the first principles for a precision tablet coating process to illustrate the scientific and statistical relationship between the critical quality attribute composite assay, material attributes, and process parameters. By isolating the "true" process capability from the overall process capability, the "noise" (from sampling, analytical methods, etc.) can be quantified. If the "noise" is a significant portion of the overall process capability, opportunities exist to improve the overall process capability by examining and reducing this "noise." The "true" process capability may be improved by adjusting the process according to the mechanistic relationship.

Dr. Choi further discussed the potential applications of process capability indices in risk assessment and control strategy establishment. For example, process capability indices and scientific relationships can be used to assign objective values to the severity, probability, and detectability for failure mode and effects analysis (FMEA)-type risk assessments. Dr. Choi concluded that the use of process capability indices should always go hand-in-hand with process understanding. This provides a better way by which to link QbD to process capability and yield superior product quality.

Panel Discussion

Audience: *How do we establish clinical relevant specification, for example, dissolution specification, for a generic product that generally does not have as much clinical data as the new drug during Phase 1-3 clinical studies?*

Panel: As highlighted in Dr. Lostritto's presentation, a risk-based approach can greatly facilitate progress in this area. For example, standard dissolution media and acceptance criteria would be appropriate for an immediate release oral solid dosage form of a highly soluble (BCS I or III) and non-narrow therapeutic index drug substance. On the other hand, for some high-risk drug products (e.g., extended release oral drug product or immediate release drug product formulated with poorly soluble drug substance), the applicant should make every reasonable effort to develop a dissolution test that is predictive of *in vivo* performance. The applicant may use USP methods or FDA-recommended methods as a starting point. As the applicant gains additional experience during product development (including any pilot bioavailability or bioequivalence studies), the dissolution methods should be iteratively modified to have appropriate discriminating power. The applicant may explore a different apparatus, media compositions, speeds, etc., to develop the appropriate discriminating conditions. The panel also referred to the FDA/Office of Generic Drugs' Example Pharmaceutical Development Report for an immediate release (IR) dosage form[12] and modified release (MR) dosage form,[13] which illustrate these principles in details.

With that said, the panel also pointed out that the dissolution approaches used today are often non-robust in that they may be inherently over-sensitive to minor changes in

the method which do not reflect relevant *in vivo* performance. For example, it is well documented in the literature that the dissolution vessel's hydrodynamics are poorly reproducible and very heterogeneous.[14] Minor mechanical and other changes in dissolution apparatus may have dramatic effects on dissolution results. It's a persistent limitation of current approaches that has hindered both *in vitro* quality control testing and the development of clinically relevant dissolution methods and specifications. It would be useful to develop new dissolution apparatus that are simple, reproducible, robust, and linkable to clinical performance to improve the antiquated vessel methodology.

Audience: *Do the data have to be normally distributed to use process capability indices?*

Panel: In general, the answer is "yes," since data normality is one of the three prerequisites to use process capability indices (Cp/Cpk) to estimate future batch failure rate. However, there are some remedies when the data are not normally distributed—for example, data transformation, distribution fit, or reference interval calculation (also known as the percentile method). The ISO 21747 guidance document[15] is cited for readers to gain further detail, as it is beyond the scope of this paper.

The panel also highlighted that it is important to meet another two prerequisites to use process capability indices (Cp/Cpk) to forecast future batch failure rate: 1. sufficient number of the subgroups is included, and 2. the process is in a state of statistical control, which means that all special causes have been eliminated from the system—and therefore there are no detectable patterns or trends exhibited and the variation observed in the data is only due to common cause (process noise) of the system.[5,6]

The audience also commented that content uniformity (acceptance value) in general is not normally distributed due to standard deviation calculation. However, assay data are generally normally distributed. It is good practice to graph the raw data to see the shape of the distribution curve and use science and product understanding to figure out if it is outliers or any scientific reason that caused the non-normal distribution.

The panel and audience also further discussed the drawbacks and limitations of the current USP content uniformity test.[16] Other alternative approaches may be considered, for example the ASTM E2709 where tolerance for variability (% RSD) is based on the sample size, confidence level, and sample mean.[17] Of course, the sampling plan is also critical to ensure the samples taken are representative of the batch.

The panel and audience further discussed the distribution of dissolution data. There is no general agreement about the shape of the distribution of the dissolution data. Saccone, et al., assumed the normal or lognormal distribution and gave the following rationale:[18] *"Normal distribution is a good model of the distribution since the amount dissolved by each unit is a function of a large number of variables. Lognormal distribution seems suitable to simulate a physical limit to the amount dissolved due to the amount of drug product in the pharmaceutical dosage form."*

Audience: *What are the challenges in implementing process capability analysis?*

Panel:

1. Many different data sources are collected manually or through automated systems. It is quite challenging to refine the data to be usable for process capability analysis and ensure data integrity during format change and transformation.
2. Both technical knowledge (statistical analysis and SPC) and cultural gaps (how to manage a change) need to be addressed.
3. A sizable investment is needed to ensure data gathering, analysis, and integrity (i.e., appropriate IT platforms).
4. Apart from the technical challenges and accountability, the firm's quality management systems need to be updated accordingly to drive the expectations (SOPs,

validation directives, statistic analysis manuals, procedures for locking and updating statistic control limits, etc.)
5. It is a cross-functional effort that requires many parts of the organization to collaborate and align (process, analytical, engineering, quality, regulatory, and procurement).

Audience: *How do we evaluate within batch variability of legacy products?*

Panel: The traditional quality control tests based on the current regulatory paradigm do not address this issue. Some companies test 10-30 samples from each drum of a large production batch to estimate the within batch variability. Some companies use the assay data from different package configurations to estimate within batch variability. The panel also mentioned that the concept of using subgroups (samples taken and tested periodically during a large production batch manufacturing) to construct a control chart is also applicable to evaluate the within batch variability.[5,6] The control charts can then be used to evaluate whether the process for manufacturing this batch is in a state of statistical control, and the process capability indices can be used to evaluate whether the process for this batch is capable. The audience also mentioned that stratified sampling of in-process dosage units based on the Product Quality Research Institute's (PQRI's) blending uniformity working group recommendation is an alternative way by which to estimate the within batch variability.[19]

Audience: *Does the generic industry also need to adopt this approach?*

Panel: We are all here for one reason: to ensure that medicines available to the American public are of the highest quality. It is very important to ensure both generic and innovator drug products meet the same quality standards—an expectation even more relevant because generic products account for more than 80% of U.S. medicines.[20] It has been and will continue to be the FDA's policy to ensure the same quality standard between innovator and generic products. This will be further supported in the proposed Office of Pharmaceutical Quality (OPQ) by integrating review and inspection across product lifecycle.

Audience: *What is the difference between "in a state of control" versus "in a state of statistical control"?*

Panel: A process is "in a state of statistical control" when all special causes have been eliminated and the variation seen in the data is random and inherent to the process itself (process noise). In order to evaluate if a process is in a state of statistical control, it is often associated with the use of a control chart and the eight Western Electric Rules for special cause tests. However, there is no general agreement on which rule or rules should be strictly applied. Each company may have different practices for when to use the eight Western Electric Rules. Nevertheless, it should be noted that a control chart is only used to evaluate whether a process is in a state of statistical control and does not address whether the process is acceptable or not since the control chart itself is not related to the specification. A process can be very stable (i.e., in a state of statistical control), but not meet customer needs (out of specification). Vice versa, a process may be out of statistical control, but still be well within the specifications. These two terms describe two different aspects of a process.[5,6]

Audience: *What is the relationship between QbD and process capability? How do we evaluate process capability during the development stage?*

Panel: During the development stage, the objective is to ensure that the product and process are appropriately designed and any aspects (e.g., drug substances, excipients, formulation, container closure systems, manufacturing processes, in-process material, and final product) that are critical to product quality, safety, and efficacy are identified. To achieve this goal, a number of input material attributes and process parameters are deliberately varied across a range of values according to experimental design. Based on the impact of these parameters on the drug product intermediates and finished drug product Critical Quality Attributes (CQAs), critical attribute of input materials and CPPs can be identified and an appropriate control strategy can then be established. In most cases, the process is not in a statistical control state during the early development phase; therefore, Cpk is not the appropriate index. However, if sufficient development batches are produced, preliminary Ppk and its confidence bound can be calculated. The data can be used to assess how the designed product and process can approximately achieve the target quality attributes in the desired range. If not, fundamental changes of the product and/or process design may be necessary to achieve the predefined target. This can significantly help the company identify incapable process during the early stage and avoid wasting resources. It is well known, however, that these development studies are often conducted at the laboratory or pilot scale. Therefore, the preliminary Ppk obtained from the laboratory or pilot scale cannot be extrapolated to production scale unless the process can be demonstrated to be scale independent or that scale up of the process can be well predicted with a high certainty. As such, extra cautions need to be taken to interpret these preliminary indices obtained during the development stage. Nevertheless, enhanced understanding of the formulation and process builds the solid foundation needed to ultimately obtain high Cpk and Ppk

for commercial manufacture. Therefore, increasing process capability and reduce product variability and defects is one of the QbD objectives.[21]

Audience: *If we implement process capability indices, is it possible to gain regulatory flexibility?*

Panel: The short answer would be, "yes, it is possible, but we are not there yet." For this exact reason, we are having this symposium to facilitate scientific discussion and collect industry feedback and input. If some common ground can be reached, it is possible to achieve the well-sought regulatory flexibility in the future with the following prerequisites: 1. the commercial manufacture process can demonstrate a state of statistical control and achieve the desired process capability (e.g., Cpk 95% confidence bound > 1 or any value to be agreed on between industry and regulatory agency), 2. the applicant commits to continue using statistical process control tools to monitor the process and ensure that the process remains in a state of statistical control, 3. a healthy pharmaceutical quality system is in place to ensure that correct and preventive actions are available when any unplanned or undesired departures are observed from the process, and 4. the applicant calculates and reports in the subsequent annual report the trending of Cpk/Ppk for all CQAs to confirm there is no negative trend or observation.

Summary

Key highlights from the symposium were as follows: 1. Clinically Relevant Specifications (CRSs) are needed in the modern world, and are worth investing in because of their benefits, 2. process capability indices can be a powerful tool by which to ensure drug product quality and process robustness, 3. case studies from both the innovator and generic pharmaceutical industries demonstrated that process capability indices can be an useful tool by which to drive operation excellence and ensure delivery of superior product quality, 4. use of process capability indices should always go hand-in-hand with enhanced scientific understanding of the product and process, and 5. some technical and culture challenges in implementing these tools still exist. The panel discussion provided an excellent source of information regarding the strengths and some of the considerations when using process capability indices. Further discussion and broadly engaging industry and other stakeholders would greatly benefit increased adoption and implementation of this powerful tool.

References

1. 28th International Forum on Process Analytical Chemistry (IFPAC) Annual Meeting, http://www.ifpac.com/cgi-bin/IFPACProgram2014.pl, accessed 10 February 2014.
2. http://www.isixsigma.com/community/blogs/what-you-measure-what-you-get/,accessed 10 February 2014.
3. Vase, P., "Achieving Six Sigma Quality in Medical Device Manufacturing by use of Design of Experiments and Statistical Process Control," *Pharmaceutical Engineering*, Vol. 27, No. 2, 2007, pp. 1-9, www.PharmaceuticalEngineering.org.
4. ASTM E2281: Standard Practice for Process and Measurement Capability Indices.
5. ISO 8258: Shewhart Control Charts.
6. ASTM E2587: Standard Practice for Use of Control Charts in Statistical Process Control, www.astm.org.
7. U.S. FDA Guidance for Industry on Process Validation: General Principles and Practices, 2011, www.fda.gov.
8. ICH Q9 Quality Risk Management, www.ich.org.
9. ICH Q10 Pharmaceutical Quality System, www.ich.org.
10. World Health Organization (WHO) GMP and Inspection for Pharmaceutical Products: Main Principles, http://whqlibdoc.who.int/publications/2007/9789241547086_eng.pdf, accessed on 10 January 2014).
11. Choi, M., "Determining the Manufacturability of Drug-layered Tablets," *Pharmaceutical Manufacturing*, No. 4, 2007, pp. 34-42.
12. Quality by Design (QbD): An Example Pharmaceutical Development Report for an Immediate Release (IR) Dosage Form, http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM304305.pdf, (accessed 10 February 2014).
13. Quality by Design (QbD): An Example Pharmaceutical Development Report for a Modified Release (MR) Dosage Form, http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM286595.pdf, (accessed 10 February 2014).
14. Baxter, J.L., et al., "Hydrodynamics-induced Variability in the USP Apparatus II Dissolution Test," *Int. J. Pharm.*, Vol. 292, No. 1-2, 2005, pp. 17-28.
15. ISO 21747: Statistical Methods -- Process Performance and Capability Statistics for Measured Quality Characteristics.
16. USP<905> Uniformity of Dosage Units.
17. ASTM E2709: Standard Practice for Demonstrating Capability to Comply with an Acceptance Procedure, www.astm.org.
18. Saccone, C. D., et al., "Statistical Properties of the Dissolution Test of USP," *Dissolution Technologies*, Vol. 11, No. 4, 2004, pp. 25-28.
19. The Use of Stratified Sampling of Blend and Dosage Units to Demonstrate Adequacy of Mix for Powder Blends (http://www.pqri.org/pdfs/DTC/Articles/Final_BUWG_Stratfied_Sampling.pdf) (accessed 10 February 2014)

20. Declining Medicine Use and Cost: For Better or Worse? (www.imshealth.com) (accessed 10 February 2014).
21. Yu, L.X., et al., "Understanding Pharmaceutical Quality by Design," *AAPS J.*, Vol. 16, 2014, pp. 771-783.

Acknowledgments

Andre Raw, Sau (Larry) Lee, Chengjiu Hu, Khalid Khan, Leila Wieser, Alex Viehmann and Karthik Iyer.

About the Authors

Daniel Y. Peng, PhD is currently a Senior Product Quality Reviewer and QbD Liaison in the Office of Pharmaceutical Science (OPS), CDER/FDA. Previously, Dr. Peng served as a Senior Formulation Scientist/ Project Lead for late stage Product Development at AstraZeneca (Wilmington, DE) and an Instructor (faculty) at College of Pharmacy, University of Tennessee Health Science Center (Memphis, TN). Dr. Peng obtained his PhD in pharmaceutics from West China University of Medical Sciences (Chengdu, China). He has published three book chapters, 16 peer reviewed papers and four US patents. Dr. Peng has extensive experience in formulation and process development for solid oral dosage forms and novel drug delivery systems. He is also skilled in applying Design of Experiments (DOE), Multivariate Analysis (MVA), Statistical Process Control (SPC), and Artificial Neural Network (ANN) software for pharmaceutical product development.

Food and Drug Administration, Office of Pharmaceutical Science, 10903 New Hampshire Avenue, Silver Spring, MD 20993, USA.

Richard (Rik) Lostritto, PhD joined the FDA in 1995 and currently serves as Acting Deputy Office Director for Science and Policy and Acting Biopharmaceutics Lead in the Office of New Drug Quality Assessment (ONDQA). Previously, Dr. Lostritto served as Director, Division-I, which includes Chemistry, Manufacturing, and Controls (CMC) responsibility for oncology, hematology, cardio-renal, neurology, and psychiatric drug products. He had also served as CMC Team Leader successively collocated in the Divisions of Oncology Drug Products and Pulmonary and Allergy Drug Products. Before joining the Agency, Dr. Lostritto worked at Boehringer Ingelheim Pharmaceuticals leading a group that developed medical aerosol formulations after serving as Assistant/Associate Professor of Pharmacy at The University of Connecticut (1983-1992). He received his MS and PhD in pharmaceutical chemistry and pharmaceutics from the University of Michigan and his BS in pharmacy from The University of Connecticut.

Food and Drug Administration, Office of Pharmaceutical Science, 10903 New Hampshire Ave., Silver Spring, MD 20993, USA.

Dafni Bika, PhD is a technology innovation and change leader with more than 20 years of international experience at top-tier companies. Dr. Bika industrializes new products by uniquely balancing technical expertise with business understanding, while developing others and inspiring discretionary performance. She is currently Vice President with Bristol-Myers Squibb leading the Global Drug Product Manufacturing Science and Technology organization located in New Brunswick, NJ. Dr. Bika joined Bristol-Myers Squibb in 2009 after spending 10 years with Merck in West Point, PA on a similar science and technology role. Prior to joining Merck, Dr. Bika was in roles of increasing responsibility as a Development and Technology Manager with Procter and Gamble in the European Technical Center in Brussels, Belgium, and Viochrom in Athens, Greece. She holds a PhD in materials science and engineering from the University of Pennsylvania, an MS in materials science and engineering from the University of Rochester, New York, and a Diploma in chemical engineering from the National Technical University of Athens.

Bristol-Myers Squibb, Global Drug Product Manufacturing Science and Technology, 1 Squibb Dr., New Brunswick, New Jersey 08903, USA.

Jean-Marie Geoffroy, PhD is currently Vice President Quality, Pharmaceutical Engineering and Analytical Services at Hospira. He is a registered pharmacist from the University of Rhode Island, and obtained his PhD in pharmaceutics from the University of Wisconsin, Madison. His 24 years of technical experience include process analytical technology, formulation development and marketed product support, focusing on technology transfer, process validation, and process optimization. He is an internationally recognized expert and speaker in the areas of advanced analytics, quality by design, risk management, process optimization and Process Analytical Technology (PAT). He has trained FDA reviewers and compliance officers in these areas. He is a member of Parenteral Drug Association (PDA), American Association of Pharmaceutical Scientists (AAPS), and ISPE. Prior to Hospira, he has held various management positions within Takeda, TAP Pharmaceuticals, Abbott Laboratories, Marion Merrell Dow and CIMA Labs.

Hospira, Corporate Quality, Pharmaceutical Engineering and Analytical Services, 275 N Field Dr., Lake Forest, Illinois 60045, USA.

Thomas A. Shepard is Director of Manufacturing Science and Technology at Hospira since 2012. He has 25 years of experience in medical device and pharmaceutical industry:

research and development and operations. His primary areas of focus are biomaterials, drug containment, and drug delivery. He is the PDA Task Force Leader for Technical Report: Identification and Classification of Integrity Defects in Large Volume Plastic Containers.

Hospira, Corporate Quality, Pharmaceutical Engineering and Analytical Services, 275 N Field Dr., Lake Forest, Illinois 60045, USA.

Brian Eden has more than 20 years of operations, continuous improvement and leadership experience in a range of industries, including energy, consumer goods, food and pharmaceuticals. He holds a BS in physics from the University of Connecticut and an MS in engineering from Purdue University. Following eight years of service as an officer and Nuclear Engineer in the US Navy, Edeb held a series of high impact roles with General Electric Company, earning credentials in Six Sigma, Lean and Reliability Engineering and is certified by GE as Master Black Belt. Since 2004, he has specialized in startup and deployment of global-scale Lean Six Sigma programs with a particular focus on holistic methodology and detailed financial analysis. Within pharmaceutical deployments, Eden is also recognized as an expert in the area of quality by design and other applications of problem solving and analytical tools to pharmaceutical quality and product development. He currently leads the Global Operational Excellence program for Mylan, one of the world's leading generics and specialty pharmaceutical companies.

Mylan Pharmaceuticals, Global Operational Excellence, 781 Chestnut Ridge Rd., Morgantown, West Virginia 26505, USA.

Kenneth Coté holds a BS in systems management, Colorado Technical University, and was trained at the GE Capital Center for Learning and Organizational Education (CLOE). He worked as a Six Sigma Black Belt in supply chain with Penske Logistics. Three years later, he was certified at GE Capital with Master Black Belt, and began teaching Six Sigma full time. He was interested in healthcare and helping people, and was recruited by Ethicon – the surgical division of Johnson & Johnson (J&J) in 2003. During this time, he also started work on a graduate degree in biostatistics from Rutgers University. Coté put his education on hold though, because he was transferred to J&J – Vision Care in London, England. In 2011, he joined Mylan Pharmaceuticals and is now the Senior Director for Operational Excellence, managing strategic projects for the North America region and directly support four manufacturing locations, a repackaging site and our regional distribution center.

Mylan Pharmaceuticals, Global Operational Excellence, 781 Chestnut Ridge Rd., Morgantown, West Virginia 26505, USA.

Alpesh Patel is working as Global Vice President, Regulatory Affairs in Amneal Pharmaceuticals of NY LLC. Patel is responsible for all strategies related to US and Global Product Portfolio including effective communicates with Global Regulatory Authorities (US FDA, MHRA etc.) and interprets and communicates to the management about the changes in strategies of regulatory authorities' and guidance's as they relate to Amneal products on the global market. In addition, he is a core member of US FDA GPhA, TAC, SARB, API Committee, IFPAC, QbD and Stability Committee and other professional organizations such as DIA, PQRI, and Inactive Ingredient Committee.

Amneal Pharmaceuticals, Global Regulatory Affairs, 85 Adams Ave., Hauppauge, New York 11788, USA.

Michael Choi, PhD is General Manager for Johnson & Johnson HyangNam Pharmaceutical plant in the Janssen Supply Chain. Previously, he served as Head of Process Robustness for Americas Technical Operations at Teva, Senior Principal Scientist for Consumer Healthcare R&D at Schering Plough, and Senior Process Engineer for Pharmaceutical Technology and Engineering at Merck & Co., Inc.

Johnson & Johnson HyangNam Pharmaceutical Plant, 45 Jeyakgongdan 2-gil Hyangnam-Eup, Hwasung-si, Gyeonggi-do, 445-937, Korea.

Dr. Lawrence X. Yu is the Director (acting), Office of Pharmaceutical Science, Food and Drug Administration, overseeing the Office of New Drug Quality Assessment, Office of Generic Drug Quality Assessment, Office of Biotechnology Products, and Office of Testing and Research. He is also adjunct Professor of Pharmaceutical Engineering at the University of Michigan. Dr. Yu is a fellow and the past section Chair of the American Association of Pharmaceutical Scientists and an Associate Editor of the AAPS Journal. Dr. Yu has authored/co-authored more than 120 papers, presented more than 100 abstracts, and given more than 180 invited presentations. He is a co-editor of the book entitled, "Biopharmaceutics Applications in Drug Development."

Food and Drug Administration, Office of Pharmaceutical Science, 10903 New Hampshire Ave., Silver Spring, Maryland 20993, USA.

The Use of Process Capability to Ensure Pharmaceutical Product Quality

by Thomas Garcia, PhD, Roger Nosal, and Kim Vukovinsky

This commentary is in response to the symposium summary report[1] featured on pages 10 to 23 of this issue. Positive aspects of the report are presented in addition to areas requiring further clarification, the impact of process capability on specification limits, the relationship between QbD and process capability, and the desire for regulatory flexibility. In general, this commentary is intended to constructively progress these topics toward a meaningful outcome.

Positive Aspects

Good discussions occurred during the symposium demonstrating how process capability indices are useful metrics for monitoring drug product quality and process robustness. The metrics should be considered in conjunction with other process knowledge, which can drive operational excellence. This approach is an integral part of the industry effort to develop robust processes thereby ensuring quality, compliance and reliable supply of our products. Participants were cautious about the application of process capability indices during drug development, as data may only be available from a limited number of batches, and differences in equipment, scale, and operating conditions can cause confusion in their interpretation. Process capability indices are best used during routine production (Stage 3 – Continued Process Verification). They also highlight that process monitoring, in conjunction with science enhanced development (e.g., Quality by Design (QbD)) can result in fewer batch reworks, rejects, investigations and product recalls.

Areas Requiring Further Clarification

There seems to be some confusion regarding the function of process capability indices. Process capability indices do not ensure quality by themselves. They are metrics that measure process performance and are an indication of how capable (or incapable) a process is to produce product conforming to a specification. Assurance of product quality is confirmed through the combination of all the elements managed within a robust Pharmaceutical Quality System (PQS). A comprehensive control strategy that addresses the relationship between critical input material attributes and process parameters and the critical quality attributes they impact is fundamental to developing confidence in product quality. Corrective actions should be implemented following investigations when trending or noncompliant values in quality attributes are noted.

With respect to the adoption of Clinically Relevant Specifications (CRS), further discussions on this topic during joint regulatory, industry, and academia forums are necessary to achieve a mutual understanding of the level of clinical investment, benefits and risks. While clinically relevant, specification criteria may improve understanding of the relationship between *in vitro* controls and *in vivo* performance, developing effective models and clinical surrogates

in addition to conducting clinical trials to understand the "performance boundaries" of a variety of experimental product formulations is not without risk.

Specifications

Specification limits should be established based primarily on product safety and efficacy. The introduction of process capability indices to set specification limits will further complicate efforts to harmonize globally divergent regulatory requirements, many of which have little or no clinical relevance.

> *"While trends in process performance and capability are useful for defining process improvements, developing performance metrics, or achieving statistical control, they should not be used as a criterion for release of a batch.*

The use of process capability indices to set specifications may be inconsistent with ICH guidelines and the adoption of CRS criteria advocated in the article. The computation of process capability indices is directly related to the range of specification's acceptance criteria. Broad ranges for acceptance criteria correlate with higher process capability indices. Tight specification ranges (generally reflecting superior quality) correlate with lower capability indices (erroneously indicating poor quality). Furthermore, wider specification ranges are often approved for manufacturing processes that have higher levels of variability, while robust manufacturing processes are often characterized by tighter limits. For example, for drug substance manufacturing processes that produce low levels of impurities, applicants are frequently challenged by regulators to tighten specification limits commensurate with empirical manufacturing performance. These enforced limits are frequently well below ICH acceptance criteria, which were originally established to be representative of clinically relevant acceptance criteria. Conversely, manufacturing processes that routinely produce levels of impurities closer to ICH limits are likely to have those limits approved by regulators without question. A manufacturing process that adheres to wide specification criteria, and therefore a high process capability index, can be misleading. It implies it is more robust than a manufacturing process where the variability is better controlled, has lower levels of impurities, yet has a tighter specification.

While trends in process performance and capability are useful for defining process improvements, developing performance metrics, or achieving statistical control, they should not be used as a criterion for release of a batch. Batch release should be performed by complying with release specifications and criteria established through science and risk-based evaluation, experience, or guidelines for setting specifications that reflect a useful boundary for safety and efficacy.

CRS may be beneficial for specific product attributes that impact safety and/or efficacy (e.g., bioavailability of a drug); however, CRS should not be expected as a default to existing specification criteria. CRS may be particularly useful for 1. drugs with narrow therapeutic indices; 2. establishing API particle size distribution criteria for drugs with low solubility; and 3. defining the rate of drug release from modified release dosage forms. However, pursuing CRS to establish an IVIVC or IVIVR relationship for an immediate release tablet containing a highly soluble (BCS-1) drug may not be warranted. Conducting *in vivo* studies to identify CRS should be balanced with regulatory relevance and technical value to product quality.

One major concern with developing CRS criteria is that they are frequently limited to the range of values studied *in vivo*, which consequently translates into relatively conservative acceptance criteria. Surrogate models also should be allowed to establish pragmatic specification acceptance criteria. While the use of models has been generally favored by industry, reluctance by regulators to approve their use without actual data to verify model predictions has been a point of contention. In one recent example, a well-established commercially available model used to identify an appropriate particle size distribution for drug substance to ensure acceptable blend and dosage unit uniformity was rejected by the FDA. The FDA stated the model was not accurate or validated; therefore, the acceptance criterion had to be tightened to reflect the range of the batch data demonstrated in the submission, despite the fact that blend and dosage unit uniformity were robust during development. Models should be confirmed with data, as appropriate; however, once established, the model is appropriate for use to help set appropriate specifications, which can be beyond the data currently in hand.

Relationship Between QbD and Process Capability

Metrics such as process capability indices are consistent with the objectives of QbD. However, QbD is not a necessary prerequisite for the use of process capability indices, which were being used long before ICH Q8(R2), Q9, Q10 and Q11

were issued. As stated in the original article, process capability information can provide confidence and contribute to the overall process knowledge generated during process development. However, process capability indices generated from data for small scale batches may not extrapolate to larger batch sizes with a high degree of certainty. Caution should be exercised and process capability assessment should continue during scale-up and technology transfer, and commercial production. If low process capability indices are observed for small scale batches, this likely signifies that the process has issues which are often magnified during later stages in the product lifecycle.

Regulatory Flexibility

During the panel discussion, a question was asked about gaining regulatory flexibility if companies implement the use of process capability indices. The short answer was, "yes, it is possible, but we are not there yet." Although highly desired, the promise of regulatory flexibility (per ICH Q8R) has not been realized except in very limited cases. The focus of developing process capability indices to monitor process performance should be on ensuring and demonstrating consistent product quality is manufactured throughout its lifecycle. Ideally, the application of a risk-based inspection approach for companies that routinely measure, trend and analyze process capability is supported. Companies that consistently achieve relatively high process capability indices could benefit from a reduced inspection frequency or depth of inspection.

Prerequisite criteria by which regulatory flexibility would be approved, should be incorporated within a pharmaceutical quality system subject for inspection, as opposed to being included as a regulatory commitment.

During subsequent panel discussion, the development of prerequisite criteria for obtaining regulatory flexibility was proposed (i.e., commit to demonstrating a state of statistical control, using statistical process control tools to monitor process that ensure it remains in a state of statistical control, and including Cpk/Ppk monitoring for all CQAs in the Annual Report). Prerequisite criteria by which regulatory flexibility would be approved, should be incorporated within a pharmaceutical quality system subject for inspection, as opposed to being included as a regulatory commitment. The level of process monitoring implemented throughout the product lifecycle should be governed by internal change management and appropriate quality metrics. It is also noted that these criteria and the link to incentives have been demonstrated in other industries to create many issues such as how long the process should be in control before being considered "controlled" and what happens when the process goes out of control? Although these are the right criteria and approach to ensure quality at the lowest cost, creating a link to flexibility can be overly complex.

Conclusion

Process capability indices are valuable metrics to assess process performance, especially during the later stages of the product lifecycle. However, they should not be used to establish product release specification limits or acceptance criteria, or as stand-alone measures to demonstrate quality assurance of a product. While process capability indices may be one element of a pharmaceutical quality system, the combination of process understanding and robust change management provides assurance and confidence of product quality.

Developing Clinically Relevant Specifications (CRS) may be useful for certain attributes of a drug product that are highly variable or may have a direct impact on the safety and/or efficacy of a drug product. The need to establish a direct correlation between *in vitro* controls and *in vivo* performance should be determined via a science and risk-based approach. The development of CRS limits and acceptance criteria should not be a default regulatory expectation.

References

1. Peng, Daniel Y., Richard Lostritto, Dafni Bika,, Jean-Marie Geoffroy, Thomas Shepard, Brian Eden, Kenneth Coté, Alpesh Patel, Michael Choi, and Lawrence X. Yu, "Symposium Summary Report: The Use of Process Capability to Ensure Pharmaceutical Product Quality," *Pharmaceutical Engineering*, September/October 2014, Vol. 34, No. 5, pp. 10-23, www.ispe.org.

Acknowledgements

The authors would like to thank: Nagesh Bandi, Stephen Colgan, Vincent McCurdy, and Ron Ogilvie.

Authors

Thomas Garcia,PhD, Research Fellow in Global CMC, Pfizer
Roger Nosal, Vice President, Global Chemistry, Manufacturing and Controls (GCMC), Pfizer
Kim Vukovinsky, Senior Director of Statistics, Pfizer

ISPE CLASSROOM TRAINING

There's still time to register...

Improve product quality and increase process understanding with ISPE in-depth training courses

New and Updated Courses and Guidance Documents!

6 – 8 October 2014
Kansas City, MO, USA

- Basic GAMP 5, Part 11 and Annex 11

14 – 15 October 2014
Las Vegas, NV, USA
ISPE Annual Meeting

- Technology Transfer – New Course and Guide!

17 – 20 November 2014
Raleigh, NC USA

- Clinical Trial Materials
- GAMP5
- HVAC – New Course!
- Pharmaceutical Water Generation – Updated Course Includes New Guide!
- Process Validation in Biotechnology Manufacturing
- Project Management – Updated!*
- Storage, Delivery & Qualification of Pharmaceutical Waters – Updated Course Includes New Guide!

1 – 4 December 2014
Tampa, FL

- Auditing
- Cleaning Validation – Updated Course Includes New Guide
- GAMP5 Process Control Systems
- Managing the Risk of Cross Contamination (Risk MaPP)
- Process Validation – New Course!
- Q7A
- QRM

20 – 22 October 2014
Manchester, UK

- A Risk Based Approach to GxP Process Control Systems (GAMP5®)
- Applying Quality Risk Management (QRM)
- Auditing
- Cleaning Validation Principles – Updated Course Includes New Guide!
- Managing the Risk of Cross Contamination
- Process Validation Lifecycle-Integration to the Pharmaceutical Quality System – New Course!
- Q7A: Implementing Good Manufacturing Practices

Register early and save!

ISPE.org/Training

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

PINNACLE PROGRAMME 2014 GLOBAL SPONSORS

CAI | Azzur Group LLC | nne pharmaplan® Engineering for a healthier world

Investigation of New Level Technologies in Single Use, Disposable Systems

by David Ladoski and Dan Klees

This article presents guided wave radar level measurement as an acceptable, less expensive alternate to load cell systems.

Different technologies have been utilized to measure level, volume, and/or mass in single use, disposable bags in the biotech industries. The most common include:

1. Load Cells (weight)
2. Floor Scales (weight)
3. Pressure Transmitters (liquid head or weight)
4. Graduated Marks (manual measurement of level)
5. Guided Wave Radar (level)

Each of the above technologies has its benefits as well as its limitations. The purpose of this article is to only discuss experience with guided wave radar transmitters – not to discuss the first four listed technologies.

There are currently several hundred guided wave radar level installations on single use, disposable bags in cGMP facilities.

Technology

Guided Wave Radar (GWR) is a well known technology that has been available for process measurement for more than 20 years. Basically, a microwave pulse is sent down a wave guide (also referred to as an antenna or probe). Energy is then reflected back from a surface where there is a change in dielectric. The amount of energy reflected is proportional to the difference in dielectric between air and the process medium. Typically, the wave travels first through air (dielectric of 1) and then is reflected off of a surface of a liquid (WFI has a dielectric of approximately 12).

In the case of biotech-type liquids, which are typically high dielectric, almost all of the energy on the wave guide probe is reflected back up the probe, resulting in a very strong signal and maximum accuracy of measurement.

By knowing the time of flight required for the speed-of-light microwave pulse to travel down the wave guide, reflect off of the surface of the liquid and then travel back, one can determine the distance to the surface of the liquid. Level in the vessel (or bag in this case) can then be mathematically calculated.

Simplified diagrams of guided wave technology are shown in Figure 1 and Figure 2.

Potential Single Use Bag GWR Difficulties

In single use, disposable bag level technology, the GWR

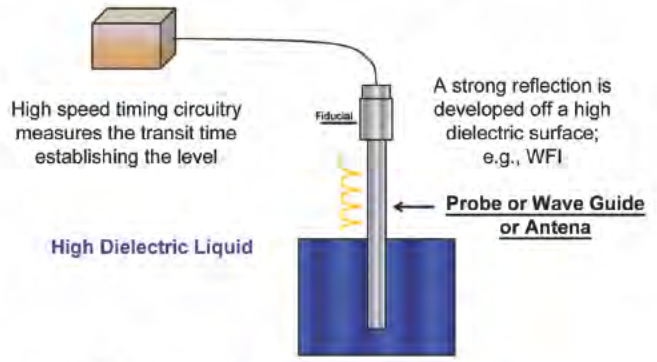
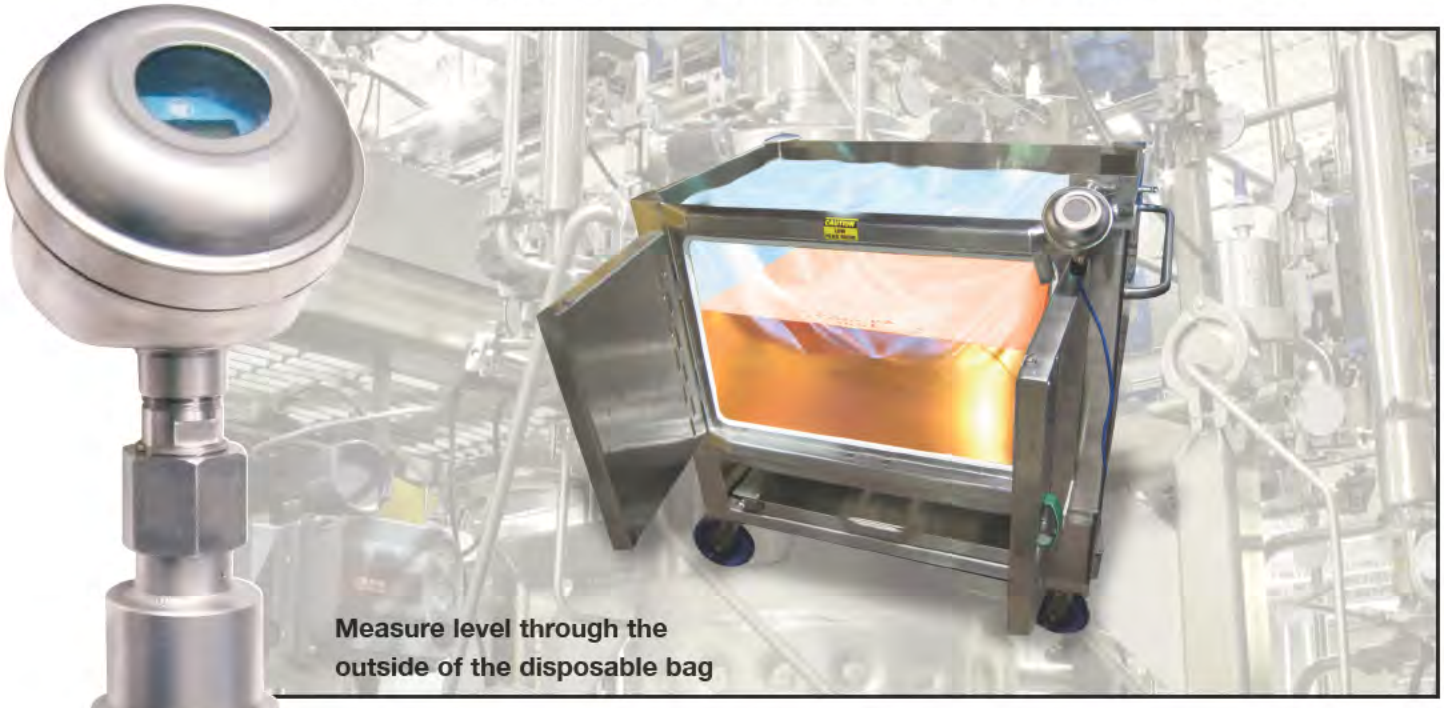


Figure 1. Guided wave technology.

ECLIPSE®

Non-Invasive Level Measurement for Single-Use Bioprocess Storage Bags

with Eclipse® Guided Wave Radar Transmitters



Measure level through the outside of the disposable bag

Magnetrol® **Life Science Solutions** specializes in the latest generation of hygienic measurement instruments. Our devices deliver precision accuracy in the toughest applications, yet are easy to configure and impose negligible maintenance demand. Eclipse® guided wave radar transmitters provide accurate and reliable non-invasive measurement for single-use disposable bioprocess bags. When sterility is important and level measurement instruments cannot be in direct contact with the process media, ECLIPSE GWR transmitters are the solution. Improve your bioprocess control with leading-edge measurement solutions from MAGNETROL.

*Email **info@magnetrol.com** to request more information.*

Magnetrol®

705 Enterprise Street • Aurora, IL 60504 • 630.969.4000 • magnetrol.com

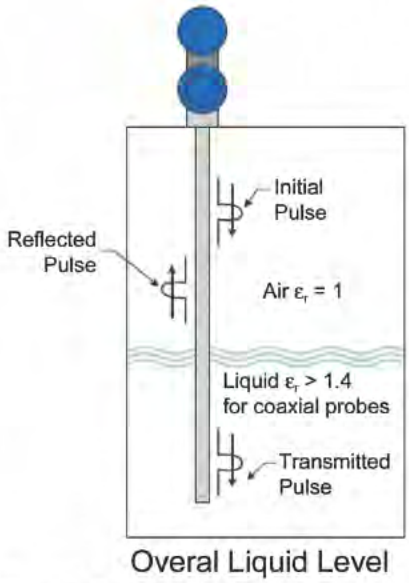


Figure 2. Guided wave reflected pulse.

probe is not in contact with the liquid – but rather, is in direct contact with the outside of the bag. This non-contact application can result in difficulties that are not normally experienced with typical GWR probes that are in direct contact with the process:

1. The microwave pulse is concentrated around the outside of the probe. Since the probe is separated from the process liquid by the thickness of the bag, only the portion of the reflected microwave pulse is actually available for processing as the level signal. This reflected signal strength is typically less than 50% of the amplitude that would be processed if the wave guide was in direct contact with the liquid.
2. The bag may not lay flat against a probe when filling or emptying – causing a deformity in the bag wall. This deformation of the bag can be caused by obstructions within the tote or bin, the GWR probe itself, the shape of the bag as related to the tote/bin shape, and even the seam of the bag. As a result, the signal propagation (speed) of the microwave pulse will vary as it traveling through both the air due to bag deformity and through the plastic of the bag itself. Signal propagation will vary as the inverse of the square of the material dielectric constant. Since the speed of the microwave pulse will be reduced when in contact with the bag as compared to when it is in contact with air, the time that it takes the microwave pulse to travel down the probe, reflect off of the surface of the liquid in the bag, and travel back up the probe will be variable depending on the position of the bag with reference to the probe. The results will not always be the same, system to system or bag to bag.
3. A disposable single use bag tends to "curve away" from the probe near the top of the fill level. Then, as the bag fills or empties, less of the bag sidewall containing liquid becomes in direct contact with the probe. This causes two issues. The first issue is that level is not proportional to volume. The second issue is that since the actual liquid level is not in direct contact with the side wall of the bag and probe, the GWR transmitter measures a different level due to the change in speed of the microwave pulse. This difficulty is avoided if the bag is preformed to the exact shape of the bin/tote/container and the bag is pre-inflated.
4. Measuring low liquid level is also challenging for the GWR since the GWR needs to fit the bottom shape of the tank. The transition between the sidewall and the bottom results in a near 90 degree bend of the GWR antennae. Tighter bends seem to reduce the GWR signal resulting in a poor level signal. A five inch or greater radius for ¼" cable seems to deliver best performance.
5. Bag seams also create a challenge especially at the bottom to sidewall transition. The bag seam is generally more rigid and does not lay completely flat to the GWR cable, which in turn leaves an air gap. This air gap generally occurs in the middle of the GWR bend radius and reduces signal.

Stainless Steel Bins with Rigid Probes

GWR transmitters will measure only to the bottom of the probe. The probe was initially a rigid 0.5" (12 mm) rod supported off the side wall of the bin by PTFE insulators. These PTFE stand-offs have typically run the continuous length of the probe and have positioned the probe about 1" (25 mm) off the bin wall. This stand-off allowed the bag to "wrap around" the probe, giving a substantial liquid surface area for the microwave pulse to reflect off of the liquid in the bag. See Figure 3, Figure 4, and Figures 5a and 5b.

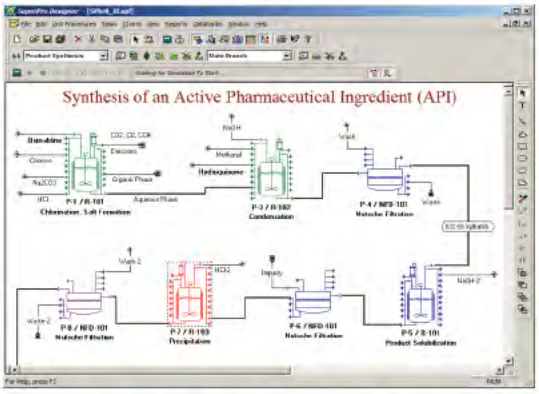
Figure 3. Guided wave in a stainless steel bin.

Figure 4. Bent rigid probe for a stainless bin.

Intelligen Suite®

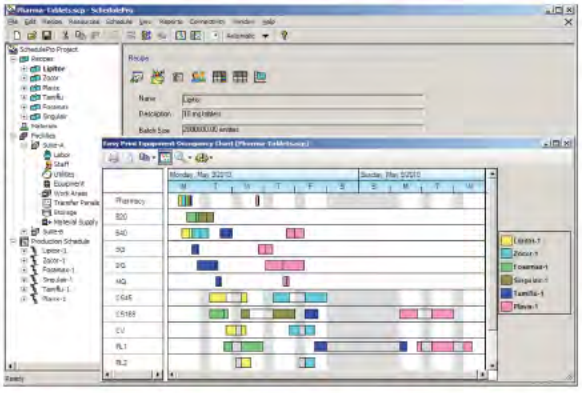
The Market-Leading Engineering Suite for Modeling, Evaluation, Scheduling, and Debottlenecking of Multi-Product Facilities

SuperPro®

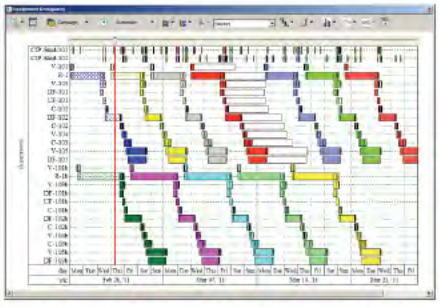


Use SuperPro Designer to model, evaluate, and optimize batch and continuous processes

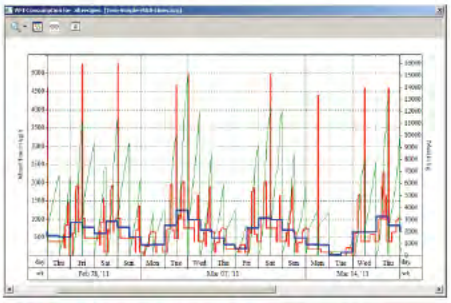
SchedulePro®



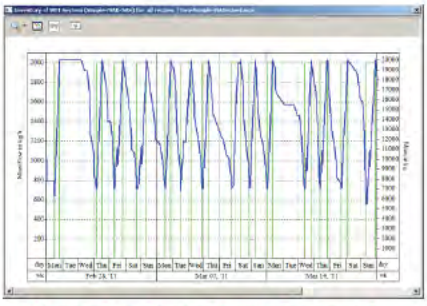
Migrate to SchedulePro to model, schedule, and debottleneck multi-product facilities



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

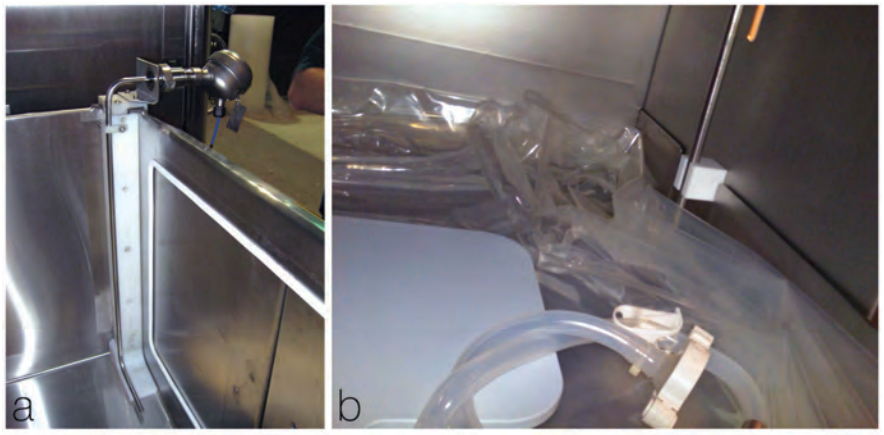


Figure 5 (a and b). Bent rigid probe in a stainless steel tote.

Since most of the licensed facilities wanted to measure level as close to the bottom of the bag as possible, the 12 mm diameter rigid probe was positioned down the sidewall of the bin and then bent across the bottom of the bin toward the lowest point of the bag as shown in Figure 4 and Figures 5a and 5b.

With the installation of the rigid bent probe, it was observed that the typical level measurement repeatability from bag to bag was better than **5%** after "strapping" the first bag and tote/bin.

Strapping Explanation: "strapping" is the configuration of a GWR level transmitter and probe to a vessel with respect to a standard. Typically, an empty bag is inserted into a tote/bin. A specific volume of liquid is metered into the bag using a highly accurate Coriolis mass flow meter or weigh load cell. Whatever the GWR transmitter reads as level at that time is "configured" to be the volume as determined by the standard. An additional volume of fluid is then added into the bag through the standard and the new level reading of the GWR level transmitter is "configured" to the new total volume, as measured by the standard. Typically, this is done 20 times and this table, which can be saved in the GWR transmitter, becomes the "strapping table." From that point on, a specific measured "level" will correspond to a specific "volume." This strapping table takes into account major factors affecting accuracy described above, such as bag positioning, differences in velocity of the microwave pulse in air vs. plastic bag, the curve of the probe, the shape of the bin/tote, and the curvature of the top of the bag where the level is.

Totes/Bins with Flexible Cable Probes

Plastic/polymeric totes/bins offer the advantage that they are non-conductive, allowing the rigid rod probe to rest directly on the sidewall of the bin/tote. Since no stand-offs are required, the bag tends to lie more uniformly against the probe. This allows for a more repeatable velocity and signal strength of the microwave pulse, and therefore, better measurement repeatability.

Two options were investigated in the placement of the wave guide/probe:

1. Probe on the outside wall of the tote/bin
2. Probe on the inside wall of the tote/bin

Since the microwave pulse can travel through the plastic/polymeric sidewall of the tote/bin, the first applications suggested that the place of the probe be on the outside wall of the tote/bin and attempt to measure the level of the liquid in the bag through the wall of the tote/bin and then through the wall of the bag. With this design, the probe was not in contact with the bag and it was anticipated that there would be:

1. Less chance of damage to the bag by the probe
2. Less chance of folding or deformation of the bag since the probe did not contact the bag
3. Better repeatability tote/bin to tote/bin and bag to bag

After testing the probe on the outside wall, the following was observed:

1. There was no chance of damage to the bag by the probe.
2. There was less folding and deformation of the bag as compared to having the probe in contact with the bag.
3. The gain (signal strength) of the GWR transmitter had to be greatly increased from the typical factory setting of 90 to more than 220 in order to propagate through the thick tote/bin walls. This increase in signal strength made it very susceptible to interference from conductive objects on the outside of the bin/tote. To minimize this interference and to keep from measuring false levels as people passed close to the probe, a grounded conductive shield had to be placed around the outside of the probe.
4. The 12 mm diameter rigid rod probe could not be accurately bent to match the outside contours of the tote/bin. A stainless steel flexible cable probe proved to be a better solution.
5. On a standard GWR installation in a metallic vessel, the top of the vessel acts as a "launch surface" enhancing the microwave pulse down the probe toward the surface of the liquid. However, in a plastic/polymeric vessel, there is no "launch surface" at the top and a much less efficient system resulted. We mounted a metallic, conductive "launch surface" at the top of the probe to give the micro-

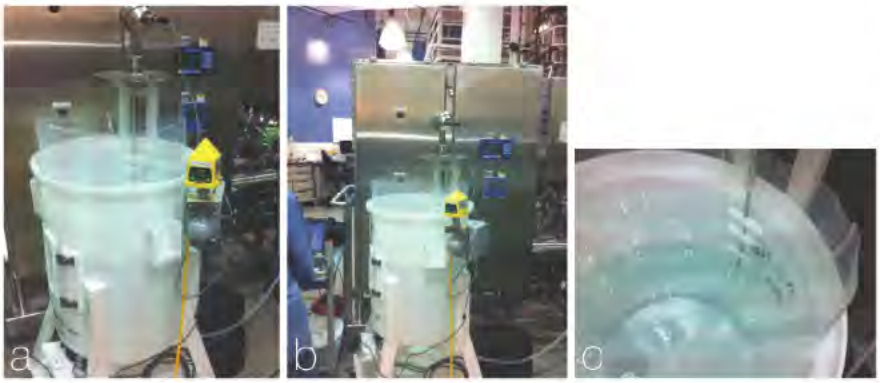


Figure 6 (a, b, and c). Cable on the inside of a 100 liter polymeric tote.

wave pulse a "push" down the probe.

6. With the installation of the 6 mm diameter flexible cable probe on the outside wall of the tote, we observed typical level measurement repeatability, bag to bag, of approximately **3%** of total volume after strapping the first bag and tote.

The licensed facility wanted to improve the repeatability of the level measurement in the tote; 3% of total volume was close to the maximum error limit based on their User Requirement Specification (URS).

4 mm Flexible Cable Probe on the Inside Wall of the 100 Liter Tote

After testing the GWR sensor on the outside of the vessel wall, performance data proved the sensor could not measure well through the polymeric wall of the 100 L Millipore Mobius® tote system. We then installed a 4 mm diameter flexible stainless steel cable probe to inside of the 100 liter polymeric material tote and attached the guided wave radar transmitter to a polymeric stand mounted above the tote as shown in Figures 6a, 6b, and 6c. The stand also had a 20 square inch diameter launch plate at the top of the probe.


Figure 7. 1.6 mm flexible cable.

The flexible cable probe ran the full length of the inside sidewall and exited through a hole drilled in the bottom of the tote. We intentionally positioned the flexible cable probe on the opposite side of the tote from other electrical devices, conduit and the magnetic mixer to prevent electrical noise, and more importantly, to prevent false level reflections (also known as "ghost levels.")

After testing the 4 mm diameter flexible cable probe on the inside wall of the tote, as shown in Figure 6, it was observed:

1. There was a very small chance of damage to the bag by the probe during bag installation and removal. Damage to the bag and subsequent breach off sterility is possible should a strand of the e cable fray from the flexible probe. Risk is further minimized by placing the flexible probe in

a polymeric spine as shown in Figures 8b and 8c.
2. There was substantially less folding and deformation of the bag as compared to having a 12 mm diameter solid rod probe in contact with the bag.
3. The gain (signal strength) of the guided wave radar transmitter had to be slightly increased from the typical factory setting of 90 to approximately 140 in order to measure through the bag wall. This smaller increase in signal strength did not make the probe susceptible to interference from conductive objects on the outside of the tote. A grounded, conductive shield did not have to be to be placed around the outside of the probe in order to minimize interference and to keep the probe from measuring false levels from people passing close to it.
4. Although we initially used tape to attach the 4 mm diameter flexible cable probe to the tote wall (as seen in Figures 6a and 6c), the owner eventually drilled several holes on either side of the flexible cable probe and secured it to the tote wall with nylon tie wraps.

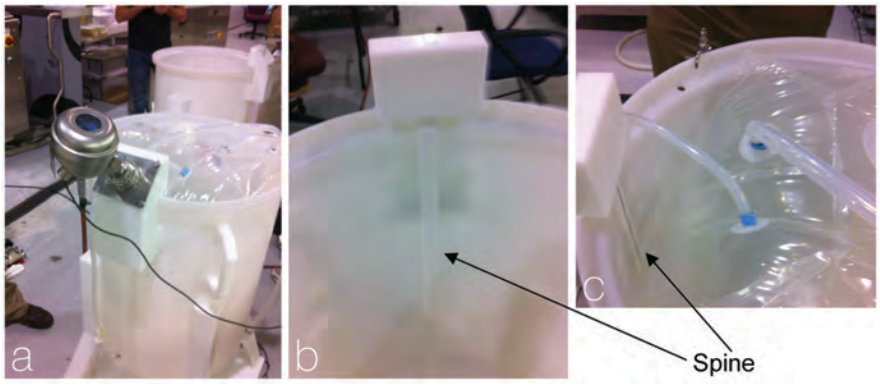


Figure 8 (a, b, and c). 1.6 mm flexible cable inside polymeric totes.

In summary, with the 4 mm diameter flexible cable probe on the inside of the plastic/polymeric tote, we were able to obtain repeatability, after strapping the first bag and tote, of about **1%** of total volume.

Note that the above tests were run on a preformed bag that sat upright in the tote and matched the contour of the tote - *see Figure 6a*. We later ran tests on folded bags that would be pre-inflated with sterile gasses before filling with similar results (as seen in Figures 8a and 8c).

1.6 mm Flexible Cable Wave Guide Probe on the Inside Wall of the 150 Liter Tote

Since the owner wanted to achieve 0.5% or better repeatability, we developed a 1.6 mm diameter flexible cable probe for testing on ahe 150 liter polymer totes as shown in Figure 7.

This probe was mounted to a prefabricated polymeric stand at the top of the 150 liter tote as shown in Figure 8a. The 1.6 mm diameter cable probe was secured to the tote wall via a "spine" fabricated of the same material as the tote. The cable probe was inserted into a groove on the spine (as seen in Figures 8b and 8c).

After testing the 1.6 mm diameter flexible cable probe on the inside wall of the tote, it was observed:

1. There was minimal chance of damage to the bag by the probe during bag installation and removal because the flexible probe was positioned in a protective spine.
2. There was substantially less folding and deformation of the bag as compared to having a 4 mm flexible cable probe in contact with the bag.
3. The gain (signal strength) of the guided wave radar transmitter had to be slightly increased from the typical factory setting of 90 to 190 in order to measure through the bag wall. This increase in signal strength did make the probe more susceptible to interference from conductive objects placed on the outside of the tote.
4. The 1.6 mm diameter flexible cable probe was placed in a groove in the "spine" to secure the cable to the tote sidewall - *see Figures 8b and 8c.*

In summary, with the 1.6 mm diameter flexible cable probe on the inside wall of the plastic/polymeric tote, we were able to obtain repeatability after strapping the first bag and tote of about **0.5%** of total volume.

Note: the aforementioned tests were run with folded bags that were pre-inflated with sterile gasses before filling.

1.6 mm Flexible Cable Probe on the Inside Wall of the 200 Liter Tote

We also conducted tests of a 1.6 mm diameter flexible cable probe for use on a 200 liter polymer tote.


Figure 9. 6 mm flexible cable for mounting inside of a tote.

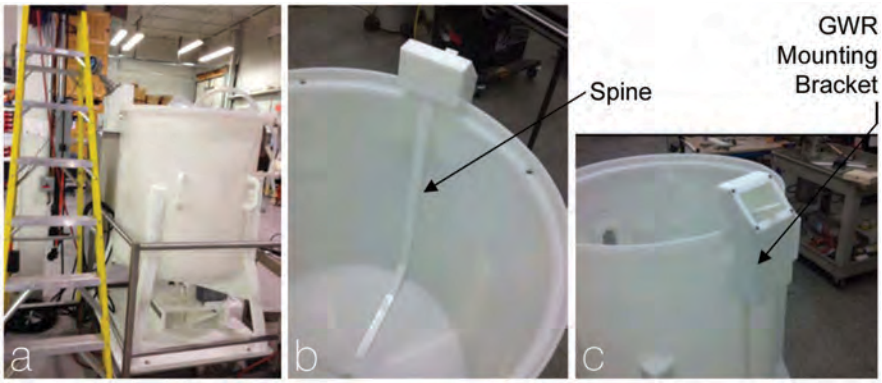


Figure 10 (a, b, and c). 6 mm flexible cable in a 500 liter polymeric tote.

This probe was mounted to a prefabricated polymeric stand at the top of the tote and the 1.6 mm diameter cable probe was secured to the tote wall via a "spine" fabricated of the same material as the tote. In addition, we used the same mounting bracket design and spine design as on the 150 liter poly totes previously shown.

After testing the 1.6 mm diameter flexible cable probe on the inside wall of the tote, it was observed:

1. There was minimal chance of damage to the bag by the probe during bag installation and removal because the flexible probe was positioned in a protective spine.
2. There was substantially less folding and deformation of the bag as compared to having a 6mm flexible cable probe in contact with the bag.
3. The gain (signal strength) of the guided wave radar transmitter had to be slightly increased from the typical factory setting of 90 to approximately 220 in order to measure through the bag wall. This increase in signal strength did make the probe more susceptible to interference from conductive objects placed on the outside of the tote.
4. The 1.6 mm diameter flexible cable probe was placed in a groove in the "spine" to secure the cable to the tote sidewall.

In summary, with the 1.6 mm diameter flexible cable probe on the inside wall of the plastic/polymeric tote, we were able to again obtain repeatability after strapping the first bag and tote of about 0.5% of total volume.

1.6 mm Flexible Cable Probe on the Inside Wall of the 500 and 1,000 Liter Totes

We then conducted tests of a 1.6 mm diameter flexible cable probe for testing on a 500 liter and 1,000 liter polymer and stainless steel totes. The 1.6 mm flexible cable did not perform at all due to the lower energy pulse from it.

It must be noted that the 1.6 mm diameter flexible cable probe should not be used on totes requiring a flexible cable greater than 36 inches in length.

6 mm Flexible Cable Probe on the Inside Wall of the 500 Liter Poly Totes

We then conducted tests of a 6 mm diameter flexible cable probe for use on a 500 liter poly tote. The prototype probe is shown below in Figure 9.

After testing the 6 mm diameter flexible cable probe on the inside wall of the 500 liter poly tote (as seen in Figures 10a, 10b, and 10c), it was observed:

1. There was minimal chance of damage to the bag by the probe during bag installation and removal because the flexible probe was positioned in a protective spine.
2. There was still minimal folding and deformation of the bag as compared to having a 1.6 mm flexible cable probe in contact with the bag.
3. The gain (signal strength) of the guided wave radar transmitter had to be greatly increased from the typical factory setting of 90 to approximately 235 in order to measure through the bag wall. There was some interference or ghost levels on the outside of the poly tote due to

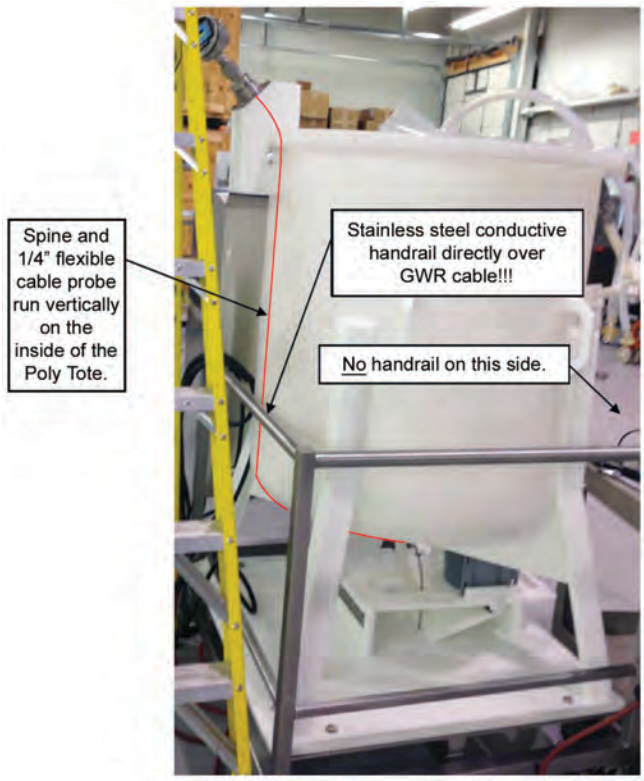


Figure 11. Ghost level due to handrail.

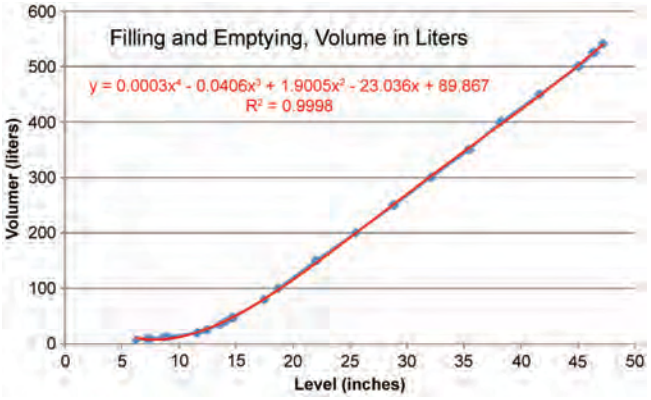


Figure 12. Strapping level vs. volume repeatability (500 liter).

the stainless steel handrail mounted about 1" from the outside of the poly tote and directly in front of the 6 mm flexible cable. See Figure 11. The handrail showed up as a ghost level and was impossible to tune out. We ended up rotating the poly tote 180° to position the flexible cable opposite the hand rail.

4. The 6 mm diameter flexible cable probe was placed in the spine to secure the cable to the tote sidewall. See Figures 10b and 10c.

We then plotted the level vs. volume based on the filling and emptying "strapping table." The results for the 500 liter polymeric tote are shown in Figure 12.

In summary, with the 6 mm diameter flexible cable probe on the inside wall of the plastic/polymeric tote, we were able to again obtain repeatability after strapping the first bag and tote of about **0.3%** of total volume.

6 mm Flexible Cable Probe on the Inside Wall of the 500 Liter Stainless Steel Totes

We then conducted tests of a 6mm diameter flexible cable probe (Figure 9) for use on a 500 liter stainless steel tote.

After testing the 6 mm diameter flexible cable probe on the inside wall of the 500 liter stainless steel tote, the following was observed:

1. There was minimal chance of damage to the bag by the probe during bag installation and removal because the flexible probe was positioned in a protective spine.
2. There was still minimal folding and deformation of the bag as compared to having a 1.6 mm flexible cable probe in contact with the bag.
3. The gain (signal strength) of the guided wave radar transmitter had to be slightly increased from the typical factory setting of 90 to approximately 235 in order to measure through the bag wall. Since the tote is conductive, there was no interference or ghost levels on the outside of it.
4. The 6 mm diameter flexible cable probe was placed and taped on the "spine" to secure the cable to the tote sidewall.

In summary, with the 6 mm diameter flexible cable probe on the inside of the plastic/polymeric tote, we were able to again obtain repeatability after strapping the first bag and tote of about **0.25%** of total volume.

6 mm Flexible Cable Probe on the Inside Wall of the 1,000 Liter Totes

We then conducted tests of a 6 mm diameter flexible cable probe (Figure 9) for use on a 1,000 liter stainless steel tote.

This probe was mounted to a prefabricated polymeric stand at the top of the stainless steel tote - *see Figure 13a.* The 6 mm diameter cable was secured in a "spine" fabricated of the same material as the tote - *see Figures 13b and 13c.* In addition, we used the same mounting bracket design and spine design as on the 150 liter poly totes previously shown.

After testing the 6 mm diameter flexible cable probe on the inside wall of the 1,000 liter tote, it was observed:

1. There was minimal chance of damage to the bag by the probe during bag installation and removal because the flexible probe was positioned in a protective spine.
2. There was minimal folding and deformation of the disposable bag.
3. The gain (signal strength) of the guided wave radar transmitter had to be increased from the typical factory setting of 90 to approximately 210 in order to measure through the bag wall. Because the tote was metallic, there was no interference with objects outside of the tote.
4. The 6 mm diameter flexible cable probe was placed and taped on the "spine" to secure the cable to the tote sidewall.

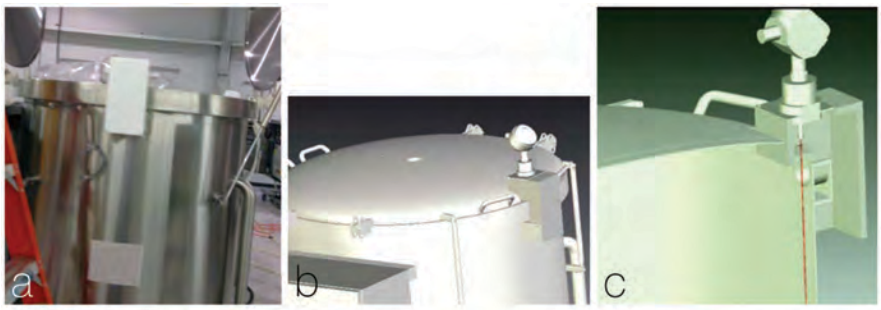


Figure 13 (a, b, and c). 1,000 liter stainless steel tote.

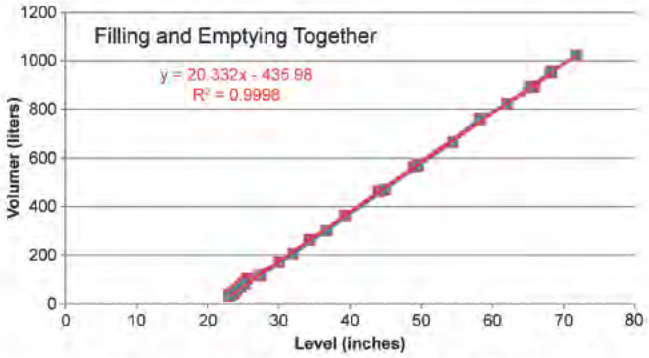


Figure 14. Strapping level vs. volume repeatability (1,000 liter).

We then plotted the level vs. volume based on the filling and emptying "strapping table." The results for the 1,000 liter stainless steel tote are shown in Figure 14.

In summary, with the 6 mm diameter flexible cable probe on the inside of the 1,000 liter stainless steel tote, we were able to again obtain repeatability of about **0.25%** of total volume.

Summary

Summary of our repeatability experience for all tested probes and totes/bins can be found in Table A.

Guided wave radar level measurement is an acceptable, less expensive alternate to load cell systems. The typical cost of a GWR transmitter and cable probe is approximately 1/3 the cost of a load cell system.

In addition, guided wave radar transmitters have the option of periodic calibration verification performed on a bench dry calibration stand. The first calibration on a GWR in a 1,000 liter bin took approximately eight hours to perform and consumed over 2,000 liters of purified water. Calibration verification on a bench stand took less than 10 minutes and did not require water.

For GWR measurement lengths of less than 1 meter, we suggest the use of 1.6 mm flexible cable as the probe. For measurement lengths greater than 1 meter, we would suggest the use of a 6mmees flexible probe.

In all cases, the positioning of the wave guide probe between the tote wall and the bag wall provided the best repeatability of less than 0.5% of total volume.

Guided Wave Radar Technology	Repeatability
1,000 Liter Stainless Steel Bin, 12 mm Solid Rod	4% of Total Volume
100 Liter Plastic/Polymer Tote, 4 mm Flexible Cable on Outside Wall	3% of Total Volume
100 Liter Plastic/Polymer Tote, 4 mm Flexible Cable on Inside Wall	1% of Total Volume
150 Liter Plastic/Polymer Tote, 1.6 mm Flexible Cable on Inside Wall	0.5% of Total Volume
200 Liter Plastic/Polymer Tote, 1.6 mm Flexible Cable on Inside Wall	0.4% of Total Volume
1.6 mm Flexible Cable Greater than 36 inches in Length on Inside Wall	DO NOT USE 1.6 mm
500 Liter Plastic/Polymer Tote, 6 mm Flexible Cable on Inside Wall	0.3% of Total Volume
500 Liter Stainless Steel Tote, 6 mm Flexible Cable on Inside Wall	0.25% of Total Volume
1,000 Liter Stainless Steel Tote, 6 mm Flexible Cable on Inside Wall	0.25% of Total Volume

Table A. Repeatability summary.

About the Authors

David Ladoski is a Principal Engineer at Amgen. He has 18 years of experience in the biotechnology field providing solutions for process equipment and instrumentation.

Dan Klees is the Hygienic Business Development Manager at Magnetrol International, Inc. located in Aurora, IL. Klees is responsible for the hygienic industries in North and South America as well as Asia and the Pacific Rim. He received his BS and MS degrees in physics from Miami University. He has 40 years of experience in the hygienic industries, having held senior management positions in sales and marketing with major automation and process measurement instrumentation companies as well as engineering management and executive management positions with integration and engineering firms. He is a member of ISPE, ASME BPE Standards and Executive Committees and is Chairman of the ASME BPE Process Instrumentation Subcommittee. Klees has published several automation and advanced control algorithm articles in leading technical journals and has presented numerous papers and seminars at International BioPharmaceutical Symposiums. He has been a graduate school guest lecturer on process automation at several universities. He holds nine U.S. and European Patents related to hygienic process measurement instrumentation innovations, single use disposable instrumentation and calibration methods. Klees can be contacted by telephone: (630) 969-4000 or email: dklees@magnetrol.com.

Magnetrol International, 705 Enterprise St., Aurora, Illinois 60504, USA.

WORLDWIDE. Raised blood pressure is estimated to cause 7.5 million deaths annually – about 12.8% of the total of all deaths. Raised blood pressure is a major risk factor for coronary heart disease and stroke.


CHINA. AstraZeneca is building a new facility for production of oral solid dosage products, including Betaloc, which is used to treat high blood pressure.
nne pharmaplan®
Engineering for a healthier world

"Paper on Glass" User Centric Batch Operations – A Productivity Game Changer for Paper Driven Pharmaceutical Production

by Robert Harrison

This article presents how technology has advanced electronic batch record into solutions which compete one-to-one with paper flexibility, opening the door to game changing production efficiencies in pharmaceutical production.

People deal with complexity and abnormality very well. The flexibility an operator gives to the nature of production in the lifescience industries is an extremely valuable resource. However, production complexities and quality demands continue to increase, using paper to drive the operator and record events may have outlived its welcome. We all feel comfortable with paper; it is something we can touch, see, and feel progress as it grows during the batch. Because you can touch it, it makes you feel like you have full visibility on the process and people's activities, paper's history in pharmaceutical production is a little like religion and its scriptures, they are deemed paramount and carry with them emotion which is never questioned.

Challenges of Managing Paper Based Production Operations

Paper and its long term storage has a large effect on pharmaceutical production cost. Pharmaceutical production requires that significant post batch analysis and reporting must be carried out. Manually extracting and analysing paper production data is an intense and demanding activity which involves highly educated and experienced people. The major cause of rejects and reworks in paper-based batches are the result of 1. missing entries and 2. errors in paper documentation. The batch ran physically perfect, only the recording of this perfect execution failed, and proving its innocence costs serious revenue. Each batch can involve about 1000 manual entries with a human failure rate of 1×10^{-2} (i.e., one in on hundred)[1] – the probability of significant failure is too high. Each of these manual paper records require Standard Operating Procedures (SOPs) from each process, which amounts to a long paper audit trail and needs to be stored in a secure location. The risks to keeping such an inefficient system are great, the cost of quality is high, which is reflected in the cost of production.

We can identify many areas where human error can enter into the system: a person generates and issues the paper documentation, the operator reads the SOP, then reads the equipment, and writes the result on the batch record. The records are then read by another person and inputted into a computer for analysis and reporting as seen in Figure 1. With each human activity, the risk of failure is increased.

When investigations are carried out, the whole paper documentation needs to be obtained and analysed once again. What happens with missing entries? What happens with entries entered incorrectly? What happens with lost paper or paper delivered to the wrong person, or the wrong SOP is issued for a particular batch?

"Benchmarks for Pharma vs. Other Industries,"[2] the


Fluid solutions
for fluid solutions.
LEWA EcoPrime® systems offer a smarter, more accurate and flexible downstream process platform.
With unmatched reproducibility and accuracy and a dynamic range that allows a single EcoPrime system to do the work of up to three competitive process units, LEWA has reinvented the standard for chromatography, buffer-in-line dilution, and other critical downstream processes. Go with the experts in fluid design. Go with LEWA.
www.lewa-inc.com
LEWA
Creating Fluid Solutions

1.	The operator: • Read the SOP → Execute the command(s) on the equipment • Requested to read process values → Read the equipment process values • Record the information in the correct location on the batch record sheet • Sign the record A potential violation is noticed → the violation is flagged, the operator contacts the quality responsible. ! Or the operator makes a judgement call that the violation is only minor → and continues.
2.	Post batch • All batch records are manually transferred to a computer system • Individual machine data is time-lined as a process • The process data is analysed • A batch report is generated
3.	The whole paper documentation, analysis, batch reports and supporting documents are secured in a large air conditioned and protected storage unit. The documentation remains in storage, in some cases for many years.

Figure 1. A basic workflow for a paper based execution of production.

"first pass yield – zero defects" indicates right first time with a value of 60%, this hints that pharmaceutical production has significant benefits to gain from the addition of technology. Right first time in paper driven production environments is far less estimated to be at 47% with the major causes of rejects or reworks being 1. errors in paper documentation 38% and 2. missing entries 29%.

Manual paper-based processes record and store production data in a disconnected and difficult to access medium. Decisions need to be made on these manual processes and with paper systems, there is a significant time delay to get the data into a usable format. This is an area where EBR aims to improve.

Current EBR limitations

Electronic Batch Record (EBR) systems are designed to gather accurate and complete information critical to compliance. With paper-driven processes, the operator and his or her memory is crucial to completing the batch information. EBR avoids mistakes common in manual transfer and integrates manual operations with automated processes.

The problem with EBR is the static workstation and its focus to the mechanical process. It relies on the operator to prove the flexible interface between what is required by quality and operations management; in some instances, this can be a large cognitive activity that the production operator needs to carry out. Paper on glass aims to be user centric and portable with the right tools available to understand how the person is linked to the process, and produce batches with little variation.

How EBR Evolves to Paper on Glass

Paper on glass is not a revolution in technology, rather a progression together of known technologies that easily interface in a high usability application to embrace the user centric environment it operates in. The key functionalities for paper on glass are:

- Mobile tablet usage is paramount for the application. Paper is portable and the application that replaces it also must be portable. With a client – server infrastructure to safeguard process information and keep a central control. The tablet can get lost or broken and the data remains secure.

Measure	Pharma	Automotive	Aerospace	Computer	Consumer Packaged Goods
Overall equipment effectiveness	10% to 60%	70% to 85%	50% to 70%	80% ti 90%	70% to 90%
Annual productivity improvement	1% to 3%	5% to 15%	5% to 10%	1% to 3%	5% to 15%
First-pass yield – zero defects	60%	90% to 99%	70% to 90%	90% to 99%	90% to 99%
Production lead times in days	120 to 180	1 to 7	7 to 120	5 to 10	3 to 7
Finished goods inventory in days	60 to 90	3 to 30	3 to 30	5 to 580	10 to 40
Labor value-add time	20%	60% to 70%	60% to 70%	60% to 70%	60% to 70%
Direct/indirect labor ratio	1:1	10:1	10:1	10:1	10:1
Pharma is decades away from achieving the performance, on key OpEx benchmarks, reached by other industries. But, experts say, pharma is still three to five times more profitable than they are. Chart source: McKinsey & Co., quoted in The Gold Sheet, December, 2009.					

Table A. Benchmarks for pharma vs. other industries.

- A batch control system which is compliant to the industry batch standard ISA 88, this gives flexibility to drive the process and usability to interact with the operator.
- Usability is of great importance as mobile tablets don't have large screens, and a batch system contains much information. Intuitive presentation of data is needed, multi-touch is an essential element linking the user to a known interface common to tablets and smart phones.
- Historian to archive batch operation data, weight dosing and media information, equipment usage, and operator events. The historian is central to batch compliance, automated archiving of recorded data provides data integrity.
- Complete batch documentation must be reported with automated analysis and clear information identifying weighing information, equipment usage, operator events, alarms, Critical Quality Attributes (CQAs) violation and electronic logbook.

To be able to stand on your own feet is a test of character, and the system outlined here supports this. However interaction with outside and connected systems is an equally important function. John Steinbeck, in his novel "East of Eden"[3] quotes *"Maybe a specialist is only a coward, afraid to look out of his cage. And think what any specialist misses—the whole world over his fence."* In pharmaceutical production, there are many sources of information that build up a batch record and additional information needs to be included. Standard industrial interfaces exist with for example SQL connectivity, MES and ERP have native mechanisms to embrace the whole supply and manufacture chain. This automates the batch record to accommodate specific batch needs.

Making the Move, What Are the Advantages and Challenges to "Paper On Glass?"

To replace paper with software requires an application with diverse behaviour. Mobile technology allows for intelligent and portable applications to be with the operator, high usability swaps their clipboard to a mobile workstation. EBR forces strict execution of the batch recipe, stage by stage requesting the operator to execute tasks and record information. The operator is not allowed to miss entries, each user input can be automatically verified to ensure correct entry of data, and violations are signalled in real-time through the correct channels. More importantly, potential violations can be alerted, key people then intervene to mitigate the situation. Batch analysis and reports need not be manual activities, these can be instant and automatic.

Any activity affecting how direct production is executed falls directly under quality management's scrutiny. The system proposed here makes no changes to the physical equipment and no changes to the current automation of the process. It does aim to replace the paper driven operator instructions, and replace the operator batch record, then digitally store the complete record. The process hasn't changed, only closer control of manual operations has been achieved with live verification of inputted information.

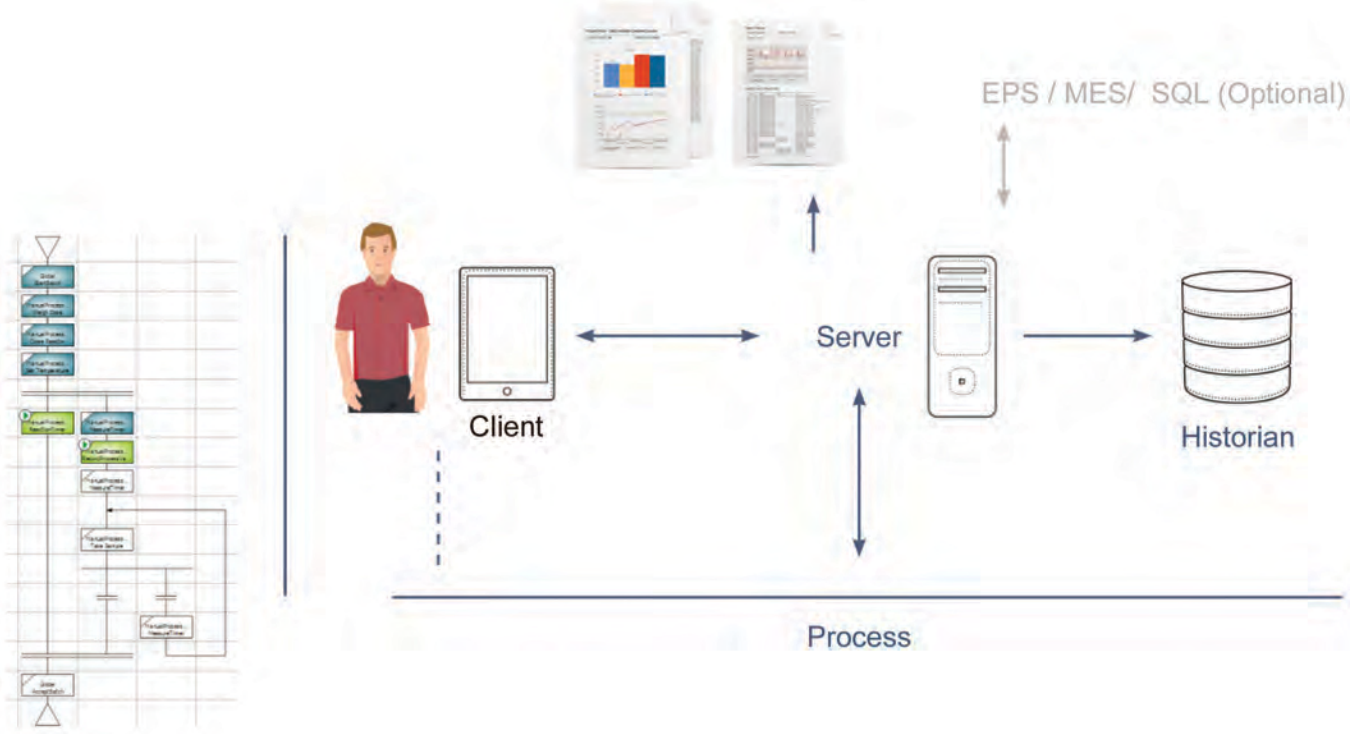


Figure 2. A simplified system overview demonstrates the linkage of the functionalities.

- Multiple batches operating concurrently
- Flexible visual recipe management
- Agile to different equipment, hardware and products
- Check, recheck, and query the operator
- Alert on violations and warnings, e.g. via SMS, email, or telephone
- Archive CQA's
- Automate analysis, Review By Exception (RBE), alarms
- Automated reporting
- Digital storage and retrieval

Figure 3. Paper on glass is more than EBR, it provides logic and intelligence to the operator.

As there are no changes to production processes, the current paper method can be executed concurrently with the digital "paper on glass" system; this would allow for several stages of production quality acceptance to be examined and tested without risk or stoppage to production.

Another challenge is that perhaps the current automation solutions in place today are not flexible enough to bring the required functions together in one portable system: Mobile tablet application, batch process understanding and operation, secure archiving of data, analysis, sophisticated reporting, real-time communication, FDA 21 CFR Part 11 compliance. Fortunately automation technology is an industry which never sleeps, these crucial individual mechanisms do exist in the market place, and can be configured to create an all-in-one mobile electronic batch record system.

Accuracy and Consistency

People are open to a wide array of influences: stress, lack of attention, attitude, sleep (the lack of it), or just having a bad day. Automated batch-driven processes repeat the same strict sequence each time and every time. Software can interrogate each user input within limits, determining at the point of entry if a human error has occurred, and with time-stamped accuracy. Electronic logbooks manage the abnormality with automated alerts and workflows enforcing the correct execution on violations.

Strict point-of-entry requirements and clarity of data is paramount to complete batch documentation and right first time. Missed entries and incorrect entries are minimized for consistent production and release.

Productivity

People and their motivation go a long way to achieve production success. Providing a familiar human interface with access to correct and complete information are the tools to work faster, smart companies create the perfect environment for increased productivity.

Production cycles can be reduced. Typical batch release cycle times of around 10 to 40 days can double in non-conformance situations. EBR forces consistent execution of the manufacturing sequence on a platform which provides accurate real-time view of process and deviation data. Time associated with detecting, tracing, and documenting deviations in the manufacturing process is much reduced. Analysis and reporting is automated, which accelerates batch release and reduces the head count of persons involved in this critical exercise.

Reduce Cost of Quality, Full Quality Compliance

Paper on glass ensures the batch documentation is correct and comprehensive. Compliance requires repeatability of batches, capturing information accurately, organizing and retaining the information, then efficiently analysing and presenting it. Do it right first time prevents errors through pro-active checks. Such mechanisms improve the demonstration of compliance to meet Good Manufacturing Practice (GMP) regulations.

Master recipe development and control recipe creation is on a graphical system with version control and recipe state control to managing GMP compliant processes. Automated batch reports easily separate production data, e.g., material weighing and dispensing data, equipment usage, CQAs and process values, user instructions and actions, electronic signatures, alarms and violations, audit trail and electronic logbook. Production is monitored as a process and not individual machines, allowing focused reports with specific analysis.

Critical Quality Attribute (CQA) deviations can be handled through automated workflows, and don't need to rely on the operator to flag violations. With automated alerts, the equipment can signal warnings via remote system such as SMS, email, or telephone. Post batch analysis can be made on non-conformities through Report by Exception (RBE) reports generated automatically from production data. Access to all information decreases the effort required to investigate product deviations.

Having data stored electronically has several advantages: information is readily available, it requires so little storage area in comparison to paper, digital data can be stored on redundant systems, and the information is widely available for example the progress status of each batch is visible across the company.

Cost Avoidance

Costs are mitigated on many fronts with 'paper on glass'. 1. Rejects and reworks are much reduced due to correct data entry and consistent production sequence. 2. Head count is reduced, as the batch information doesn't need to be re-entered into a computer system; therefore, data alignment of individual machines in to a process is automatic. 3. Paper doesn't need to be generated with automated master and control recipes. 4. Large volumes of paper don't need to be stored in a secure and controlled environment, the storage can be digital and redundant.

Improve Right First Time

Improvement in RFT comes from strict operator workflow and point of entry verification, which creates more consistent and repeatable batches with shorter release time. Paperless recipe systems reduce manufacturing errors, provide investigations with easy access to all required data, and instant batch analysis.

Conclusion

"Paper on glass" transforms a paper-based production system into something quite remarkable – without change to any production equipment or process. Automating the operator and production reporting means post batch analysis is reduced to an absolute minimum by removing the manual heavy element of batch analysis. Products are released to the market potentially faster than paper production methods. Quality is optimized and risk is mitigated as production flow is consistent between batches, execution is strict and no information is missing from the record. With errors in recording information as far as humanly possible eliminated, reworks and rejects are significantly reduced. The benefits of a complete batch control system, integrated on mobile tablets, avoids cost and is a game changer for pharmaceutical production efficiency. No paper needs to be generated with no mountains of paper to be stored in secure locations – instant batch analysis means instant revenue. Production activities are aligned in real-time to the gravity of business.

References

1. Smith, David. J., *Reliability, Maintainability and Risk, Butterworth-Heinemann,* 2005, 7th Edition.
2. Shanley, A., "Is Pharma Stuck on the Way to Six Sigma?" PharmaManufacturing.com, http://www.pharmamanufacturing.com/articles/2011/005/, accessed March 2014.
3. Steinbeck, J., *East of Eden,* The Viking Press, 1952.

About the Author

Robert Harrison leads the pharmaceutical industry division at COPA-DATA, Salzburg, Austria. With more than 20 years of international experience, Harrison has served in varying management and engineering roles across industry and research, gaining his BSc in electronic engineering while working at CERN, Geneva, Switzerland. He is currently responsible to drive strategy, technology development, global growth and worldwide performance of zenon technology in the life science industries. He may be contacted by telephone: +43 662 43 100 20 or email: RobertH@copadata.com.

COPA-DATA GmbH, Karolingerstrasse 7B, A-5020 Salzburg, Austria.

PHARMACEUTICAL ENGINEERING Interviews

Chi-Wan Chen, Executive Director Global CMC, Pfizer

by Linda Evans O'Connor and Jean Poulos

Chen discusses possible regulatory changes in China, the impact of these changes on various guidance documents, and the evolution of CFDA's draft comment process.

Chi-Wan Chen serves as Executive Director in Global CMC, Pfizer, responsible for regulatory policies and strategies with a focus on the Asia Pacific region. She is a member of ISPE's Regulatory and Compliance Committee currently chairing the Asia Pacific Focus Group and serves as an ad-hoc CMC advisor to the multinational companies' trade organization in China and in the South East Asia region. Prior to her joining Pfizer in March 2008, Chen spent 22 years with the US FDA. She represented the FDA at the ICH on several Quality Guidelines, including Q1AR, Q3AR/Q3BR, and Q8R. During 2005 to 2008, she provided technical leadership and management oversight for the FDA Quality by Design (QbD) Pilot Program.

In your opinion, is 2014 an especially active year for regulatory changes in China?

Maybe, because we don't know for certain. There is no published list of proposed guidelines so we don't know what is coming. At the end of last year, around November/December, the Center for Drug Evaluation (CDE) did indicate to both local and multi-nationals that they are planning to update a series of technical guides, most of which were published around 2005. They requested assistance from the R&D-Based Pharmaceutical Association Committee (RDPAC) to provide a gap analysis of 13 technical guides compared to US, EMA and ICH guidelines and to provide suggestions on how to update the technical guides. They want the guidelines to be updated in accordance with ICH CTD guidelines. These are all CMC guides, not GMP. This is an indicator that 2014 can be a very active year for regulatory changes in China. The CFDA has developed their own CTD based largely on the ICH CTD. The CTD published in 2012 was to encourage local generic companies to use it. Many large multinationals have started to submit in the CTD format and that is acceptable. There is no CTD format for new drugs, only for generics.

Are any recently published guidelines particularly burdensome?

Two guidelines are very burdensome. These relate to compatibility of injectable drugs. One for compatibility with glass was published a year ago, and the other in plastic was published in November. These are drafts. There is another draft, not necessarily burdensome, but is the first attempt to incorporate ICH guidelines. This is the stability guideline. It was first

published in 1995. It was published in February 2013 in draft and has not been finalized.

When a guideline is published in draft, do they ask for comments on the draft?

Yes – most draft guidance has a 30 day comment period, which includes translation of the document and translation of the comments. If the guidance is published in Chinese, companies need to translate the document and then translate the comments for submission.

What are the guides that are used to perform submissions?

- Requirements for Preparing Application Dossiers in CTD Format for Chemical Drugs (July 2011)
- Format and Content of the Overall Summary of Chemical Drugs – Summary of Pharmaceutical Development (March 2005)
- Chemical Drug Quality Control Analytical Method Validation (March 2005)
- Studies on Impurities in Chemical Drugs (March 2005)
- Studies on Residual Solvents in Chemical Drugs (March 2005)
- Standardization Process of Chemical Drug Specification Establishment (March 2005)
- Basic Technical Guidance for Chemical Drug Product (March 2005)
- Studies on Manufacture and Characterization of Chemical Drug Substances (March 2005)
- Chiral Drug Pharmaceutical Research Techniques Guidelines (September 2007)
- Pharmaceutical Studies on Synthetic Polypeptide Drugs (September 2007)
- Pharmaceutical Study of Oral Sustained Release Preparations for Chemical Drugs (September 2007)
- Research on Quality Control of Inhalant (September 2007)
- Dissolution Test of Common Oral Solid Dosage Technical Guidelines (draft revision October 2012)
- Stability Study of Chemical Drugs (Drug Substances and Drug Products) (draft revision February 2013)

These are in the process of being updated or finalized this year. There are also three technical guides published in draft or in final form in the last year:

- Draft Technical Guideline for the Stability Study of Chemical Drugs (Drug Substances and Drug Products)
  - This draft stability guideline is a revision of the 2005 technical guide on the same subject by incorporating ICH Q1A(R2), Stability Testing of New Drug Substances and Products, and part of Q1B, Photostability Testing of New Drug Substances and Products. Certain information is not consistent with the source Q1A guidelines: (a) some added recommendations, e.g., stress testing, intended to serve as a guide to local companies during drug development, are very proscriptive; and (b) certain concepts, e.g., those underlying statistical analysis, from the Q1A guidelines have been revised or omitted. These discrepancies can lead to divergent requirements and practices.

> *"The Chinese government came up with a compromise and that is to rely on dissolution testing to determine if the generic is the same quality.*

- Draft Guideline on Compatibility of Injectable Chemical Drugs with Glass Containers (being updated to incorporate ICH Q1A)

- Final guideline on Technical Requirement for Quality Comparability Studies for the Change of Vaccine Production Site

We understand that there is a comment period after the draft is published, but is there any pre-consultation with industry or does CFDA decide how they want to proceed and then send out for comments?

It varies. In some cases, the CFDA or CDE would have informal meetings with trade representatives – local or multinational and inform the trade reps of their intent and open the door for them to provide suggestions. However, in most cases, the CDE or CFDA would issue the draft without consultation. In the case of the revised draft stability guidelines, because there was already a guideline, CDE who was responsible for the update, had informal meetings with local and multi-nationals, without showing a preview of the draft; however, they did highlight some major changes. After it is published as draft, the draft is officially published.

The industry has 30 days to comment – is there a set period of time that CFDA has to address the comments and publish the final guidance?

There is no set timetable for CDE or CFDA to respond to the comments and to issue the final guidance.

There are a couple of other technical guides related to national level, top priority. There is five year plan. Currently, it is in the 12th five year plan, driven by economics. Under this umbrella, there is a Generic Drug Quality Consistency Evaluation (GDQCE). This started end of 2012. Last year, there were two technical guides: one policy and one technical guide – related to this initiative to enable companies to participate. This initiative is to reassure the quality and performance of generic drugs approved prior to 2007, which was the year that the regulations in China was revised to require BE studies for generic applications. Prior to that, there was no requirement to perform a BE study for generic drugs. In China, there is a general negative impression that generic drugs are not as safe and effective as innovator drugs. This is a sentiment shared by medical professionals and the general public. There are 1000s of applications before 2007 and many manufacturers that make products. The economic impact would be too great. There is no infrastructure to perform BE studies for all these products. The Chinese government came up with a compromise and that is to rely on dissolution testing to determine if the generic is the same quality. There are many problems to start – there is no list of reference drugs, and so they have to start establishing the RLD. They are identifying companies that they think can be the reference drug. Companies are invited to prove themselves as the RLD. Reference manufacturers have to submit samples, dissolution testing and profiles. Other than the procedural problems, which are large, the approach is non-scientific. They are worried about quality, safety and efficacy. The compromise approach will not assure this.

About the Authors

Linda Evans O'Connor, Vice President Supplier Quality Management, Teva Pharmaceuticals and **Jean Poulos,** Vice President Global Regulatory, Aceto Corporation both serve on ISPE's Regulatory and Compliance Committee (RCC) working on the Publications/Communications Subcommittee focused on increasing visibility and awareness of ISPE's global regulatory initiatives.

Claim Your Spot Among the World's Leading Pharmaceutical Innovators

Submit an Entry for the 2015 ISPE Facility of the Year Awards!

The 2015 Facility of the Year Awards (FOYA) Program is your chance to spotlight your company's commitment to innovation and excellence in pharmaceutical manufacturing.

FOYA Category Winners are acknowledged by global regulators, industry colleagues and business leaders alike as the driving forces in the future of the pharmaceutical industry. Don't miss your opportunity to participate in this premier awards program – start assembling your submission today!

Submissions Due 24 October 2014

For full program information and submission criteria, visit www.FacilityoftheYear.org today!

2015 Facility of the Year Awards
Awarded by ISPE

ISPE

Incorporating Lean Principles into Pharmaceutical QC Laboratory Design

by Mike Dockery, Federico Gabardi, Javier Garay, Jim Gazvoda, Luke Kimmel, Pietro Orombelli, Christophe Peytremann, Tom Reynolds, Tanya Scharton-Kersten, Graham Shoel, and Jeanne Sirovatka

This article presents a case study based on an international workshop hosted by Novartis Vaccines to prepare guidelines for incorporating lean principles into pharmaceutical quality control laboratory design.

Novartis Vaccines (Novartis) has applied a structured implementation of lean principles across Quality Control (QC) laboratories in Europe, India, China, and the United States. The aim has been to significantly improve internal work processes, communications, customer interfaces, and operational performance.

As a result of this critical effort, analysts have been trained in basic lean principles, 5S organizational strategies were introduced, and visual management was implemented for daily and weekly performance reviews. In addition, the QC team gradually applied effectiveness tools for capacity management and budget processes.

As different QC teams – operating in both legacy and new state-of-the-art facilities – implemented lean principles, it became clear to Novartis that laboratory design and layout have a strong, direct influence on processes, behaviors, and communication.

While some designs proactively enable and support lean practices, such as flows, visual management, standardized work, and excellence in workplace organization; other design solutions result in teams spending extra time and resources. In the less than optimal facilities, the very layout and design of the space introduces waste, discourages communication, and even impedes workflow throughout the laboratory.

Based on these observations and aiming to improve future laboratory designs, Novartis developed a draft of comprehensive laboratory layout and design guidelines that would support lean principles. The guidelines were then reviewed, refined and augmented in an intensive two-day workshop that brought together key Novartis stakeholders with the industry's leaders in laboratory design, planning, and lean operations.

The mechanics of the workshop allowed the team to first develop a common understanding of lean practices in laboratories in order to identify design features that foster proactive communications, optimize data information and support effective work practices. The team identified and consolidated initial concepts around facility layout, critical adjacencies, visual management, shared equipment, consumable storage access, and furniture/bench and equipment layouts. Once a common understanding was achieved, the team broke out into three to four person work cells to develop a case study re-design of a new Novartis quality control laboratory facility.

As a result of the workshop, a three-zone concept for laboratory design emerged along with a solid set of layout guide-

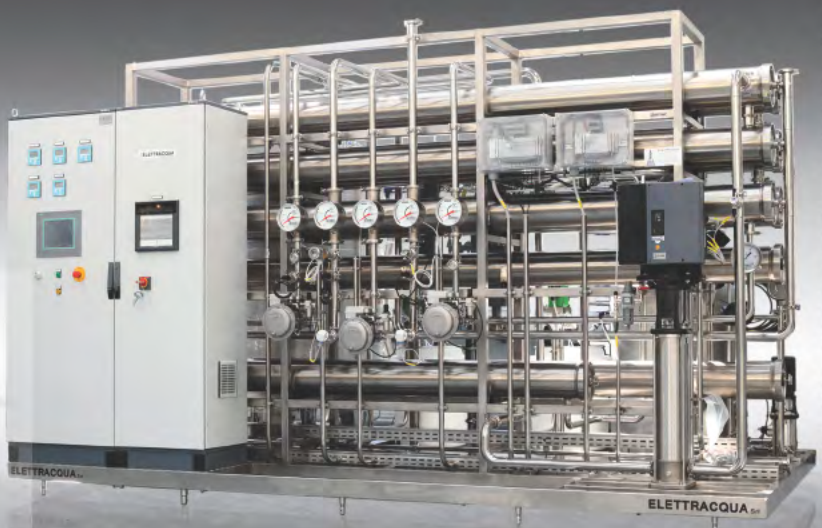
ELETTRACQUA

pure water technologies

SINCE 1966

PHARMACEUTICAL WATER SYSTEMS

OSMOSIS + EDI UNIT HOT WATER SANITIZABLE



DOUBLE PASS REVERSE OSMOSIS (14M³/H - 62 GPM)
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

lines that are applicable to existing legacy laboratories, newer state-of-the art facilities, and future "greenfield" laboratories.

Lean in Laboratory Environments

Lean is a philosophy and a concept of operations that focuses on the elimination of waste and the application of leveling, flow, pull and standard work. Lean was first developed in the Japanese automotive manufacturing sector, but has since migrated across the globe and into every sector of industry.

It is usually defined as the "elimination of waste" where waste ("muda" in Japanese) is anything above the minimum effort, time, resources, movement, materials, and space required to add value from the customer's perspective. However, this is only a partial definition. The real intent of lean is to maximize value by minimizing all wasteful practices. This, of course, includes muda (i.e., the waste within processes) but also:

- Mura – unevenness (workload volatility)
- Muri – overburden (overloading of people or equipment)

Mura and muri are especially significant in lab environments.

Even though QC laboratories are not the same as manufacturing environments, the key principles of lean still apply and should be implemented in their operation and space planning. However, there are some unique challenges involved in implementing lean in the laboratory environment that require careful adaptation of the techniques used in manufacturing. When these adaptations are based upon a thorough understanding of laboratory processes, lean implementation will deliver significant benefits in terms of productivity or speed, or both.

In most laboratories, short term volatility (in overall workload and in the mix of sample types) is by far the biggest lean opportunity. This volatility causes low productivity (during lulls) and/or poor lead time performance (during peaks). Very often the capacity of the lab is not well understood and there is no mechanism to level the workload coming into the lab. If left unchecked, this volatility results in the consumption of excess resources and valuable lab space. Lab processes also become stressed, leading to constant re-prioritization and "stop start" progress on individual batches or samples. This reduces effectiveness and adds waste. The rate of failures and rework also often increases. In short, mura (volatility) creates muda (waste).

Poor utilization of analyst resources (usually in the form of volatility and imbalance in individual analyst workloads) is usually the second largest lean opportunity. Leveling, flow and standard work allow the development of 'productive roles' for the more routine work elements in a lab.

Applying lean principles in a laboratory environment shifts the focus of improvement initiatives from individual tests or activities to the flow of samples and data through the total lab process. It uses leveling techniques to address workload volatility and generates flow by creating "defined test sequences" that move samples quickly through all required tests and reviews. Test activities are combined into balanced, productive, and repeatable analyst roles that use people's time well (i.e., standard work).

A lab design and layout that actively supports these principles will increase the effectiveness and sustainability of the lean processes.

Defining Lean for an Organization

The primary issue to consider when introducing lean principles into the design and planning of the QC labora-

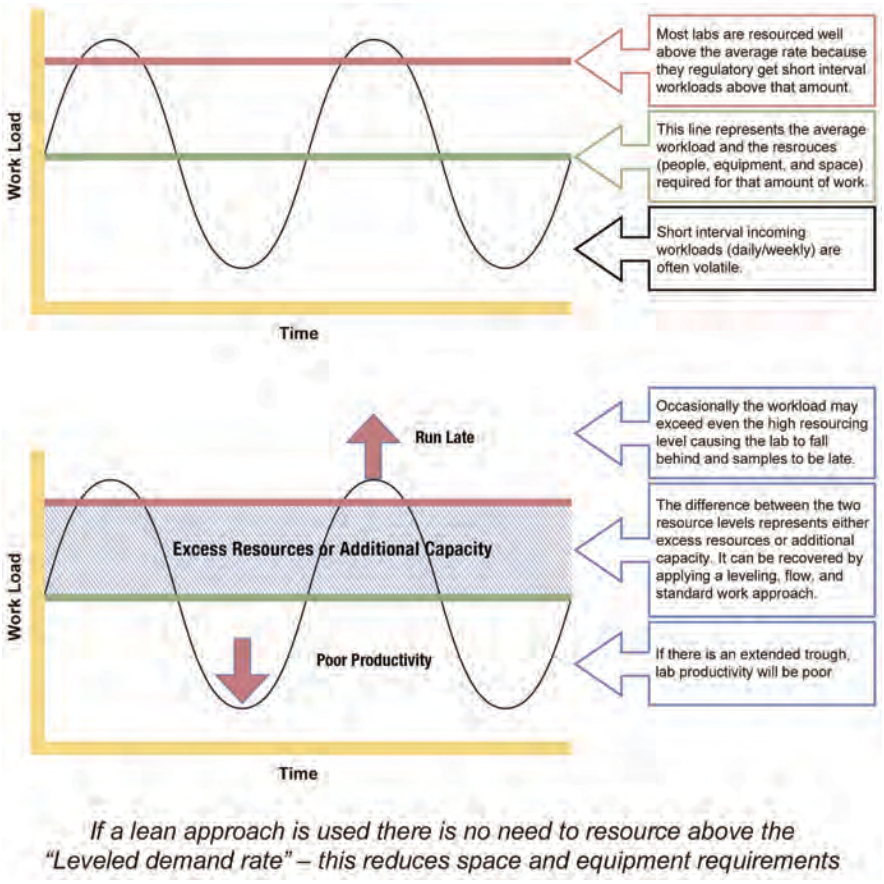


Figure 1. The impact of volatility.

tory environment is defining exactly what lean means to every part of the organization. Quality, manufacturing, environmental health and safety, and engineering need to define together what makes an efficient and effective use of available resources (people, space and equipment). Variables such as energy use, first cost, operational cost, regulatory compliance, financial justifications, and the quantity and quality of the space need to be weighed against each other and prioritized with the underlying premise that safety in the laboratory comes first.

Understanding the differences between manufacturing and quality control testing is key – the first is a revenue generator, the second is perceived as overhead. This creates a different level of tolerance for the initial and operational costs of each. Regional differences also may come into play in facilities in different world locations. Some cultures may require different shift strategies, cross functional training possibilities may be affected, and the reliability of the supply chain could affect the quantity of space allocated to consumable storage, etc.

Space Needs – Quantity and Quality of Space

Implementing lean principles in QC laboratory environments starts with determining the right *quantity* of space required to effectively carry out testing operations. In addition, identifying and implementing the ideal adjacencies between the different testing, office, write-up, and support spaces of a facility will ensure the right *quality* of space is provided in a way that enables lean practices and behaviors. Finally, a clear understanding of the equipment required, how it is used, who uses it, and how often is essential to maximize the use of resources.

- **Needs Assessment** – a thorough assessment of space needs includes both a top-down and a bottom-up analysis. The combination of these two approaches creates a holistic picture of the quantity of space required. Benchmarking studies are also used when initially planning a facility.
  - In the **top-down approach**, we utilize pertinent metrics, such as headcount, benchmarking, and historical data to determine space drivers, functional areas, the amount of rooms, their size, and the amount of equipment that can be placed into each. Subsequently, we analyze how many samples can be tested in the amount of space provided.
  - The **bottom-up approach** examines how many

batches and how many lots are being manufactured to determine how many tests are required, the equipment needed for each test, and the frequency of equipment use. This information dictates how much space is needed for each test.

- **Benchmarks** are commonly used when initially planning and sizing a QC testing facility. If used correctly, benchmarks can establish range of magnitude criteria for high level estimation. Benchmarks also can assist space justification and lean applications for specific functional space types. When right sizing labs, it is essential to consider a number of variables in the analysis. Benchmark metrics vary for different types of testing areas, such as microbiological, analytical and physical testing. In some labs, the space requirements are equipment driven, while in others they are people driven. It is important to address these differences when applying benchmarks, as one could over size or under size the testing space needs.

  Common benchmark metrics include Net-Square-Feet (NSF) per person for the primary lab, lab support, and office spaces, as well as Equivalent Linear Feet (ELF) per person, which is the linear measurement of bench and equipment within the lab space.

  For example, benchmarks were used to determine if reducing a 12-person biochemistry testing area from 260 NSF/person to 162 NSF/person was not only feasible, but also functional and safe. In the end, the benchmarks showed that for this specific operation, the appropriate range was 216 NSF/person. In the process, the ELF/person was only reduced from 429 to 385.

- An important consideration in determining space needs is **lab expansion**. It is important to ensure the lab has expansion capability in case the testing demands should change in the future.

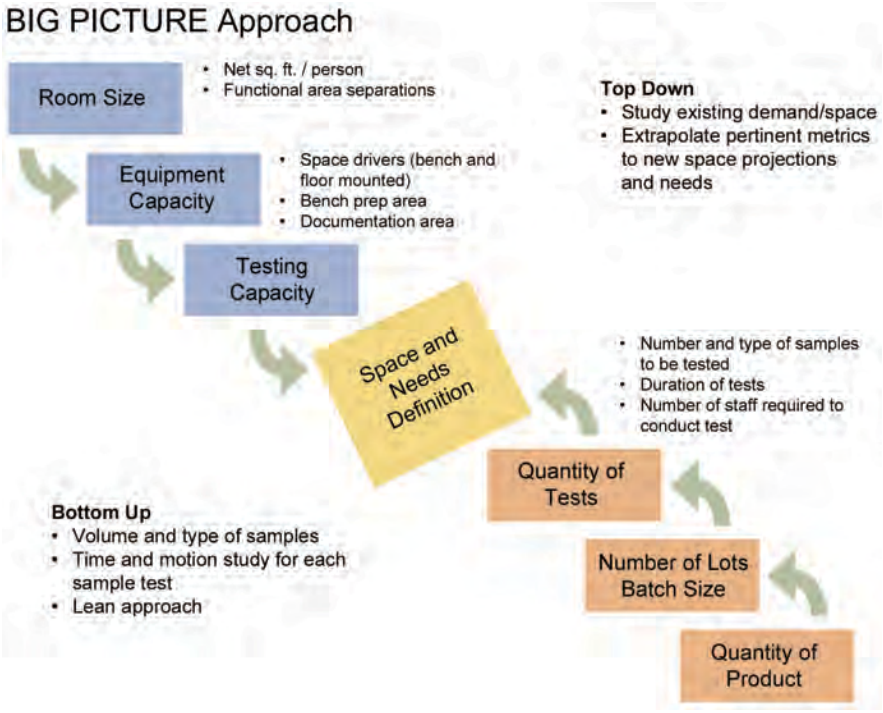


Figure 2. Space needs planning approaches.

- By mapping the locations of each team member's activity throughout the days/weeks and where that activity takes place, an **Activity Location Analysis** provides a thorough understanding of the patterns of movement and can help establish the most effective adjacencies possible.

  Equipment Utilization Studies capture data that can provide an understanding of the importance of each piece of equipment to the team's overall mission. Through such a study, a QC organization can better understand how equipment should be allocated. This data can then be charted – from most frequently used and most critical, to least used and non-essential – and used to help optimize the quantity, type, and placement of equipment in order to support lean practices. Equipment identified as high value/high use can be allocated directly to the group. Those pieces identified as high value/low use can then be shared among groups. One also must incorporate an equipment back-up strategy and risk assessments of specialized assays into space planning and provide flexibility for assay evolution and new technology platforms.
- Consideration must be given to the use of movable/portable lab furnishings to allow for interchangeability of equipment. Lab automation is also a significant trend in leaning QC operations.

Lab Location and Shared Equipment Areas Within the Facility

The location of individual labs and of services or equipment that are shared among labs within the overall facility can significantly impact workflow, material transportation, and traffic flow. Building layouts should be designed to:

- Centrally locate shared services and support functions (e.g., sample management/glass wash).
- Minimize throughput times and transport waste by the use of passthroughs and by co-locating or amalgamating "supplier" and "customer" labs that can share equipment,

storage, samples, analyst resources, test results, or information.
- Locate labs adjacent to production areas, simplifying sample management and facilitating improved flow and communication.
- Co-locate or amalgamate labs that will share samples, equipment, or storage.

Creating Suitable Laboratory Work Spaces

For Novartis and the nature of the tasks involved, creating suitable laboratory work spaces involved the utilization of a three-zone concept. In order to promote lean behaviors and efficient operation, the analysts' work spaces are tailored to their daily activities and desired workflow. Utilizing shared spaces where possible and implementing critical adjacencies, a three-zone arrangement offers the flexibility to support testing, write up and documentation tasks, non-testing project type work, and community interaction. Each zone is designed to support a specific type of work and to promote lean behaviors:

- **Zone One** embodies the laboratory space for sample testing.
- **Zone Two** encompasses the documentation area where the analysts record results.
- **Zone Three** provides an area for non-testing project work and community interaction.

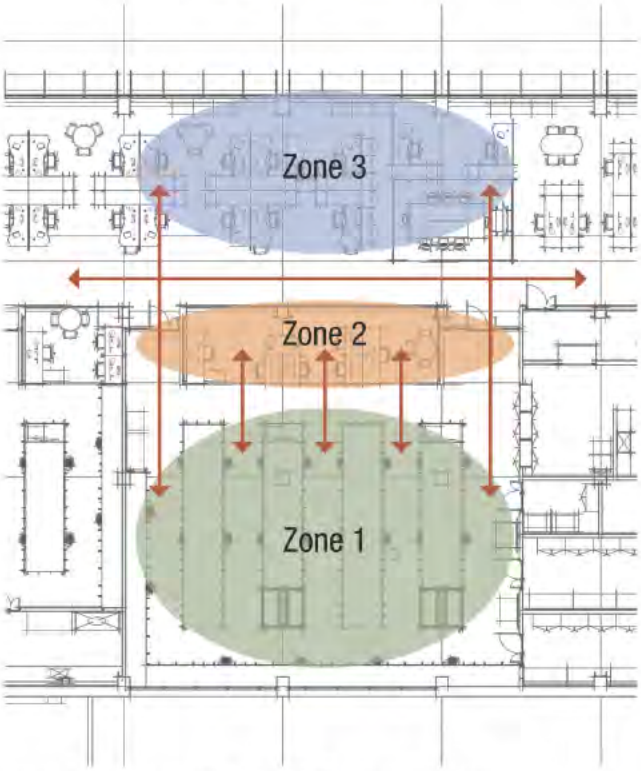


Figure 3. Three-zone QC laboratory design concept.

The key to the success of this arrangement is the adjacency between zones one and two. They need to be integrated, but still require a certain amount of separation in order to create a suitable and safe environment. In order to support lean best practices, both zones need to be located within the laboratory space. This will eliminate the need to gown in and out as the analysts move directly from the testing environment to the shared write-up stations.

The level of separation between zones one and two needs to be carefully considered to ensure safety protocols are met and sufficient partitioning is provided to allow for the analysts to safely remove their glasses while seated at the shared write-up stations to record the results of their tests.

A change in the qualities of the environment between zones one and two is also desired. Given that the analysts will perform their write-up activities within the laboratory area, the visual separation established through the selected materials and color palette of zone two will provide a psychological respite throughout the work day.

Zone three provides a work community space where the analysts can perform computer-based, non-laboratory activities, such as checking email and participating in online training. The space also provides opportunities to connect and interact with co-workers, as well as locker space to store personal items.

All three zones are connected through the elimination of visual barriers. This creates transparency to allow monitoring of the visual management boards in zone two and visibility of personnel in all three zones, giving them the ability to identify issues promptly and without needing to gown in or out of the laboratory space. In addition, the transparency connects the analysts to the rest of the community at the facility through visual connections and access to daylight.

Bench Configurations

In a lean lab process, it is normal that individual tests are combined to make good use of the "unattended" time inherent in some tests and to help create balanced productive analyst roles. For example, a HPLC test run has significant periods in which the analyst does not need to be present. In a lean lab solution, this test will be combined with other shorter more manual tests to allow that time to be used productively.

Because of the leveling and defined test sequences, these combinations can be fixed and repeated each time the tests are run. In turn, this makes it worthwhile to create dedicated work cells for these fixed test combinations. Bench layout and configuration has a significant impact on how well these work cells operate, and can reduce motion wastes. By far, the most common bench configuration in labs today is a straight run, which is almost never the optimum configuration.

The key objective in work cell design is to have clearly defined work areas and sample flows with all necessary equipment, services, and materials close at hand and with reaches and movement minimized. Achieving this normally requires a bench configuration which loops around. The classic work cell shape is the "U" (also known as the horseshoe), but there are several other alternatives that can achieve the same objectives.

Products, samples, tests, equipment, and workloads can and will change over time. Bench layouts and services need to be re-configurable to accommodate this type of change.

Arguably, the most versatile and re-configurable option is the "comb and spine" in which the spine can be fixed with services supplied from above and the comb elements are movable. This allows multiple "U" and "L" shapes to be easily created and re-configured when required.

Enabling Flexibility

Furniture in laboratories must fit with the needs of the activities that will take place in the lab, and not vice-versa. This simple principle may seem obvious, but is not always respected.

It is not unusual to find situations where the testing activities are not as lean as they could be due to the constraints caused by the furniture arrangement and by the utilities distribution. Furthermore, the user needs, type of tests, equipment, and activities carried out in a laboratory evolve over time and a design that was originally perfect may become obsolete. Sometimes obsolescence can come about so rapidly it is necessary to revamp a lab area immediately after the conclusion of the construction phase.

To mitigate this issue, in the last ten years, laboratory designers and furniture suppliers have developed flexible solutions at three levels:

- **Level One – Flexibility at Bench Level** – traditional benches are fixed and are difficult to relocate in practice. Flexible benches are on wheels to allow a rapid reconfiguration of the lab layout. They can be "detached" and therefore need to have a utilities wall behind them (although it should be noted that this solution may be more expensive). To be even more flexible, the benches can be fully mobile, only requiring being in close proximity to the utilities and services distribution that can be pendants hanging from the ceiling. This option could be less expensive and well suited to lean principles.

- **Level Two – Flexibility at Utilities and Services Connections** – the distribution of services, such as gases, electrical power, vacuum, and water can be rigidly fixed on the bench in a traditional non-flexible configuration. Alternatively, the services and utilities distribution wall can be detached from the bench, breaking the rigid connection between bench and services while still having some constraints. Finally, the utilities and services can be distributed from above via flexible connections allowing full flexibility.

- **Level Three – Flexibility at Distribution Level** – a further level of flexibility can be provided by installing some blind connections in the lab ceiling void to allow the future relocation of utilities and service distribution panels.

With all these options, which one is best? There is a trade-off between the cost of the furniture and its flexibility. Normally, benches on wheels are slightly more expensive than traditional ones. In the same way, the utilities distribution from high level panels is more expensive than traditional distribution on benches. Nevertheless, in most laboratories the cost of these options is negligible compared to the benefit in flexibility. However, the flexible distribution system (blind connections ready in the ceiling void) is justified only when a high frequency of lab reconfiguration is required: for example, in non-validated research activities. In any case, GLP implications should be considered when reconfiguring the labs layout.

Consumable Inventory Management and Storage

In most labs, effective management of laboratory consumables is a key enabler for lean operation. The storage requirements for these materials are an important consideration in the design and layout of labs. Considerable inefficiency and unnecessary costs can result from analysts hoarding or unnecessary multiple storage locations. Poorly managed inventory processes also can result in materials running out, needing to be ordered on short notice or expiring due to oversupply. Effective stock management systems can increase analyst productivity, increase work satisfaction, reduce the resources spent on inventory management, and reduce test delays.

The Consumable Inventory Management (CIM) process should itself be based upon lean principles with an objective of minimizing:

- "Stock-outs" and "Write-offs"
- Cost of Inventory
- Inventory Management Effort
- Space Requirements

Achieving these objectives normally involves minimizing the number of stock locations for individual materials, controlling inventory volumes, minimizing the effort required to replenish stocks at the point of use, reducing travel by centrally locating lab and site stores, reducing inventory ownership duration, minimizing inventory management effort, and reducing transaction and documentation efforts.

Energy Efficiency in a Lean Laboratory

Laboratories are among the most difficult facilities to make energy efficient. Typical labs are three to eight times as energy intensive as office buildings – filled with complex equipment, consuming large amounts of electricity, and requiring complex air-handling and waste management systems. Better, safer, and more economical are typical drivers for lean laboratory design and realization; however, sustainability should not be ignored.

The strategies which can be adopted for an energy efficient laboratory are the reduction of demand, the harvesting of free energy, the recovery of waste, and the increase of efficiency; the HVAC system should be designed taking into consideration the indoor environmental quality.

Adaptability and flexibility should be the drivers for design of an energy efficient lab; the HVAC system must be flexible and adaptable to accommodate changes without significant modifications.

Guidelines

The initial Novartis concepts for lab design and layout were validated and refined by the multi-functional team at the workshop and an agreed set of guidelines were established. In addition, a new three-zone concept for test-review-collaboration emerged based upon a review of design options and a case study exercise.

The final high level guidelines endorsed by the workshop participants direct that laboratory areas should be designed to:

Support Leveling, Flow, and Standard Work – leveling flow and standard work are key lean lab principles. To proactively support these fundamental work balance concepts designers should:

- Incorporate fewer internal walls and less separation of labs – this promotes flexible operations and the sharing of workloads and resources to level short interval workloads.
- Incorporate space for sample management and visual cues – visualization of workloads is a core concept of lean.
- Use sample centric and/or test centric cells and cellular bench arrangements – cellular workspace design facilitates the combination of tests to create balanced productive analyst workloads and standard work and reduces travel and motion wastes.
- Allow space for visual management systems of laboratory performance – for example, daily and weekly meeting boards to allow visualization of work to be performed in the short term and of lab performance over time.

Support Effective Use of Time

- Integrate write up, review, and approval areas to enable efficient and timely documentation and review of tests supporting both flow and leveling of workloads.
- Use a limited number of adjacent, but separate "hot" desks for project work and non-test tasks.
- Include adjacent collaboration areas and meeting rooms.

Minimize Transport and Motion Wastes

- Locate labs close to manufacturing (simplifying sample management and chain of custody).
- Co-locate or combine labs that will share samples, equipment, or storage.
- Centrally locate shared lab services (e.g., glass wash).
- Centrally locate equipment or storage that will be shared within a lab.

Minimize Space and Equipment Requirements

- Space and equipment requirements should be calculated based on leveled demand rates rather than peaks.
- There should be a move away from personal ownership of equipment, bench space, or desks. Analysts should operate as true teams sharing resources and workloads.

Maximize Future Configurability
- Employ flexible bench configurations and (semi) configurable services (air/extraction, etc.)

Support Effective Laboratory Inventory Management
- Implement limited and defined storage at the point of use.
- Establish central lab storage for shared materials or high volume unique materials.

Support Effective Performance Management
- Incorporate areas for visual management displays, huddle meetings, etc.

Foster Lean Behaviors and Communication
- Centrally locate glass walled offices for lab managers and supervisors.
- Employ extensive use of glazing to visually link lab areas.

Support Excellence in Workplace Organization and Cleanliness
- Utilize open or glass fronted cabinetry.
- Limit and define storage throughout the lab.
- Eliminate drawers.

Principle	Procedures vs. Facility Design	Facility Design Main Contribution	
		User	Designer
Eliminate uselessness and waste	Procedures / Facility Des.	★★★★	★
Value as determined by the end customer at every step	Procedures / Facility Des.	★★★	
Identify the value stream	Procedures / Facility Des.	★★★	★
Allow a flow without interruption	Procedures / Facility Des.	★★★	★★★
Continuous improvement	Procedures / Facility Des.	★★★	
Minimize queues and follow the customer priority	Procedures / Facility Des.	★★★	★★
Level the workload	Procedures / Facility Des.	★★★	
Manage performance (KPI)	Procedures / Facility Des.	★★	

Figure 4. Relationship between lean approach and design.

Implementing Lean Principles in Quality Control Laboratories

By bringing together designers, users and lean experts, the Novartis Lean Lab Design Workshop generated innovative approaches to incorporating support for lean processes and behaviors in the design and layout of lab spaces. These went far beyond the obvious opportunities related to sample flow and analyst motion and have had a significant impact on Novartis' thinking and approach to lab design. It has allowed them to develop guidelines that will help ensure that all new builds and refurbishments include design elements and approaches that pro-actively support lean lab initiatives.

While pharmaceutical QC laboratories are different from manufacturing environments, they are none the less operational entities. They have a major impact on the release of product and are often significant cost centers in their own right. Lean principles can and should be applied in order to optimize lab processes and operational performance. The design, layout, and placement of labs can have a significant positive or negative impact on the implementation and sustainability of lean processes and behaviors within the lab.

Authors

The development of Novartis Vaccines' lean lab guidelines were spearheaded by a team of users and consultants. These experts came together as a group to share their experiences and understanding through the joint authorship of this article. Primary contributors included:

Mike Dockery, Jacobs, Lab Design Consultant

Federico Gabardi, Jacobs, Project Manager

Javier Garay, Flad Architects, Principal

Jim Gazvoda, Flad Architects, Principal

Luke Kimmel, Novartis Vaccines, Associate Director, Global Engineering

Pietro Orombelli, Foster Wheeler, Senior Project Manager

Christophe Peytremann, Novartis Pharmaceuticals, Global IQP Champion

Tom Reynolds, BSM, Operations Service Director

Tanya Scharton-Kersten, Novartis Vaccines, Divisional Quality, Sponsor – Lean Laboratory Program

Graham Shoel, Novartis Vaccines, Director of Project Planning, Global Engineering

Jeanne Sirovatka, Sandoz, Associate Director, Supply Chain

ISPE

24th Annual Aseptic Processing Technology Conference

Cost Saving Solutions to Solve Quality Concerns

23 – 24 February 2015

Hilton Baltimore, Baltimore MD

If you could go to **one conference** to get up to speed on the best practices and the latest thinking in aseptic processing technologies, **this is it!**

ispeak

There is no question that managing the complexities of aseptic environments and processes is a constant challenge. Your company feels the effects daily of the high cost and sensitive nature of manufacturing these products. We recognize that you need practical solutions to address everything from big quality concerns to dealing with the constant attention and maintenance that consumes your time.

Conference Highlights:

Regulatory Panel Discussion Featuring these Invited Speakers:

Thomas Arisita, FDA
Dave Doleski, FDA
Rick Friedman, FDA
Bob Sausville, FDA
Destry Sullivan, FDA

Two Comprehensive Tracks:
Barrier Isolation
Aseptic Processing

Discussion Groups and Interactive Workshops

www.ISPE.org/2014-Aseptic-Conference.org

2014 GLOBAL PINNACLE PROGRAMME

BAI | Azzur Group LLC helping life sciences succeed | nne pharmaplan® Engineering for a healthier world

Legacy Products and Process Validation: Bringing Old Drugs up to Current Standards

A Framework for Implementing Stage 3 Continued Process Verification for Legacy Products

by Bikash Chatterjee and Wai Wong

This article presents a method to account for missing information and provides recommendations to understand a legacy product and how to apply the three stages of the new guidance to satisfy the FDA and other regulatory agencies.

The FDA's new 2011 Process Validation Guidance January 2011 constitutes a revolution in process validation, because it requires a new type of justification, based on sound science and risk analysis. Many pharmaceutical products in the market for the past 20 to25 years have had little R&D records to use as back up. What can a company do when a product starts to break down or fail? What should be done first? What is the best way to assess risk and to demonstrate consistency in the way we manufacture our products?

The transition to implementing the new risk-based process validation philosophy has dominated the discussion ever since the FDA issued its landmark guidance *"Guidance for Industry Process Validation: General Principles and Practices"* in 2011. For most API, pharma and biotech companies today, the challenge in implementing the new guidance is not for new drug therapies under development, but for those currently in the marketplace. Many older products are hampered by the absence of the solid development data required to satisfy the requirements of the new Stage 1 and Stage 2 Process Validation (PV), making Stage 3 a potentially untenable undertaking. How can companies move these products into a state of compliance?

This article pre-supposes a baseline understanding of the three stages of the new PV guidance. It is intended to guide the reader through a framework for establishing a Stage 3 program for legacy products that is compliant with the 2011 guidance, tailored to organizational needs, and that does not hinder manufacturing and quality processes.

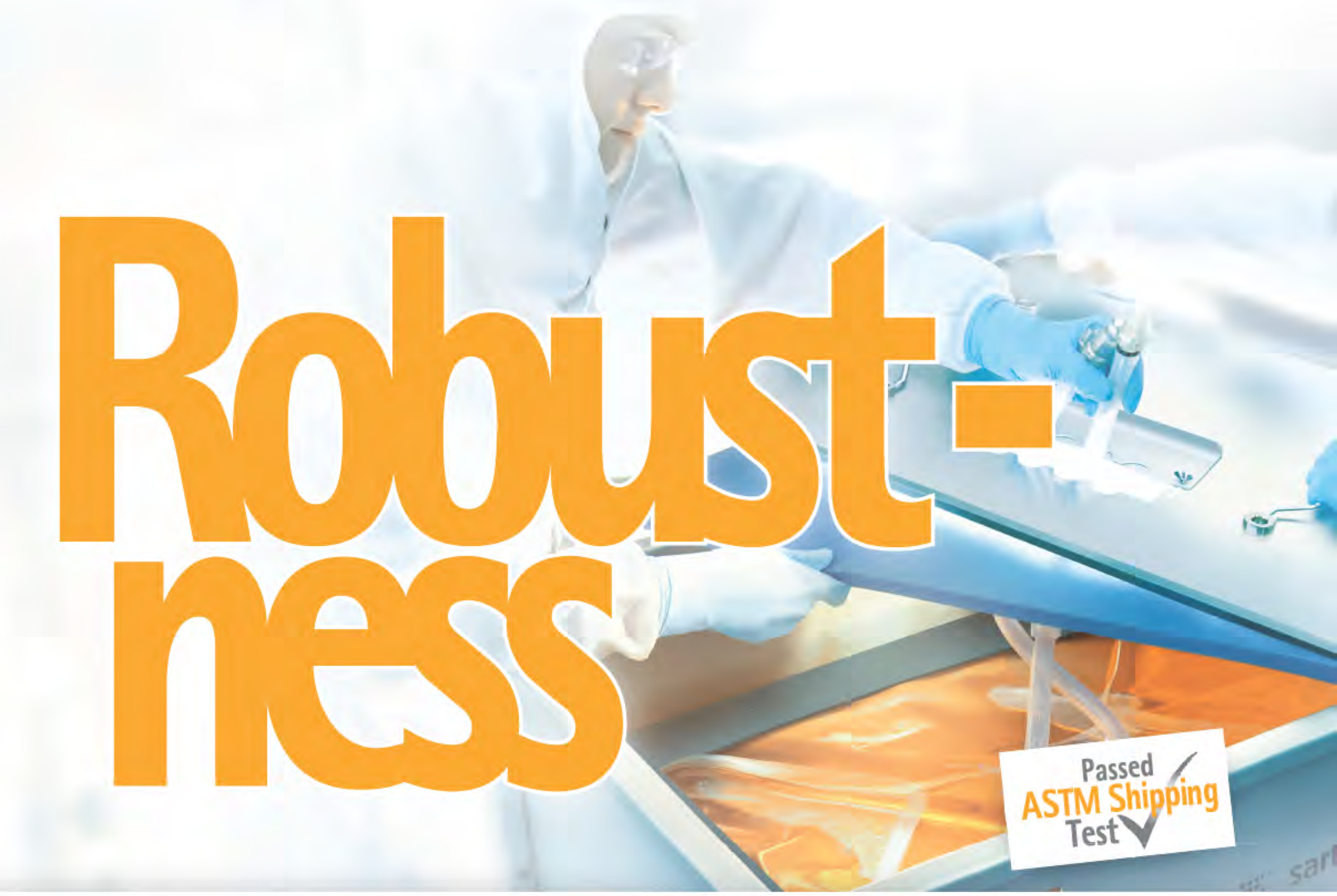
Framework for Stage 3 Continued Process Verification

A number of excellent reference documents exist that discuss designing and implementing a Stage 3 PV program. ISPE issued a Discussion Paper[1] defining a framework and decision tree for evaluating legacy products. The Parenteral Drug Association (PDA) issued Technical Report (TR) 60[2] as a comprehensive discussion of all three phases of the new 2011 PV Guidance. While these papers do an excellent job of capturing all of the considerations in designing and implementing a compliant Stage 3 program, adapting them to an organizations' capabilities requires organizational consensus, which is often difficult to achieve.

sartorius stedim biotech

New Flexsafe Bag Family.

New PE Film. New Benchmark.



Flexsafe meets your requirements for outstanding robustness and ease of use at all steps of your manufacturing process. The film's strength and flexibility provide consistent performance and easy handling – even in the most stringent applications like cell culture, long-term storage or shipping of drug products.

ONE FILM FOR ALL

USP - DSP - F+F

Watch Videos:
www.sartorius-stedim.com/flexsafe

Stage 3 – Continued Process Verification Requirements

Stage 3 of the new PV guidance represents the FDA's concept of leveraging Quality by Design (QbD) understanding to accommodate **sources of variability** that can only be identified from long term processing history. Sources of variability include raw material variability, equipment duty cycle, multi-shift variation, etc., that are often difficult to fully characterize in a development or scale-up scenario.

Stage 3 of the new PV lifecycle is intended to be an ongoing program to collect and analyze product and process data to ensure the process remains in a state of control. Many firms rationalize this as the process equivalent of the system used for monitoring product performance as part of the Annual Product Review (APR) Process. For new products developed with the new guidance in mind, the FDA has made it clear that science- or risk-based tools should be used to determine to creating a program to collect, measure and monitor at a minimum **process** performance and variability as opposed to product performance and variability against specification. The components of the continued process verification model for legacy products are shown in Figure 1. Each section will be discussed.

Prioritization Scheme

The first practical dilemma most companies face when moving to compliance with the 2011 guidance is how to evaluate and prioritize existing commercial products. There can only be one standard for process validation and eventually all products have to meet it. Even so, it can be difficult to gain organizational consensus to establish a practical path forward. One simple framework for incorporating diverse prioritization criteria is to employ a Pugh Matrix. A Pugh Matrix is a structured, semi-quantitative tool for evaluating alternatives. Like all risk frameworks, the primary advantage of a Pugh Matrix is to establish a common criterion for evaluation, minimizing subjectivity while providing sufficient quantitative criteria for measurement. Factors to consider include:

1. Patient Criticality – life sustaining drugs
2. Product Volume – percentage of the site's manufacturing volume
3. Business Risk – site revenue impact
4. Process Complexity – number of unit operations and control strategy complexity
5. Process Quality History – incidence of non-conformances and CAPAs generated

The Pugh Matrix approach allows weightings to be added to the evaluation criteria and to measure each product against a standard baseline for evaluation by assigning a value of (+) if better than the nominal criteria agreed by the evaluation group, (S) if equivalent to the nominal criteria and (-) if much worse that the nominal criteria. Five scores are summarized for each product: sum of positives, sum of negatives, sum of sames, weighted sum of positives, and weighted sum of negatives. An example of a simple product prioritization analysis is shown in Table A. The weighted decision Pugh Matrix product prioritization is Product 5, 4, 2, 1, 3, 7 and 6.

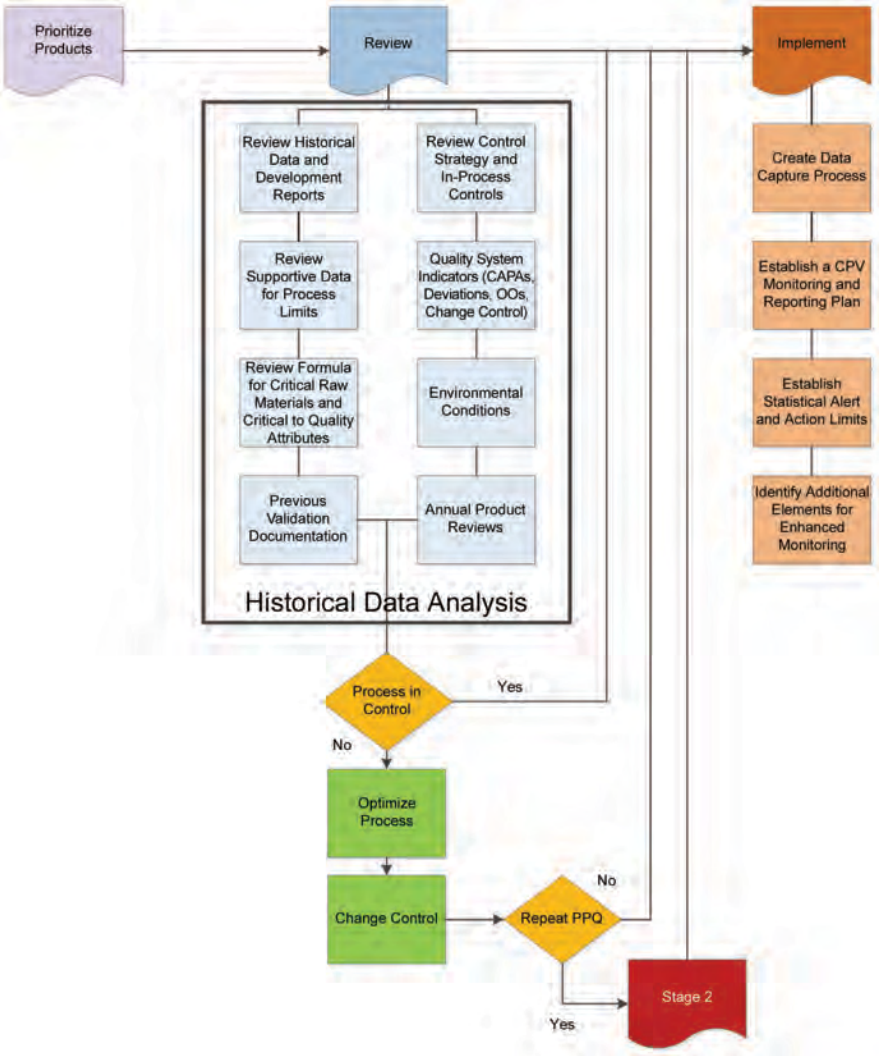
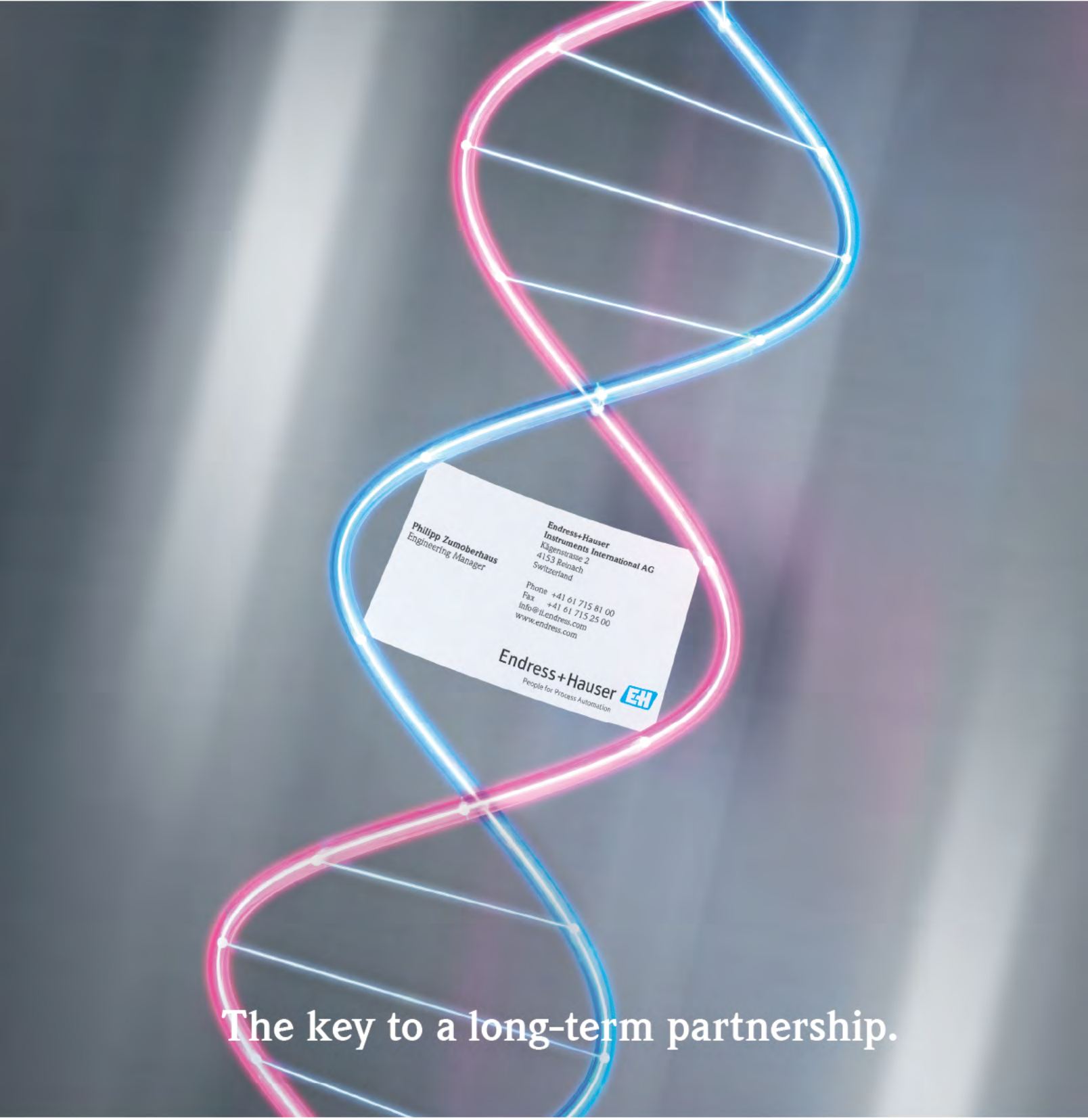


Figure 1. Continued process verification model for legacy products.



The key to a long-term partnership.

Throughout the twists and turns of product development, clinical processes and large-scale production, Endress+Hauser is your binding link to compliance, productivity and profitability. In the long run, our solutions not only benefit our clients but also their patients. And working together, we'll achieve the best results. www.endress.com/life_sciences

Endress+Hauser
Instruments International AG
Kägenstrasse 2
4153 Reinach
Switzerland

Phone +41 61 715 81 00
Fax +41 61 715 25 00
info@ii.endress.com
www.endress.com

Endress+Hauser
People for Process Automation

		Alternative Concepts						
Criteria	Rating (1-10)	Product 1	Product 2	Product 3	Product 4	Product 5	Product 6	Product 7
Patient Criticality	10	-	+	s	+	+	-	-
Product Volume	7	-	-	+	+	+	-	s
Business Risk	7	0	-	s	-	+	-	-
Process Complexity	5	+	-	-	-	s	-	-
Process Quality History	5	+	+	-	s	s	s	+
Sum of Positives		2	2	1	2	3	0	1
Sum of Negatives		2	3	2	2	0	4	3
Sum of Sames		0	0	2	1	2	1	1
Weighted Sum of Positives		10	15	7	17	24	0	5
Weighted Sum of Negatives		17	19	10	12	0	29	22

Table A. Weighted product prioritization (Pugh Selection Matrix).

Historical Data Review and Quality Assessment

The new guidance is tantalizingly vague on the level of data analysis required for legacy products. *"Manufacturers of legacy products can take advantage of the knowledge gained from the original process development and qualification work as well as manufacturing experience to continually improve their processes. Implementation of the recommendations in this guidance for legacy products and processes would likely begin with the activities described in Stage 3."*

Evaluating the state of control for legacy products requires a two-prong approach: evaluating product performance and evaluating process predictability. For the former, most organizations have a retrospective product review mechanism in place. In the U.S., the Code of Federal Regulations[3] mandates APRs. In Europe, the European Medicines Agency requires a Product Quality Review. Though not identical in their requirements, they share the same objective: to review a product's Critical Quality Attributes on an annualized basis to determine any trends or quality issues that must be addressed.

The more difficult of the two is **assessing process predictability.** For new products, this is a natural extension of the work performed in Stages 1 and 2 to identify Critical Process Parameters (CPPs) and final control strategy. Often for legacy products, the development work performed does not provide the necessary insight to identify and defend CPPs by current scientific and regulatory standards. This requires a detailed assessment of the available historical data. Typical sources of historical data along with the potential types of analysis are summarized in Table B.

Process Control Assessment

If the process is found to be out of control, baseline process characterization studies need to be conducted. Tools for assessing process control and remediation should be formalized in procedure. Processes that are found to be in control can move forward toward the implementation phase for continued monitoring.

Implementation

The process to this point has identified CPPs for each product in the prioritization matrix that is suitable for CPV. Moving to implementation, there are four elements that comprise an effective CPV program:

1. Defining a data capture strategy
2. Establishment of a CPV monitoring and reporting plan
3. Determine alert and action limits
4. Enhanced monitoring components

Defining a Data Capture Strategy

With most of the product's historical and background information identified in the previous steps, we now focus on implementing controls and assessing the manufacturing process. The biggest obstacle for legacy product manufacturers is how to obtain data to analyze and evaluate that their process is operating within a state of control. Many legacy product manufacturers do not have reliable methods of monitoring CPPs other than capturing process inputs and verifying if the products have met their product release criteria. Tracking process performance is not the same as analyzing product performance. A data capture process will

determine the best means of obtaining the relevant data for analysis. How often data should be collected, from what source, and when are factors to report in creating this data capture process.

Data Source	Data of Interest	Possible Analysis	Considerations
Development Reports	• Product Design • Critical Raw Material Tests • Design Space • Sampling Plan • Method Capability	• Product Design Pre-Hazard Analysis • Process Risk Analysis • Design Space Data	• Formulation design and function? • Were studies orthogonal? • Were raw material tests capable? • Are the raw material and process limits meaningful?
Master Batch Records	• Unit operation control ranges and data	• Control Charting • IMR Chart • Process Capability	• Look for evidence of process control • Must address parameters which are not in control
IP and Release Test Data	• Individual and summary test data	• Mean and standard deviation analysis • Trend Analysis • X-Y curves	• Look for process issues hidden within the method
Deviations	• Lab OOS level 1 and 2 • Process and testing excursions	• Recurring failures • Method capability issues • Trend Analysis • Raw Material Supplier	• Are there process excursions that cause quality issues? • Is the supplier related variation driving process instability?
CAPAs	• Identify process and control strategy corrective actions implemented	• Root Cause analysis data and the methodology	• Are the corrective actions based on symptoms or true root causes?
Change Controls	• Quality assessment related to changes • Validation criteria evaluated	• Correlation analysis between changes and process stability or product performance	• Are changes adding instability to process
Annual Product Reviews	• Product CQA trends analysis	• Correlation between product performance, deviations, and change controls	• Is product performance capable?
Prior Validation Testing	• Sampling Plan • Process capability • Control Strategy	• Baseline process control charting • T-test comparison of means • CPP baseline data	• Has the process center shifted? • Does the data support parameters identified as CPPs • Were both inter- and intra-batch variation evaluated?

Table B. Sources of historical process and data.

Although each product's manufacturing process is different, there are some common methods for obtaining the relevant data to evaluate process performance and predictability. Methods include obtaining information from batch records and introducing new methods of gathering data such as in-process monitoring or using new equipment capable of monitoring CPPs that are specific to process. Common data capture solutions include:

1. Creating additional sampling and testing procedures and records which can be used to manually capture the data required
2. Data acquisition through equipment PLC and microprocessors
3. SCADA systems for equipment process monitoring

Establishing a CPV Monitoring Plan

With legacy products there is potential for more process inputs and CPPs than with new programs if the original design space establishment was incomplete. The monitoring plan should be the result of a clearly defined procedure for data acquisition, receipt, statistical analysis, and reporting. Many firms start with the APR process as a model and adapt it to create a CPV process. Alternatively, it may be more efficient to create a dedicated quality engineering function to address CPV. The reporting process is one of the most critical elements to address. Establishing a frequency for reporting, based upon a measure of contribution to CQA movement by a CPP is one well-accepted approach to establishing a data collection and reporting frequency.[4,5,6]

Establishing Alert and Action Limits

Legacy products have the advantage of manufacturing history in establishing alert and action limits. Even in the absence of a robust manufacturing process design and key monitored elements, there should be sufficient data to establish alert and action limits for each CPP. Each limit will require a discussion

on what actions to take when approaching a limit from a manufacturing and quality perspective.

Monitoring Lot Performance

With the data capture process identified, begin manufacturing lots and initiate the monitoring plan, then evaluate the results. Based on the results, temporary statistical control limits are established to continue monitoring more lots as they are manufactured. As each lot is produced, the performance of the process with respect to the CPPs and CQAs are continually assessed. As part of the assessment, several items should be considered:

- Is the sampling plan robust enough to predict process performance? The sampling plan may need additional elements to be monitored.
- Is intra-batch variation sufficiently evaluated with the sample size being implemented?
- Are there instances that could trigger changes to routine sampling?
- Can the number of CPPs be reduced based on the results of the initial monitoring performed? This would help narrow down the number of points needing to be continually monitored during Stage 3.
- Is there an appropriate response to out of control events? The FDA will specifically look for SOPs that provide clear directions on remediation. A decision tree can be part of the SOP.

These considerations will be critical in assessing process control throughout the life of the product.

Conclusion

Legacy products represent the largest compliance risk against the new PV guidance for an API, pharmaceutical and biotech manufacturer. Establishing a formalized process for risk management, process evaluation and on-going monitoring will permit the organization to prioritize and address legacy products that are not in control while integrating those that are in control into a formalized monitoring program.

References

1. *ISPE Discussion Paper: Topic 2 – Stage 3 Process Validation: Applying Continued Process Verification Expectations to New and Existing Products,* www.ispe.org.
2. *PDA Technical Report No. 60: Process Validation – A Lifecycle Approach,* Parenteral Drug Association, www.pda.org.
3. Code of Federal Regulations Citation: 21CFR211.80(e).
4. Mitchell, M., "Determining Criticality-Process Parameters and Quality Attributes Part I: Criticality as a Continuum," *BioPharm International,* Volume 12, Issue 26, pp. 38-47.
5. Mitchell, M., "Determining Criticality—Process Parameters and Quality Attributes Part II; Design of Experiments and Data-Driven Criticality," *BioPharm International,* Volume 27, Issue 1, pp. 32-40.
6. Mitchell, M., "Determining Criticality–Process Parameters and Quality Attributes Part III: Process Control Strategies—Criticality Throughout the Lifecycle," *BioPharm International,* Volume 27, Issue 3, pp. 26-35.

About the Authors

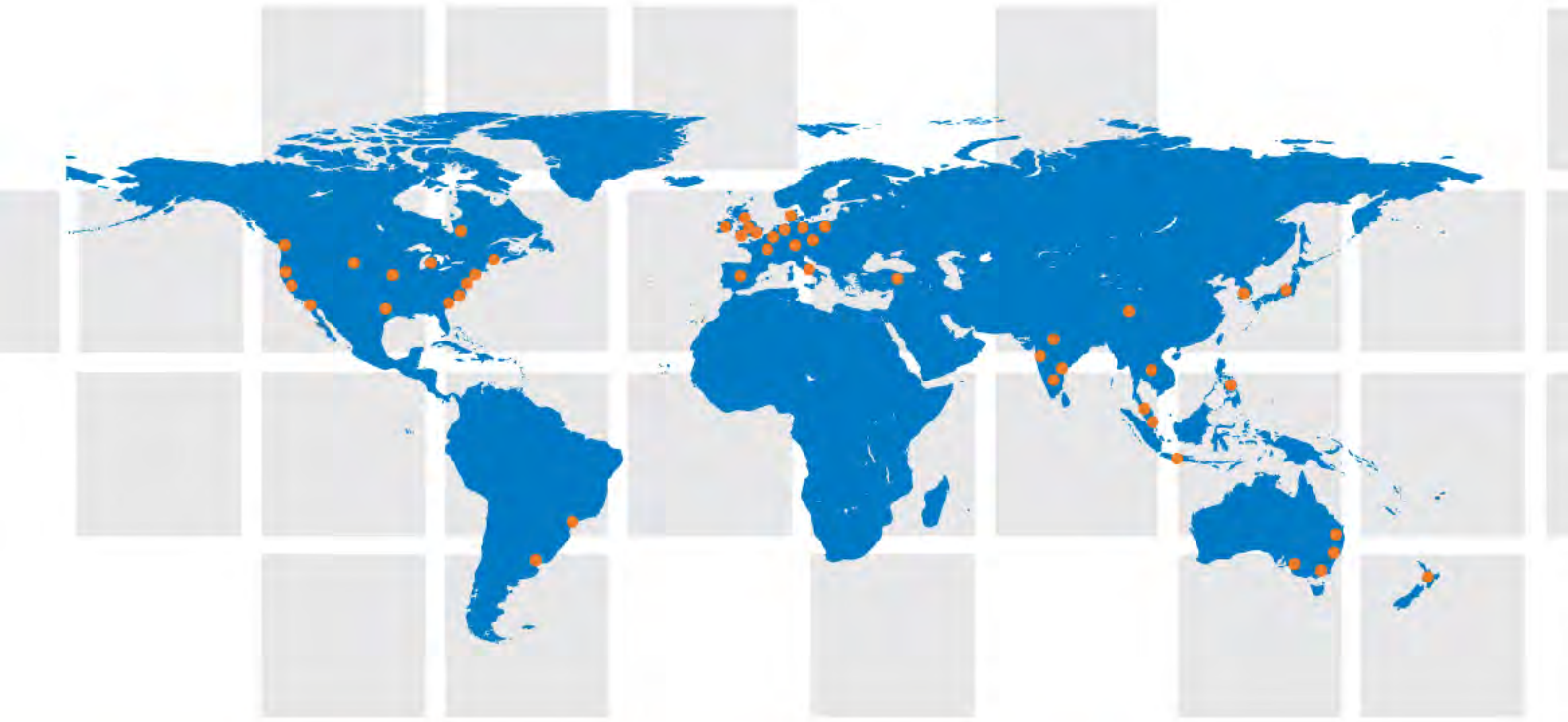
Bikash Chatterjee is President and Chief Technology Officer at Pharmatech Associates. He has been involved in the pharmaceutical, biopharmaceutical, medical device and diagnostics industry for 30 years and has guided the successful approval of more than a dozen new products within the U.S. and Europe. Over much of his career, he has developed and transferred products and technology processes to satellite operations and Contract Manufacturing Organizations (CMOs). He has extensive experience with the design and implementation of systems to satisfy the regulatory requirements for ICH Q8, Q9, and Q10 as well as e-pedigree, and the application of risk-based approaches in the area of validation. Chatterjee is a member of the USP National Advisory Board and past Chairman of the Golden Gate Chapter of the American Society of Quality. He holds a BA in biochemistry and a BS in chemical engineering from the University of California at San Diego.

Pharmatech Associates, 22320 Foothill Blvd., Suite 330, Hayward, California 64541-2719, USA.

Wai Wong is Vice President and General Manager of Worldwide Operations of Pharmatech Associates, Inc. He has worked in the life sciences industry for more than 15 years, starting with Genentech as an aseptic filling technician and has held positions as project lead, validation manager and West Coast regional manager. Wong began his career in the biopharmaceutical industry at Genentech, working his way from aseptic filling technician to the role of process engineer responsible for introducing new equipment and processes into Genentech's fill-finish operation for both clinical and commercial manufacturing. A Six Sigma Green Belt, he manages FMEA, commissioning, validation and consulting projects at numerous client sites. He holds a BbA in molecular and cell biology with emphasis on iochemistry from the University of California, Berkeley.

Pharmatech Associates, 22320 Foothill Blvd., Suite 330, Hayward, California 64541-2719, USA.

ISPE Affiliates and Chapters: Local Connections. Global Impact.



Boost your knowledge. Expand your network.

ISPE's Affiliates and Chapters are your local resource for all things ISPE—from translations of ISPE's world-renowned Guidance Documents to education on regional industry and regulatory trends.

Get involved with your regional Affiliate or Chapter to meet industry leaders in your area, contribute your expertise to industry-advancing initiatives at the local level and share best practices with like-minded professionals.

ISPE

Connecting a World of Pharmaceutical Knowledge

Get Involved With Your Affiliate or Chapter Today!
ISPE.org/Affiliates-and-Chapters

Regulatory Mythbusters – Sorting Fact from Fiction

by David Churchward, Ron Ogilvie, Bryan Wright

The authors tell us that there are GMP-related "myths" created and propagated through industry. These myths may be created for a variety of reasons – regulatory changes, perceived regulatory inconsistencies, and regulatory misinterpretation. In this article, several myths are "busted" and better communication with regulators is recommended to help prevent future myths from rising.

Anthropologists tell us that people in all societies – past and present – create myths. Myths are often created and perpetuated because there is no apparent rational explanation or identifiable cause for the misfortunes that befall us. Thus, in the pre-scientific, tribal world, random and unexplained misfortunes, such as a poor harvest, an unexplained death, flood and famine, are often explained through myth-making.

Are There Myths in the Pharmaceutical Industry Created and Propagated Related to GMP?

Often, conclusions about regulatory interpretation can be generalized from one example and thus conclusions may be based on supposition or myth. Many myths develop because the propagation of someone's view or interpretation of a regulatory "requirement" goes unchallenged or – worse – gathers momentum. Some myths may be picked up upon inspection, but many are also discovered when inspectors have meetings with companies or when answering questions about licensing.

Regulatory changes also can generate myths, but so can resistance to new ways of working, even when the GMPs are not changing. For example, proposals for changes in company practice might be challenged by a suggestion "that would not be allowed under GMP." That response may be a myth in the making or, worse, a well-established one that has been influencing decision-making.

There are a wide range of GMP changes in progress and interpretation of revised guidelines may create opportunities for new myths to be generated about regulatory interpretation. Sometimes it is easier to "sign on" to the myths rather than challenge them by looking for fundamental understanding. Thus, both industry and regulators would benefit by working on stopping the propagation of myths. The best way to do this is to raise questions internally and externally and to clarify expectations early on. In other words, we need to "bust' those myths before they get started.

Case Study #1 – Are Regulators Inconsistent in Regulatory Interpretation?

The majority of manufacturers will experience process deviations from time to time. Some may impact the regulatory filing for the method of manufacture. Whether affected batches can continue to be certified for release to market (often referred to in the EU as "QP discretion") is a topic of much discussion, interpretation and at times, confusion. *The potential for myth-making is high.*

Consider the same deviation from the registered process experienced by two different companies. Could the specifics surrounding each case give the impression of inconsistency?

Company A was not aware of the process deviation at the time of manufacture. The finished product complied with its

specification and there was evidence to show no detrimental impact from the deviation, which was unexpected and shown through scientific rationale to be 'minor' in nature. The EU Qualified Person was able to use discretion in the release of these batches and the regulatory filing was changed for future batch manufacture.

In contrast, *Company B* proactively decided to make a change to the registered method of manufacture and *did not* update the filing and therefore, the deviation could not be classified as being "unexpected." QP discretion in this case will not be acceptable under the planned revision to EU GMP.

> *"Although regulators are often challenged on perceived inconsistencies, industry – including sites within the same company – can also appear to be inconsistent. At times, this appearance of inconsistency can be due to a lack of visibility of the full facts of the case."*
>
> – David Churchward, Expert GMDP Inspector, MHRA

Interpretation and application of GMP regulatory expectations can result in subtle, but significant differences in assessment of apparently similar situations. "One size does not fit all" and dialogue with the regulator can help clarify specifics relevant to each case, and if necessary, widen the discussion to other regulators. For example, the EU Compilation of Community Procedures – the Quality Management System for EU regulators – establishes a foundation upon which cross-EU dialogue can take place. The participation of PIC/S authorities in GMP working groups further extends the reach of this coordinated discussion. Such dialogue can drive consistency in GMP interpretation and application.

Regulators cannot be approached regarding the consistency of regulatory interpretation: MYTH

Case Study #2 – Are There Regulatory Barriers to Changing Approved Product, Process or Facility Registrations?

Often, proposals to make innovative changes to registered methods of manufacture or analysis can lead to fears of regulatory challenge, additional regulatory burden, and delays in implementation.

Changes are allowed and even encouraged. Important issues here are robust change control and validation where required. A good understanding of what is registered – and what might require variation submission – is needed. This means having good links between production/QA and regulatory.

A challenge for industry may be the operational management of changes to multi-market registrations. What regulatory approaches might help avoid these difficulties? One might consider inviting regulators from different markets, such as the EU and US to discuss timelines and approaches to align work as much as possible. Closer international regulatory collaboration through initiatives such as International Collaboration of Medicines Regulatory Agencies (ICMRA) might facilitate this approach going forward.

There is already EU guidance published on marketing authorization changes (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000090.jsp&mid=WC0b01ac0580023398). However in contrast, similar guidance is not so readily available for authorized manufacturing sites. In such cases, the advice of local regulatory authorities should be sought. Making contact at an early stage helps understand expectations and avoid difficulties (such as myth-making) later on.

> *"Rather than preventing changes to registrations, Article 23 of Directive 2001/83/EC requires that registered methods of manufacture and QC are revised as necessary to take account of scientific and technical progress. Companies need to be clear as to what is a* ***significant regulatory change*** *– requiring an update to the product filing, and what is a* ***quality improvement change*** *– one that can be managed under the pharmaceutical quality system."*
>
> – Bryan Wright, European Regulatory Affairs Advisor, ISPE

Changes to approved product, process or facility registrations are not permitted: MYTH

Case Study #3 – Application of GMP – Guide or "Handcuffs"?

The EU GMP Guide is divided into three parts. Part one covers dosage form manufacture, part two active substance manufacture, and part three non-mandatory guidance as supplements to parts one and two.

The *Common Technical Document*, used for submission of product approval applications, is also structured into discrete modules and sub-sections that describe specific aspects of the product under assessment. The structure of GMP/CTD Module 3 is based on historical administrative convenience, rather than any specific scientific or quality requirement. It should therefore not be seen as a barrier to novel manufacturing proposals which do not specifically fit the established dossier structure.

> *"There may be, at times, an apparent unwillingness for companies to pursue implementation of innovative manufacturing or control approaches due to concerns about presumed 'restrictions' in GMP. Robust links between manufacturing/QA and Regulatory Affairs is important in helping to dispel such myths"*
>
> – Ron Ogilvie, Senior Director, Global CMC, Pfizer

While there are already established examples of crossing boundaries between parts one and two of the EU GMP Guide and different sections of Module 3 of the CTD (for instance sterile APIs, or APIs stabilized by blending with one or more excipients), there is a need to view EU GMPs as the standards for defining *what* should be achieved, not necessarily *how* it should be achieved.

EU GMPs are written in a non-prescriptive manner to permit a flexible approach. Companies need to consider the sum total of activities designed to achieve a defined outcome. Inspections will assess the effectiveness of these arrangements, not just the words on paper.

A "common sense" approach is required, questioning whether innovative proposals breach an explicit regulatory requirement; perhaps the proposed option is just a different way of achieving the same outcome? If a particularly novel approach is proposed, speaking to a regulator at an early stage will likely clarify whether the proposal is 1. acceptable in principle and 2. define what work may be required during process design and validation in order to demonstrate compliance with regulatory requirements.

Communication is key, and that means having good communication, both externally and internally. For example, MHRA and other EU regulators encourage meetings between industry and regulators to clarify ways forward and helping industry to navigate the regulatory process. At MHRA, this is coordinated through the Innovation Office (www.mhra.gov.uk/Howweregulate/Innovation/index.htm). One also can challenge the internal myths and ask "on what basis is something considered to be unacceptable?" Is lack of communication or lack of facts a barrier?

If it's not specifically mentioned in GMP, it's not permitted: MYTH

There is a great opportunity to use the themes above to reflect on the rationality and utility of your quality system. Consider whether the right questions have been asked and whether important business and regulatory compliance conclusions are being reached based on fact or "myth." Breaking down regulatory myths will benefit industry and the patient. Clarification of expectations can increase industry confidence in implementing innovative approaches to manufacture or process design and enable the focusing of limited resources toward real requirements, rather than fueling a myth. As a result, the ability to realize ways of efficient and innovative working in compliance with the regulations can benefit patients by improving access to cost effective medicines and avoiding shortages through more robust supply chains.

Future Myths: Stopping Them Before They Start

What might future myths look like? Every interpretation of guidelines invites myth-making about implementation. This means that both industry and regulators need to work hard to stop myths from being created and propagated. Regulators really are there to help and the perception of inflexibility of regulatory barriers might be the most important myth to dispel.

Are important quality and productivity decisions being made based on fact? Or based on myth? If you think you have enshrined a myth in your quality system or simply wish to check out the regulatory need for a particular activity we would like to hear about it. Please review your own activities and feel free to raise issues with the "Mythbusters" so they can be discussed in future articles. Please contact: Bryan Wright, ISPE EU Regulatory Affairs Advisor

About the Authors

David Churchward has been a GMDP inspector with the UK Medicines and Healthcare Products Regulatory Agency since 2004 with responsibility for leading inspections of pharmaceutical manufactur-

ers and blood establishments in the UK and internationally. In his current role, Churchward is responsible for leading the GMP Inspectorate's compliance management activity, including membership of the MHRA's Inspection Action Group which considers regulatory action in response to serious GMP non-compliance. He has also participated in a number of EU and international working groups to develop and revise GMP regulatory texts. Prior to joining the MHRA, he was a Principal Pharmacist and production manager in the UK's National Health Service, responsible for the manufacture of aseptically prepared radioactive diagnostic agents, chemotherapy and parenteral nutrition products. He is a member of ISPE's Regulatory and Compliance Committee (RCC), serving on the Europe Middle East Africa (EMEA) Regional Focus Group.

Ron Ogilvie is a Senior Director and Internal CMC Advisor in Global Regulatory CMC within Pfizer, with 13 years of experience in CMC (and 10 years previous experience in Chemical Process R&D in Pfizer). Ogilvie has experience of leading global new drug applications for Pfizer and has strong interests in impurity management (he chairs Pfizer's Impurity Council) and quality by design (representing Pfizer at the EMA QbD Workshop in London in 2014). Ogilvie has been a member of the IFAH-Europe Quality ad hoc group and has supported EFPIA activities on several topics, including the EFPIA Q11 support team (joining ICH discussions in St Louis on Q11 and working with the European focus team as Q11 was developed). He also joined an EFPIA Group who met with EDQM on the topic of starting materials selection in June 2011 and represented EFPIA at the QWP Breakout session on API Starting materials in December 2013. He spoke on a 2013 AAPS webinar on API Starting Material selection and is currently working on an ISPE sub-team on the topic of API starting materials. He is a member of ISPE's Regulatory and Compliance Committee (RCC), serving on the Europe Middle East Africa (EMEA) Regional Focus Group.

Bryan Wright is ISPE's European Regulatory Affairs Advisor and current chair of the ISPE Europe Middle East and Africa Regulatory Compliance Committee (EMEA RCC) focus group. In April 2011 Wright moved to ISPE from his position as Group Manager GMP and GDP for UK Medicines and Healthcare Products Regulatory Agency (MHRA). During his 22 years with the MHRA his expertise encompassed GMP, GDP, GCP, GPvP, and the GLP Monitoring Authority. He can be contacted by email:bryan@bjwright.co.uk.

Challenges for Regulated Life Sciences Companies within the IaaS Cloud

by Robert Streit and Anders Vidstrup
Members of the GAMP Cloud Computing Special Interest Group (SIG)

This article presents the key items that must be addressed to adopt an IaaS model within a regulated firm.

In the introductory article of this series, *Cloud Computing in a GxP Environment: The Promise, the Reality and the Path to Clarity* (*Pharmaceutical Engineering*: January/February 2014), an overview was provided of some of the primary challenges and/or concerns the regulated industry continues to debate as to whether cloud solutions can be adopted or not. Key issues from that discussion are highlighted as:

- The regulated company must be willing to give up levels of "hands-on" control and oversight to the cloud provider, yet remain accountable for the integrity and compliance of the solution and data.
- The regulated company should apply the same good outsourcing/supplier management practices that it operates for all other outsourcing activities.
- Cloud vendors typically approach quality assurance or the traditional Quality Management System (QMS) differently from the regulated industry

The GAMP COP Cloud SIG was formed of representatives of a cross-section of small and large life sciences companies and cloud service provider SMEs. The perspectives provided within this article represent real-world experience, research, and interaction with both the cloud provider industry, and various regulatory bodies.

This article will focus on the key items that must be addressed to adopt an IaaS model within a regulated firm. To do that, one must first understand what IaaS is, the variation of the model offered by the provider, and what compliance-enabling services the provider can supply. One of the most useful IaaS definitions is provided by the National Institute of Standards and Technology (NIST), which defines IaaS as:

> *"The capability provided to the consumer is to provision processing, storage, networks, and other fundamental computing resources where the consumer is able to deploy and run arbitrary software, which can include operating systems and applications. The consumer does not manage or control the underlying cloud infrastructure but has control over operating systems, storage, and deployed applications; and possibly limited control of select networking components (e.g., host firewalls)."*

Figure 1 depicts the shift in ownership of infrastructure from the traditional IT approach. (Light blue denotes the elements of greatest risk in this model. Note: this figure includes the full range of IT outsourcing models for the sake of completeness. This article focuses on the models enclosed within the dotted lines.)

To understand IaaS, one must understand that the IaaS model is not just hardware. When a customer requests an environment, a significant amount of automation has been developed behind the scenes to build and deploy an environment, potentially inclusive of networking, storage, and virtual machine.

There are some who advocate that this infrastructure layer has become a commodity, and that the abstraction

Finesse.com

Accelerate your process

Turbocharge into cGMP production

Take the direct route from development to production with scalable, flexible Finesse upstream SmartSystems. SmartParts – modular plug-and-play hardware – grow with the process. Pre-calibrated single-use sensors are ready to use. TruBio® software requires no programming and is easily configured by lab or factory personnel. Skilled validation assistance ensures cGMP compliance.

Need more speed? Our expert Finesse Team will help tune your loops and accelerate your process.

G3Pro Universal SmartSystem

SmartParts > SmartSystems > SmartFactories > Smart Bioprocess Solutions > Finesse

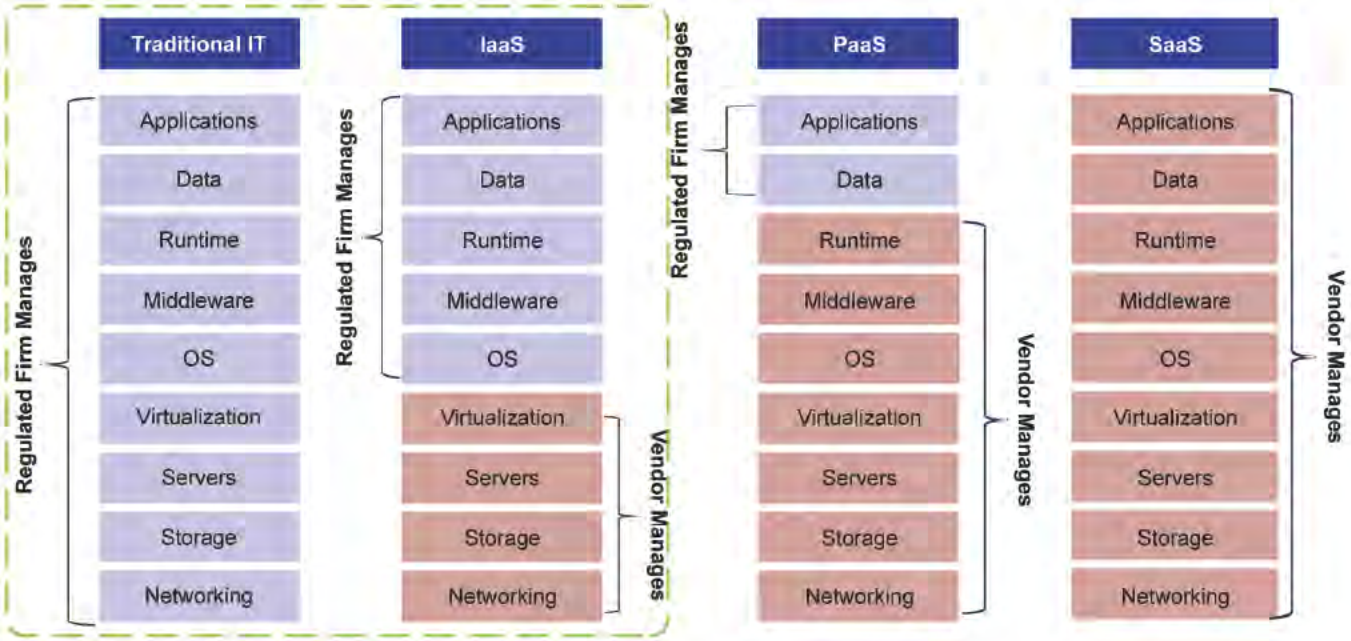


Figure 1 . IaaS Service Model vs Traditional IT Elements.

enabled by virtualization, creates an environment that has extremely low potential for impacting the platforms and applications in the upper layers. By virtue of not being tied to any specific server, this infrastructure model provides a layer more fault-tolerant and highly available than dedicated hardware. Despite these benefits, the regulated customer's data is processed by such virtual machines and is stored at the supplier on the supplier's hardware, and therefore the current definitions of a computer system per the FDA and EU Annex 11, still apply, (as do the associated requirements for the IaaS supplier to maintain specifications and diagrams). When it comes to the size of the supplier, the question becomes the ability to "partner." Larger suppliers may have great performance metrics, but the pure size of the customer base makes it difficult for them to agree to contract terms or perform activities and documentation unique to any one customer.

All IaaS providers are not the same and a variety of business models with varying capabilities exist. All hope to support the regulated life sciences industry. Figure 2 is one possible way to classify these providers, but is not in any way considered absolute. We expect this to continue evolving as awareness and understanding increases. Choosing a supplier with lower cost generally places a greater burden on the regulated company to establish qualification processes.

Figure 2 is based on experience from the SIG members, and illustrates the potential for a wide disparity in IaaS vendors' awareness and their understanding of quality assurance or a QMS as it pertains to the life sciences.

Many of the IaaS providers view quality as providing high availability and data integrity, which are only elements of what the regulated company defines as quality. Is a QMS implemented? And if so, has the infrastructure undergone formal qualification in line with GAMP® 5 practices, or has it been implemented following good IT practices? The following parameters lead to the understanding of the differences between IaaS cloud providers in the market:

- *Qualification Documents:* the provider executes and maintains the objective evidence that the IaaS solution is qualified and sufficiently documented as expected with reference to the Infrastructure GPG. Generally, good documentation practices are followed.
- *Customer Specific Change Agreement:* the provider agrees to key customer specific requirements related to the change process, and incorporates these elements into their daily operations.
- *Qualification/Verification Assistance:* the IaaS provider is aware of the regulated life sciences industry QMS definition, but not having an established QMS, may have tools, white papers, etc., that can be leveraged to assist the regulated customer in executing qualification documents.
- *Permits Onsite Audit:* the provider will allow the customer to conduct quality and security audits at the provider site(s). Dependent on the provider, this may be considered standard, or will be allowed via pre-agreed limitations and incremental fees (time and material).
- *Enterprise Scale:* the SIG's experience indicates that non-GxP service providers typically have business models and

There are many reasons to select the new BioPure LSX High Efficiency USP High Purity Water System

Two are **Clear.** Superior **Technology.** Low **Price.**

GUARANTEED 24 Hour Quote Generation GUARANTEED

Guaranteed 24 Hour Turnaround Time On All Standard Quotes.

Mar Cor Purification Life Science Markets

• Pharma/ Medical • Cosmetics • Lab & Research • Beverage • Semiconductor

ISO 9001 & ISO 13485 Certified · US: 800-633-3080 · Canada: 800-268-5035

For more information email us at info@mcpur or visit www.mcpur.com

MAR COR® PURIFICATION

A Cantel Medical Company

Capability Enabler	Life Sciences Targeted	Life Sciences Aware	Life Sciences Aware (Low)
Qualification Documents	✓		
Customer Specific Change Agreement	✓		
Qualification Assistance		✓	
Permits Onsite Audit	✓	✓ (may charge a fee)	Some
Enterprise Scale		✓	✓
Service/ Deployment Models	Private Cloud, IaaS, PaaS, some SaaS	IaaS, PaaS	IaaS, some PaaS
Cost Profile	$$$	$$	$

Figure 2. Characteristics of an IaaS provider of interest to a regulated firm.

capacity to handle requests for large scale operational tasks.

- *Cost Profile:* the providers with no formal QMS or quality awareness are usually the lowest cost – and could be the right solution for some low risk business activities. As additional customer specific services are provided, the cost increases

Deciding What to Move to the Cloud

The approach to IaaS should be based on the regulated company's risk assessment factoring in product and process in combination with the intended use of the IaaS. The risk assessment should incorporate the five key-elements from GAMP® 5 in Figure 3, but should focus on the two areas at the supplier end (those in the green circle). For the most part, impact/risk to the end user will be consistent, since in most cases the infrastructure layer will not have a product-specific issue. The five-stage risk assessment framework in the accordance with GAMP® 5 principles would be helpful.

Key risk considerations are:

- An understanding of both the functions and risks of the supporting and business process(es) is needed before the risks associated with specific functions of the IaaS can be assessed.
- Focus on risk to patient safety, product quality, and data integrity. Specification of requirements should include mitigating critical risks. The extent and detail of the requirements specification should be based on the associated risk, complexity, and novelty of the IaaS. Once the risks are understood, refer to the the GAMP® Testing GPG,[1] Appendix E2 – Testing of Cloud Applications, for further guidance on the overall testing approach.

In some situations, the outcome of the risk assessment may indicate, that an IaaS solution is not acceptable; whereas in other situations it could be used with very few controls. In any case, the decision must never have a negative impact on patient safety and data integrity.

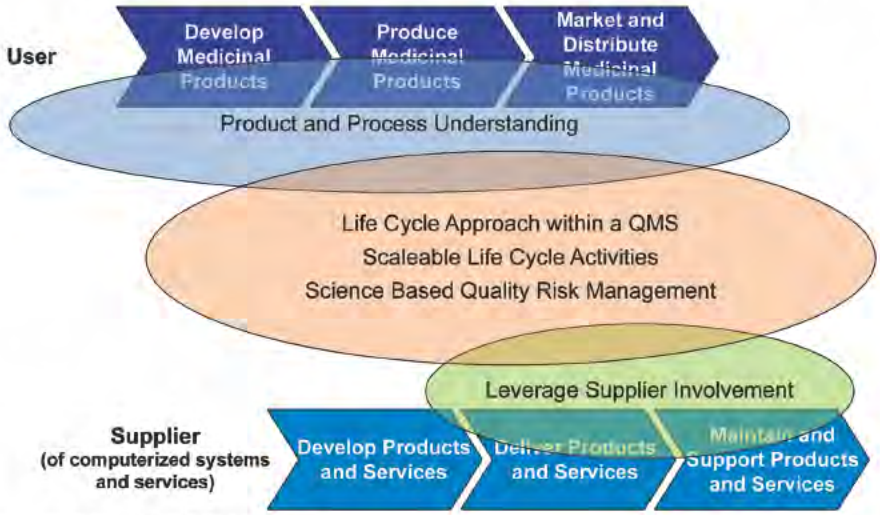
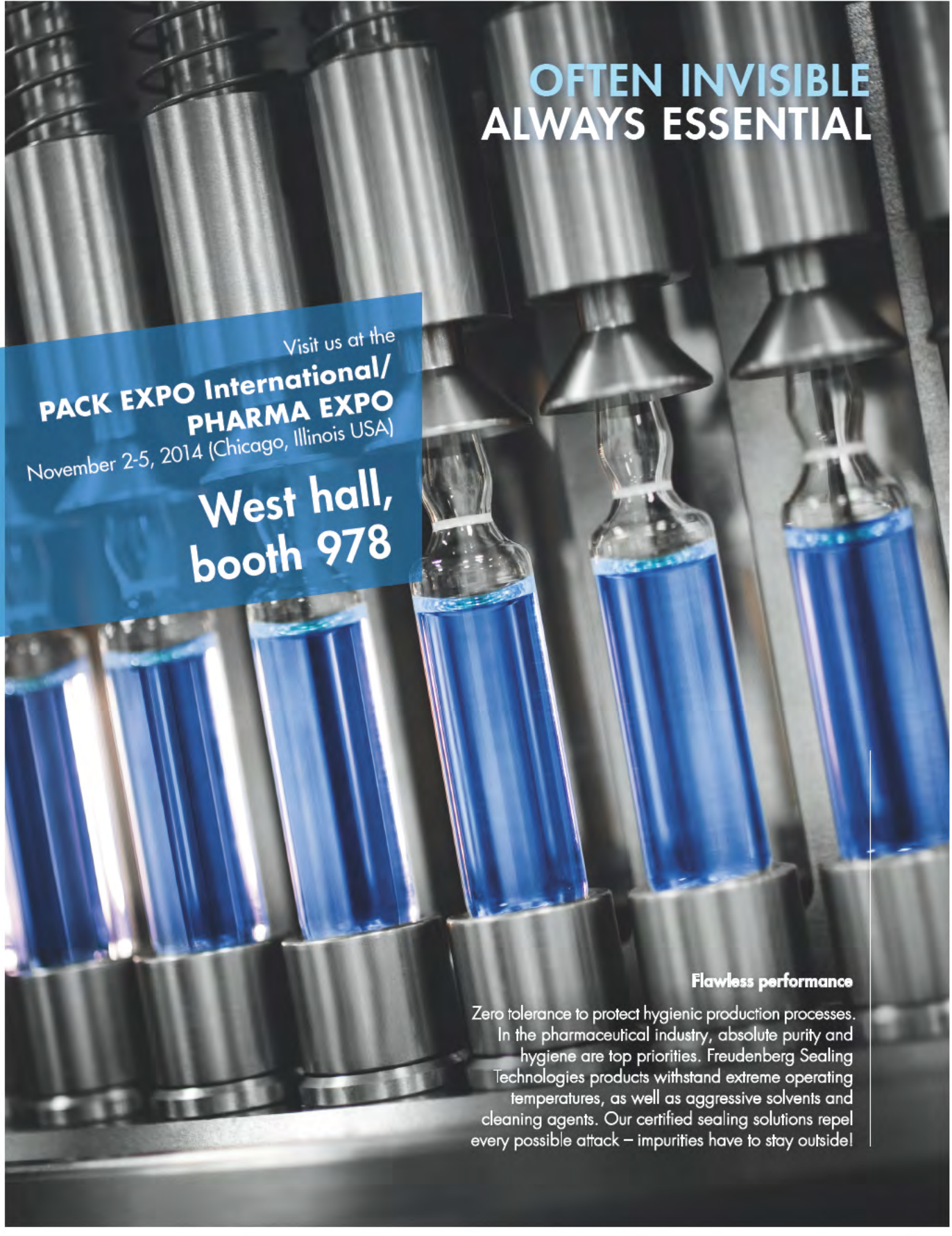


Figure 3. GAMP® 5 Key Concepts.

IaaS and Regulatory Controls

The required controls for the regulated company are independent of whether the infrastructure is in house or is outsourced to a supplier, e.g., in a IaaS cloud solution. Table A lists the basic regulatory requirements of the end-user and related consequences to the IT delivery/IaaS from an operational level.

In general, the activities at the provider site should comply with the principles of the regulations listed in Table A, even if the approach taken differs from the client company's internal processes. From a technical point of view, many of the requirements are adopted from, e.g., ISO 90003[2] and ISO 27001[3], section 7.The IaaS implementation should be based on the supplier's domain knowledge and



www.fst.com

Freudenberg
Sealing Technologies

QMS (or equivalent), and not verbatim from the regulated company's point of view.

To secure quality and security in the deliverables from the IaaS provider site, there should be quality assurance

Regulation		Phrase	Consequence
EU, GMP Volume 4, Annex 11: Computerized Systems	Principle	The application should be validated; IT infrastructure should be qualified.	In practice, basic principles described in the *ISPE GAMP® Good Practice Guide: IT Infrastructure Control and Compliance* should be applied, both at the provider's site, and at the regulated company.
	§1	As part of a risk management system, decisions on the extent of validation and data integrity controls should be based on a justified and documented risk assessment of the computerized system.	It requires that data integrity and security controls at both the provider site and the regulated company are handled as described in *GAMP® 5* (Appendix M3: Science Based Quality Risk Management) and the *ISPE GAMP® Good Practice Guide: IT Infrastructure Control and Compliance.* **The Challenge:** the provider has the key knowledge related to their business, and should answer questions related to the IaaS. The regulated company should have controls in place to verify if the solution satisfies business needs and risk tolerance.
	§2	All personnel should have appropriate qualifications, level of access and defined responsibilities to carry out their assigned duties.	The principles described in the *ISPE GAMP® Good Practice Guide: IT Infrastructure Control and Compliance* should be applied at the provider site. In practice it means "limit the required qualifications" and focus on the essential discipline for infrastructure. This is intended to simplify and not complicate.
	§3.1	…. and these agreements should include clear statements of the responsibilities of the third party.	In practice: 1. Provisioning the service. 2. Ongoing management and maintenance of the service will be for a substantially longer period. In both cases, roles and responsibilities should be clear, and both the SOW (provisioning) and SLA (ongoing) are important.
	§3.2	The need for an audit should be based on a risk assessment.	The requirement doesn't state that an audit must be conducted – but the regulated company must from a risk-based approach evaluate the provider's ability to comply with regulations. Principles from *GAMP® 5* (Appendix M2: Supplier Assessment) could be applied. Relevant certifications may provide an opportunity for a simplified or expedited assessment of the provider. The scope for the assessment should be clarified based on the risk assessment.
	§3.4	Quality system and audit information relating to suppliers or developers of software and implemented systems should be made available to inspectors on request.	It should be possible to obtain evidence of an appropriate assessment process and subsequent judgement of supplier suitability, including significant findings and outcomes should be made available to regulators on request. Some detailed aspects of assessment finding, especially those related to supplier intellectual property and technology may be covered by confidentiality agreements between the regulated company and the supplier. **The Challenge:** if a regulator requests supplier information, a request may be passed on to the supplier – and when necessary further confidentiality agreements discussed. In the case of service suppliers of high risk processes, contracts should notify them of the possibility for direct inspection and request timely access to their QMS if needed during regulatory inspection.
	§4.5	The regulated user should take all reasonable steps to ensure that the system has been developed in accordance with an appropriate quality management system. The supplier should be assessed appropriately.	In general, *GAMP® 5*, Chapter 4 related to the project phase describes all validation activities aligned with general validation principles. These activities should also cover the IaaS elements of automation used to provision the infrastructure with reference to the principles in Annex 11.
	§7.1	Data should be secured by both physical and electronic means against damage. Stored data should be checked for accessibility, readability and accuracy. Access to data should be ensured throughout the retention period.	This requirement should be implemented via controls both at supplier site and at the regulated company site. This involves implementation of the proper security controls, verification of backups, periodic testing of restoration, and contingency planning. In practice the requirements for disaster recovery at supplier side may be limited to just Recovery Time Objective (RTO) in reality. Recovery Point Objective (RPO) may also be stated in the contract.
	§12.1	Physical and/or logical controls should be in place to restrict access to computerized systems to authorized persons. Suitable methods of preventing unauthorized entry to the system may include the use of keys, pass cards, personal codes with passwords, biometrics, restricted access to computer equipment and data storage areas.	Consideration should be given to, e.g., establishing VPN connectivity, so that the regulated company standard identity access management practices could be leveraged. These requirements are fully aligned with good engineering practice as described in e.g. ISO 27001, section 7.[2]
21 CFR 211 Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General and Current Good Manufacturing Practice for Finished Pharmaceuticals	§211.25(a)	… shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions.	The principles described in the *ISPE GAMP® Good Practice Guide: IT Infrastructure Control and Compliance* should be applied at the provider site. In practice it means "limit the required qualifications" and focus on the essential discipline for infrastructure. This is intended to simplify and not complicate.
	§211.68(b)	A backup file of data entered into the computer or related system shall be maintained …. designed to assure that backup data are exact and complete and that it is secure from alteration, inadvertent erasures, or loss shall be maintained.	This requirement relies on the associated risk assessment, and must be conducted according to the principles described in the described in *GAMP® 5* (Appendix M3: Science Based Quality Risk Management) and the *ISPE GAMP® Good Practice Guide: IT Infrastructure Control and Compliance*, both at the supplier site and at the regulated company.

Table A. Basic regulatory requirements of the end-user and related consequences to the IT delivery/IaaS from an operational level.

activities in place monitoring processes and methods used to ensure quality. The methods by which this is accomplished could include ensuring conformance to one or more standards, such as ISO 9000 and/or ISO 27001.

In practice, there should be a quality responsible person at the IaaS provider organization with the authority to reject or approve deliverables to the customer. Generally, a quality-responsible person should also approve periodic evaluation of the different GxP-related services at the IaaS provider.

Industry Expectations Based on GAMP Approach

Qualification/verification is a process that demonstrates an entity has fulfilled specified requirements. In the context of an IaaS provider, this means demonstrating the ability of components such as network, firewalls, and Storage Area Networks (SANs) to fulfill the specified requirements for the various platforms regardless of whether they are specific or of a generic nature.

Basic requirements of qualification in the context if IaaS includes:

- Involvement of IaaS quality-responsible person at the appropriate level
- Formally verified and approved design solutions that meet specified requirements
- Documentation quality, detail, and degree of testing consistent with the level of risk of the specific use case.
- Tests and verifications aimed at establishing conformance to specifications
- Provisions to ensure that the qualified status of the entity is maintained
- Traceability of actions and activities

An IaaS providers' activities should be based on a lifecycle approach covering all phases from initial requirements until retirement including design, specification, programming, testing, installation, operation, and maintenance, even if it is infrastructure.[4] In reality, the ongoing deployment of new components and the client awareness of such may be based on the size of the vendor and ability to have a change agreement in place. The goal is to leverage the tools and the processes of the provider that have been assessed to meet compliance requirements, and incorporate outputs from these tools in the regulated company qualification documents as supporting evidence. A regulated firm's qualification strategy should be established after performing the assessment of the provider's QMS and core processes. Scope and depth of the qualification should be determined by a risk assessment.

When a customer wants its own service, based on an IaaS cloud providers standard service, this should be stated in the contract with additional details provided within the service level agreement (discussed later in the contract). In general, a gap analysis with focus on general requirements from the regulated company should be conducted, to verify customer needs and policies. Gaps should be handled appropriately.

Service Provider and Regulated Firm Shared Activities

The adoption of an IaaS model will normally be done in two steps:

- Qualification of the environment including:
  - Qualification of the infrastructure components to be used as shown in Table B
  - Qualification of the automated deployment and configuration of the customer specific IaaS (if applicable) as shown in Table C
- Definition of the operation and maintenance roles and responsibilities between the IaaS provider and the regulated company. The activities listed in Table D are all activities, that are related to the operational and maintenance of the IaaS from the regulated point of view.

These two bullets above should be reflected in the SOW and or contract.

The tables shown list different activities from a lifecycle approach related to IaaS provider and regulated company.

(The deliverables in the following tables reflect what may be required. However, depending on the risk associated with the desired use case and degree of automation available from the provider, a subset of these deliverables may be enough to satisfy requirements).

Table D indicates activities related to the automated deployment process that may be compared to and considered equal to the disciplines of a facility process control system. The automated deployment process is normally based on a generic tool, where appropriate business specific code is implemented to reflect the IaaS providers' proprietary method of deploying infrastructure solutions.

The operation and maintenance activities listed in Table C should secure the IaaS availability and performance in operation for which it was designed. The activities are generally based on the GAMP® Good Practice Guide: IT Infrastructure Control and Compliance Guide and don't differ from the main concept in this guidance. Regardless of the difference in cloud models, the intensions in the guidance still are applicable.

IaaS Provider Activities	Activities in the Regulated Company
Applies to components to be included in the technical solution regardless of automated or manual deployment of the IaaS: Input to the process: - Service description Output from the process: - Quality Activity Plan and/or equivalent for bringing the component into Compliance with pharmaceutical regulations - Requirement Specification - Technical Design Specification (TDS) - Risk Assessment as appropriate - Design Review Report - Traceability Matrix - Code review report for scripts that might handle deployment or configuration automatically - Installation verification - Verification of technical functionality and verification that IaaS is ready for production (transition phase) – in practice "Installation and Operational Verification" - Configuration Item List are in place (CIL)	Vendor assessment/on-site audit GAP analysis to requirements for infrastructure; e.g., company specific security requirements Input to the process: - Customer service related requirements The output of the gap analysis is a list of activities to be done before the approval status can be stated. This could include: - Qualification/Validation Plan, or similar - If applicable, additional customer specific TDS - Customer specific Risk analysis - A design review reflecting the changes above - Additional Installation Test regarding Customer service related requirements, installation guides/scripts and image - Hardware Qualification (or equivalent evidence able to be generated by the service if not done by provider) - Additional Functional Test for Customer related requirements, or requirements for test areas - Updated processes captured in controlled documents reflecting agreed unique operational processes between the provider and customer

Table B. Qualification of components (building block system for VLANS, switches, routers, back-up systems, monitoring etc.). Activities also reflect tools and implicit automation software for deployment of IaaS.

The Contract

The contractual agreement with an IaaS provider is a critical tool for effectively managing the relationship between the regulated company and the provider. It must be treated as a partnership between the two entities. Beyond the standard legal agreements and warranties, the contract should have at least the following three key sections to ensure expectations are clear. These sections may be exhibits, addendums, or independent documents but should include:

Compliance Requirements or Quality Agreement

Although the regulated company still has the responsibility for deploying and maintaining the operating system(s) and applications running in the IaaS model, the data is located at the supplier, and therefore, the supplier must provide and/or maintain certain elements over the lifecycle of the relationship.

Compliance Requirements

To the regulated firm, the presence of the elements is not the end point. SOPs need to have a periodic review, and there

IaaS Provider Activities	Activities in the Regulated Company
Input to the process: - Requirement specification for deployment Output from the process: - Change request - Customer related Technical Design Specification (TDS) if standard components, scripts, or configurations cannot be used (depends on provider's ability to manage revisions, manual changes, etc.) - Risk Assessment as appropriate - Design Review Report if applied - Traceability Matrix - Installation Qualification and Report - Configuration Item List (CIL)	Input to the process: - Order to the IaaS cloud – depending on automation, this may serve as a defined script/set of scripts Output from the process: - Documentation from the Supplier, that components are installed as expected include a CI List. Depending on automation, this may be represented by on-demand reports reflecting confirmation of successfully executed scripts above.

Table C. Qualification of automated deployment process.

needs to be evidence that existing procedures are followed. Compliance requirements include:

- Change Management SOPs – change records should be executed for all changes to infrastructure and maintained for the life of the combined set of hardware, software, networks, facilities, etc. that comprise the infrastructure.
- Incident Management – scope of incidents should include excursions from specified environmental parameters, unexpected outages/failures, and items impacting performance of hardware/networking equipment. Incident records should be maintained and associated with any root cause analysis or CAPA items resulting from the incident investigation.
- Individuals responsible for data center operations and infrastructure support shall be adequately trained and qualified for the role(s) being performed.
- Training procedures shall exist to ensure personnel associated with the procured services are trained for their role. Evidence of training shall be captured and maintained.
- Infrastructure and network diagrams. The diagrams should be readily available to reflect current state.
- Backup and Recovery SOPs of the supplier's infrastructure and configuration settings should be maintained, with documented evidence of periodic testing captured.
- Adherence to SOPs for the qualification/deployment of infrastructure items with documented evidence available. If highly automated, tools should be available to provide reports verifying that the provisioned service matches requirements.
- Timely support in the event that the regulated company is subject to a regulatory authority audit.
- Notification in the event the supplier becomes subject to such an audit.

IaaS Provider Activities	Activities in the Regulated Company
The IT infrastructure typically changes frequently – sometimes on a daily or hourly basis depending on the size of the infrastructure. The IT infrastructure should be maintained in a documented state of control by ensuring appropriate: - Change Management - Incident Management - Configuration Management - Security Management - Network Management - Problem Management - Help Desk Provision - Backup, Restore and Archiving (of Provider Key Systems, etc.) - Disaster Recovery - Performance Monitoring (Service Outages, etc.) It is expected, that the IaaS provider periodically evaluates the complete service (standard service and associated customer approved services) to ensure that the service are in control. This should be accomplished via management review, internal audit, or similar business responsibility and include any/all of the following: - Key Performance Indicator's (KPI) - Configuration Management, e.g., CIL Reviews - Major Incidents - Customer Complaints - Changes - Capability - Review of Related Disaster and Recovery Plans - Evaluation of Risk Assessment - Reviews of Physical Security of Infrastructure	The regulated company will maintain the application in a manner equivalent to how applications hosted internally would be managed. These items include: - Define Application Requirements - Application Validation - Application Testing and UAT - Performance Monitoring - Security Monitoring - Backup Jobs Verification - OS, DB, and Application Level Security Management Vendor management becomes a key task in a cloud model. Ongoing activities in this model include: - SLA Management - Periodic Audit of the Appropriate IaaS Provider Activities

Table D. Operation and maintenance.

- Exit Strategy – based on the scenario, expectations of the supplier in the event that the relationship terminates, should establish what data, any other assets, and method of retrieval/media would be used to recover the information.

Statement of Work (SOW)

Specified deliverables in the SOW should be focused on supplier commitments that are required for the regulated company to go-live in production with the desired services. These should include:

- Any documents as described in Table A that are regulated customer specific should be in place prior to moving forward with the supplier.
- Remediation items identified during the audit/assessment process should be contractually agreed to with target dates for implementation. These items should be verified as being in place prior to any deployment.

Service Level Agreement (SLA)

Defined operational measures of the service on an ongoing basis. Elements should include:

- Escalation and communication processes should be established in the event of major incidents that have significant risk to the service availability, reliability, and data integrity.

- Specific requirements of the supplier in the event the regulated company is audited by a regulatory authority, such as providing process documentation and evidence within a specified time frame.
- Notification of proposed/planned changes. The regulated company requires time to evaluate the change, and determine the degree of testing required to be performed before migration to production. Changes that pose little or no risk to the regulated company platform, should be classified as such, and may be implemented without the regulated company testing.
- Key compliance metrics such as definition of incident severity, time to perform a root cause analysis report from an incident occurrence, change controls executed successfully first time, etc.

Conclusion

In an IaaS model, the regulated company is still the accountable entity for the application and data. IaaS solutions should be qualified based on the principles in the GAMP® Good Practice Guide: IT Infrastructure Control and Compliance. This article demonstrates that the predicate rules are applicable regardless of where the infrastructure resides. The continuing challenge is how the service provider's network, supporting systems, and processes for deployment of the IaaS solution meet what is described in the GAMP® Good Practice Guide: IT Infrastructure Control and Compliance Guide.

> *"In an IaaS model, the regulated company is still the accountable entity for the application and data.*

Sufficient documentation and controls, and effective supplier management may permit an IaaS to be verified as fit for purpose according to principles from ISO 90003 and ISO 27001. The exact format of the controls may be based on the technology used to provide the controls and should be assessed in that light.

The intention of the future SIG work is to describe in detail how to address supplier activities related to the key concepts shown in Figure 3 in a manner that meets regulations and satisfies client needs. Future articles in this series will focus on PaaS and SaaS models, and illustrate how the risks associated with cloud exist in all models, but the risk elements shift as the provider's processes and controls become more closely tied to the O/S and application(s).

References

1. *ISPE GAMP® Good Practice Guide: A Risk-Based Approach to Testing of GxP Systems*, International Society for Pharmaceutical Engineering (ISPE), Second Edition), December 2012, www.ispe.org.
2. ISO 90003:2004, Software engineering – Guidelines for the application of ISO 9001:2000 to computer software.
3. ISO 27001:2005, Information technology – Security techniques – Information security management systems – Requirements.
4. Annex 11 definition on Life-cycle.

About the Authors

Robert Streit is a Senior Manager with Johnson & Johnson Quality and Compliance possessing 24 years of extensive experience in IT working with engineering, quality, manufacturing and control systems inclusive of MES. This work has included defining solutions for multiple regulated environments, developing system requirements, establishing computer systems validation plans, and creating support models for critical systems. More recently, his efforts have been focused on establishing compliant approaches for emerging technologies, particularly cloud and mobile technologies. More specifically, this has involved vendor evaluations and establishing supplier compliance requirements, both for assessments and contracted service agreements. He can be contacted by email: rstreit@its.jnj.com.

Anders Vidstrup is Senior IT Quality Subject Matter Expert at NNIT. He works with quality aspects of computer related systems. Over the last 14 years, he has been involved in qualification of PCS systems and applications in large plants for drug-productions. He also works with principles for qualification of cloud solutions and infrastructure. From 2004 to 2009, he had overall QA responsibility for the Novo Nordisk A/S infrastructure, including infrastructure components. Today, he develops the Quality Management System in NNIT, and work as Quality Responsible on deliverables to both customers in the food and drug industry as well as financial customers. He is currently part of the GAMP SIG "Testing of GxP Critical Systems" and the GAMP SIG revising the Infrastructure Good Practice Guide. He provided input into GAMP® 5, including the test appendix. Over the years, he has been a frequent speaker at conferences on the topic of GAMP. He can be contacted by email: avid@nnit.com.

Seeking practical GMP solutions to meet regulatory requirements?

Take ISPE eLearning

NEW EXPANDED COURSES:

THE DEPTH OF AN IN-PERSON CLASS, ONLINE.

ISPE GAMP® ISPE, the Developers of GAMP®

- GMP Auditing for Pharmaceutical Industry
- Biotechnology Basics
- Containment Fundamentals
- Basic Principles of Computerized Systems Compliance: Applying the *GAMP® 5 Guides A Risk-Based Approach to Compliant GxP Computerized Systems*

Acquire the knowledge you need immediately with over 150 offerings in 22 topics

TRY A FREE MODULE NOW!
www.ISPE.org/FreeModule

REGISTER TODAY!
www.ISPE.org/eLearning

ISPE®

PHARMACEUTICAL ENGINEERING Interviews

François Sallans, Chair of ISPE's Drug Shortages Initiative Team

Sallans talks candidly about the objective of ISPE's Drug Shortages Prevention Plan, including lessons learned from the survey, the importance of a corporate quality culture, and the role metrics can play in preventing shortages.

François Sallans is Vice President and Chief Quality Officer for Johnson & Johnson. In this role, he is responsible for Quality and Compliance activities for Johnson & Johnson. Sallans is a member of the International Leadership Forum and is the Chair of ISPE's Drug Shortages Initiative Team, which was awarded the Committee of the Year Award at the 2013 ISPE Annual Meeting in November 2013. The team's work, as led by Sallans, has helped establish ISPE as the leader in the area of drug shortages and motivated ISPE to run drug shortage workshops at every ISPE event in 2014, along with plans for further research in the initiative's findings.

What is the objective of the drug shortages prevention plan?

The objective of the drug shortages prevention plan is to help guide the pharmaceutical and biopharmaceutical industry in establishing reliable, robust and resilient supply chains to provide quality medicines to patients without interruption. The plan will serve as a roadmap that, when effectively implemented, can significantly reduce drug shortages.

The drug shortages prevention plan is ISPE's second major output on this topic since launching its Drug Shortages Initiative in 2012. It builds on the results of ISPE's 2013 Drug Shortages Survey, which provided clear evidence that avoiding and mitigating shortages requires a holistic approach that encompasses both the organizational and technical issues that affect drug manufacturing and quality.

The survey also showed that quality systems and strong management controls are key to avoiding shortages. Recently, the Drug Shortages Task Team conducted a more detailed review of the survey data and interviewed leaders from more than 30 major companies, regulators from 10 health authorities, and regional industry associations to address questions that arose from the survey.

What did the Task Team hope to learn from those interviews?

One thing they hoped to learn was why a number of companies that focused primarily on IT systems or building redundancy across the supply chain had failed prevention plans and other companies who did not focus on either of these two areas had successful prevention plans.

From these interviews, they were able to develop recommendations for avoiding or mitigating drug shortages. They also developed a framework to organize recommendations and highlight the strategies and challenges associated with operationalizing each recommendation that included the potential interactions that may exist between each other.

Drug shortages are often the result of problems with a

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

company's culture rather than a problem with production. What is it about the nature of a *corporate quality culture*, as it has been called, that can be so instrumental in preventing drug shortages?

Company culture plays a fundamental role in drug shortages. Data from the ISPE Drug Shortages Survey made it clear that corporate quality culture is a necessary foundation for and key enabler of a well-functioning and robust quality system.

Quality systems can only be effective where there is a strong emphasis on a "quality culture" throughout the organization. This became clear when data from ISPE's 2013 survey on drug shortages was analyzed. *Corporate quality culture* is the key enabler for a well-functioning and robust quality system.

What comprises a corporate quality culture?

Thousands of decisions are made every day by all employees, yet the guidelines for making decisions may not actually be described in a quality system, or found in a company's standard operating procedures. It is up to each person to make decisions in the light of rules, guidances, SOPs, risk management principles and the overarching culture of a firm.

A patient-centric focus, combined with individual responsibility and management accountability for quality, set the foundation of a quality culture. This action-oriented mindset, with the support of proper systems, processes, and practices engenders continuous improvement.

The drug shortages prevention plan provides guidance for companies to develop holistic strategies and metrics that cross multiple functional areas in an organization to ensure that employees understand not just the importance of "what," but also the "why" of what they are doing.

You mention metrics. What role can metrics play in preventing shortages?

It is well recognized that there are supply chain metrics that can predict product demand and can be leveraged with other quality metrics to prevent shortages or plan for remediation. Both lagging and leading indicators are needed to measure the overall quality performance of a site. Taken together, these quality metrics can be predictive of a company's ability to reliably supply quality products. The question remains, however, which *specific* metrics will be the best predictors for preventing shortages? The drug shortages prevention plan provides a range of possible metrics to assist companies in selecting appropriate measures and indicators. It also includes case studies that show how companies have used metrics to identify or avoid shortages.

Many companies struggle with understanding how a pharmaceutical quality system should be implemented across the global supply chain. Does the drug shortages prevention plan provide guidance in this area?

Yes. Valuable input from both industry and regulators led the task team to look at the underlying technical, scientific, manufacturing, quality, and compliance issues associated with a company's supply chain. They looked at its ability to source, manufacture, and distribute products. In addition to leveraging the survey findings and getting feedback from ISPE members and regulators, the team also interviewed a number of senior executives responsible for supply chain operations to better understand challenges they have faced. Those discussions focused on solutions they implemented as they worked to build a supply chain that would help prevent shortages, one that was robust, reproducible, and resilient.

Where in the drug shortages prevention plan is that discussed?

The section on *Business Continuity Planning* integrates the supply chain network – from development to commercial manufacturing – with a robust quality system, including governance and management strategies and decisions used to help achieve a robust supply chain. It identifies specific mechanisms to test and monitor

potential problems within the supply chain, such as weaknesses, that, if not addressed, could lead to a shortage.

How do you envision companies using the drug shortages prevention plan?

I first envision companies to use the drug shortages prevention plan as a reflection paper, to help them look holistically across their entire supply chain and challenge their current processes, systems and practices to identify the potential gaps. The drug shortages prevention plan is comprehensive and helps companies articulate what are the essential elements and processes to be improved or implemented.

Second, I envision the companies to use the drug shortages prevention plan as a tool-kit. It's easy for companies to navigate through the plan and select the relevant chapters to support their approach (corporate culture, robust quality system, metrics, business continuity planning, communication with authorities, building capabilities). Companies can immediately benefit from the discussion points and the industry examples provided in each chapter and use it to facilitate the elaboration of their action plan.

What was most surprising to you while working on the drug shortages prevention plan?

Originally, our team started to work on how the gaps first highlighted by the survey could be resolved. As we made progress and these strategies started to take shape, we realized that a holistic and comprehensive approach was required to address effectively the multifactorial dimension of the drug shortage problem and the needs for strategies that are holistic in nature and that cross over multiple functional areas in an organization.

What are the next plans for ISPE's Drug Shortages initiative?

We have identified the key elements in a good drug shortage prevention program and provided recommendations for their implementation. As a next step, ISPE will be further exploring and examining the key topics covered in the drug shortages prevention plan through conference sessions, training programs, and publications. This will help companies increase their capabilities in these key areas, such as CAPA and building a quality culture. By strengthening their capabilities in these areas, we feel that companies will be able avoid drug shortages. The avoidance or mitigation of drug shortages is a topic that needs to be woven throughout every step of the pharmaceutical lifecycle. ISPE has the technical know-how to help companies do this.

ISPE Drug Shortages Prevention Plan – **Introductory Summary**

Introduction

The International Society for Pharmaceutical Engineering's (ISPE) *Drug Shortages Prevention Plan* is aimed at guiding the pharmaceutical and biopharmaceutical industry in establishing reliable, robust, and resilient supply chains that can, without interruption, provide quality medicines to patients. The Plan was created from a cross-industry initiative in response to a 2013 request from the European Medicines Agency (EMA) to address the prevention of drug shortages caused by manufacturing and quality issues.

ISPE announced in April, 2014 that it would work with global stakeholders and other industry associations to produce a Drug Shortages Prevention Plan – its second major effort in its continuing efforts on the topic. The ISPE Drug Shortages Task Team used the results of ISPE's 2013 Drug Shortages Survey[1] as a starting point for developing strategies and practices to prevent shortages.

This Introductory Summary is aimed at highlighting important areas of the Team's work. The full ISPE Drug Shortages Prevention Plan will be published in October 2014.

The Plan is organized around a "six dimension" framework: Corporate Quality Culture; Robust Quality System; Metrics; Business Continuity Planning; Communication with Authorities; and Building Capability, each of which are interlinked.

Work on the Plan engaged Team members with leaders from more than 30 major pharmaceutical companies. The Team also utilized information offered at recent ISPE conferences held in Frankfurt, Germany (April 2014) and Baltimore, Maryland, USA (June 2014) and other conferences and workshops where presentations included valuable information from members of industry, as well as from regulators, regarding how drug shortages might be mitigated or prevented.

How should the Plan be used?

Avoiding or mitigating drug shortages is a crucial issue, and the Task Team Members who compiled this plan hope that it will find wide use in industry and be a valuable guide for solving drug shortage problems and preventing the interruption of supplies due to manufacturing or quality issues, thereby focusing on the prevention of events that may lead to drug shortages.

The Plan may be thought of as a "reflection paper" to help industry members look holistically across all elements of their company and evaluate whether their current drug shortage prevention strategies, as well as their policies and procedures, meet current challenges, or whether changes need to be implemented and processes improved.

Team members also suggest that the Plan could be seen as a "toolbox" that companies may use to select the proper tool for the appropriate problem that may potentially cause a drug shortage. That toolbox has six dimensions, each of which can be utilized as needed, whether to measure and test the integrity of the supply chain, build a robust quality system, enhance corporate quality culture, or find ways to better communicate with regulators.

Dimension 1 – Creating a Corporate Quality Culture to Prevent Drug Shortages

Drug shortages are often perceived as resulting from material non-availabilities or product recalls. However, the root causes of drug shortages are many and often involve a trigger in production factors or technical processes that can set into motion a cause-and-effect chain that can lead to a shortage. Lack of controls and human errors contribute to root causes, as do problems and insufficiencies in manufacturing, infrastructure and materials. However, a general failure to implement a robust quality system across the life cycle of the product, as reported in 2013 by the ISPE

ISPE Drug Shortages Prevention Plan – Introductory Summary

Continued.

Survey, is considered to be a critical factor for causing drug shortages.

The Plan cites the responsibilities of leadership and management to implement robust quality systems by creating an effective Corporate Quality Culture, one that encompasses an organization's practices, central values and philosophy with regard to quality, and requires that employees at every level subscribe to its requirements. A company's Corporate Quality Culture is an indicator of its ability to routinely provide quality service and products and must be supported by management principles and practices aimed at quality. It is up to the CEO and other executives to communicate the concept of Corporate Quality Culture to all employees.

Dimension 2 – Developing a Robust Quality System

In the search for the *true root causes* of drug shortages, questions regarding what makes a quality system robust and, conversely, what triggers can affect the supply chain and lead to a drug shortage, are important. Accordingly, this section discusses what is needed to develop a robust quality system.

Validation – a key tool in the industry, and for which the principles are well-known – is aimed at demonstrating that a process operates effectively, consistently and produces the expected and desired results, which in this case are robustness and quality. Validation, also a legal GMP requirement, needs to occur in the context of continual improvement during the product's lifecycle.

Corrective and preventive actions (CAPAs) are key tools in creating a robust quality system, and CAPA processes need to be actively managed in such a way that their appropriateness is endorsed by senior management, complete with a process for escalating problems to top managers.

Robustness and quality can be achieved by compliance with preventive maintenance programs for facilities and equipment used in pharmaceutical manufacturing as equipment failures (as revealed in the ISPE Survey) can often lead to production interruption.

All this should be embedded in a Pharmaceutical Product Life Cycle management in the sense of continual improvement as outlined in ICH Q10, "The Pharmaceutical Quality System," for all marketed products, including legacy products.

This chapter of the Drug Shortages Prevention Plan also includes a discussion of subject matter experts and the role they may play in helping to create robust quality systems.

Dimension 3 – Using Metrics to Track Quality

This chapter examines parameters for measuring and tracking performance and offers metrics for discovering any weaknesses that may be in process or product. The chapter emphasizes that there is no "one size fits all" metric. Rather, there are a variety of tools and the right one needs to be chosen.

While many companies use metrics as part of their Quality System Management Review (as driven by ICH Q10 Ch 4), this chapter discusses quality indicators provided by and recommended to the U.S. Food and Drug Administration (FDA) by ISPE, and the collective knowledge gained from many discussions held at conferences and workshops over the past two years.

The ISPE Survey revealed that well-defined metrics, tailored to identify potential shortages risks, can help mitigate them. Both lagging and leading indicators are needed to measure the overall quality performance of a site and the products it produces. In relation to drug shortages, appropriate metrics need to be present across the quality system to: 1) identify and allow mitigation; 2) monitor supply and demand within the supply chain; 3) monitor and predict actual shortages in terms of scope, duration and patient impact and; 4) demonstrate corrective action for future prevention.

The ISPE Plan recommends that companies leverage their CAPAs, Annual Product Quality Review (APQR) and Quality System Management Review (QSMR) programs to pull the appropriate metrics for improving the prediction of shortages. Which metrics to use as predictors, whether leading or lagging, is a key question addressed in the chapter.

Case studies are presented to demonstrate the use of metrics to anticipate, prevent, and solve problems of product quality and supply chain integrity:

- A company that experienced problems with its supply chain and experienced shortages uses metrics to overcome challenges.
- Another company experiences supplier disruptions that led to a shortage. Learn in this chapter how one company established a "reliability room" to help prevent shortages by gaining more insight into supplier and a product performance.

The chapter notes that in June, 2014, ISPE launched its Quality Metrics Pilot Program to test sets of metrics for relevance and effectiveness. A system of metrics is offered in this chapter as examples of "relevant indicators of the quality system for preventing drug shortages."

Continued on page 90.

ISPE Drug Shortages Prevention Plan – Introductory Summary

Continued from page 89.

Dimension 4 – Business Continuity Planning

The ISPE Survey suggested that to avoid drug shortages, companies should develop drug shortage mitigation programs built around production and process. Production includes product, factory, material, machines and equipment and experts. Process includes environment, production and behavior and human error. The chapter makes suggestions on how to achieve robustness, evaluate the value redundancy and test, monitor and refine the supply chain.

The chapter also recommends how to integrate the supply chain network (from development to commercial manufacturing) with a robust quality system, especially important at a time when supply chains have become global and more complex. The importance of having good governance systems across the organization, IT systems, the use of metrics and organization design receive consideration as do materials, machines and equipment, and technology transfer as topics that are related to business continuity planning. The chapter offers several objectives for attaining continuity as well as "real world" case studies gathered from industry members and illustrating by situation not only the challenges but the application of principles aimed at meeting the challenges and strengthening the continuity of business. The objectives and case study results are linked to the three important aspects of building continuity – robustness, redundancy and resilience.

Case studies include:

- A pharmaceutical company faced significant quality issues and subsequent recalls. True root causes were discovered by an end-to-end assessment of the company's operations.
- A major supplier of pharmaceutical excipients consolidating manufacturing and supply sites found that one site was responsible for supplying 20 percent of the market and that disruptions took up to one year to correct. Find out how they mitigated these problems.

Dimension 5 – Communication with Authorities

In parallel with the development of a plan to address shortages resulting from manufacturing and quality issues, the European Federation of Pharmaceutical Industries (EFPIA) and the European Generic Medicines Association (EGA) led an initiative also requested by EMA to propose an EU-wide process for informing regulatory agencies of a "meaningful interruption to supplies." Complementing this initiative, the ISPE Drug Shortages Prevention Plan addresses what companies can do to improve their communication with regulatory agencies and make certain that all communication is carried out using consistent and transparent dialogue aimed at identifying problems quickly and notifying regulators of a shortage in a timely manner. Examples in this chapter describe how several companies facing shortages were able to effectively communicate their long-term and short-term goals with regulators.

In collaboration with other industry associations, such as EFPIA and EGA, the chapter focuses on communication with regulators both in the US and in the EU with an emphasis on the importance of informing regulators about problematic issues – whether with the site or a CMO – early-on and quickly. How problems can be more quickly escalated to top management and key decision-makers (also a communication issue) is also discussed.

What kinds of communication work best? The Team offers insight into call centers and "media message maps" and explains how to use them. Again, a number of real world case studies are offered to highlight good communications strategies and practices.

Case studies include:

- Problems with a sterile injectable made at a CMO required discontinuation after an inspection. However, quick and effective communication with Health Authorities lessened the impact on patients. Find out what steps they took.
- A year after a company discontinued manufacturing a product, the FDA asked them to resume production because of a problem in the supply chain. What steps did they take to ensure a reliable supply for patients?
- Visible particulate matter showed up in one kind of container. A recall of the product loomed, plus the shelf expiration date had to be changed from 24 months to 12. How did this problem work out for the best thanks to good communication between the manufacturer and the Health Authority?

Dimension 6 – Building Capability

The final chapter summarizes capability needs for each of the other chapters described in the Plan. This dimension encourages a holistic approach, which means looking at production, quality, supply chain integrity, the commitment of all employees to quality and, most importantly, using that analysis to better build the capacity to meet the variety of challenges and root causes of drug shortages, whether they are derived from issues of process, governance or skills.

The chapter notes that 60 percent of recent warning letters cite "weak organizational effectiveness" as the cause behind the citation. How organizational effectiveness can be improved is the key issue tackled in Dimension Six. Atten-

ISPE Drug Shortages Prevention Plan – Introductory Summary

Continued.

tion is also paid to how staff members can better understand the "what" and the "why" of their roles.

This chapter specifically outlines how improvements in capability building can be made and summarizes the capability needs that other chapters highlight. The chapter is forward looking by recommending potential courses and conferences that could be developed regarding training, knowledge management and mentorship to identify, prevent, or mitigate drug shortages.

Conclusion

The Plan concludes with recommendations taken from each of the chapters relevant to each dimension. The Team re-emphasizes that there is "no one size fits all" solution to ensuring supply and preventing drug shortages. However, the recommendations, gleaned from each chapter, also emphasize, and are linked to "real world cases" where quality, management responsibility, and knowing capabilities couple with proactive risk management and crisis management to play a strong role when it comes to preventing drug shortages.

The Plan ends with a chapter that promises to make the necessary "Next Steps" in making drug shortages an important topic at the top of ISPE conference agendas in order to continue raising awareness of drug shortages and further the effort to make them a thing of the past. ISPE will continue to provide resources aimed at that end.

Reference

1. Report on the ISPE Drug Shortages Survey (ISPE), 2013, http://www.ispe.org/drug-shortages-initiative/about-the-survey.

Don't miss the worldwide release of the

ISPE Drug Shortages Prevention Plan

Tuesday, 14 October, 13.00-14.30
at the 2014 ISPE Annual Meeting
Las Vegas, Nevada, US

Bournas Joins ISPE as CEO

SPE has hired John Bournas as President and CEO, succeeding Nancy Berg who announced plans to leave the Society last fall. He brings to the Society a clear vision for the expansion of its global initiatives and business operations including leveraging technology to extend ISPE's Membership and educational programs. Bournas has extensive competencies in the healthcare association industry as well as significant international experience.

Bournas is currently CEO/Executive Director of the World Federation of Hemophilia (WFH), an international healthcare organization, officially recognized by the World Health Organization and comprised of 127 country-based societies, where he led growth of the group's mission and awareness raising; executed successful corporate affairs partnerships and evolved the group's digital delivery of educational programs and content. Prior to WFH, he was Senior Director of International Affairs at the American College of Cardiology, the largest global professional society for cardiologists, where he advanced international membership and Chapter establishment abroad; Senior Director, International at Cardinal Health and was a former diplomat, with postings in Chile, Australia and Japan.

Bournas takes the helm at ISPE on 20 September and will oversee ISPE's Annual Meeting, 12 – 15 October, 2014 in Las Vegas, NV (http://www.ispe.org/2014-annual-meeting), which will coincide with the opening of the ISPE's office in Washington, DC to establish a permanent executive presence there. He earned his MBA at Macquarie University (Australia); MA, Political Science at Fordham University (New York) and BA, International Studies from Fairleigh Dickinson University (New Jersey).

Look for an interview with Bournas in an upcoming issue of *Pharmaceutical Engineering*.

Educating in the Windy City

ISPE's Pharma EXPO Conference Program

SPE will host the Pharma EXPO 2014, collocated with PACK EXPO, on 4 November 2014 at Chicago's McCormick Place. The world-class, multi-media, pharmaceutical manufacturing and packaging expo brings together the leading suppliers and industry professionals to discover the latest in technology and regulatory trends. The expo includes the Pharma Conference with presentations offering solutions, updated best practices and applicable strategies relevant to the entire lifecycle of pharmaceutical manufacturing. ISPE's educational opportunities are available throughout the expo and presented on stage, in exhibits and expert-focused conferences.

With educational sessions and industry presentations hosted simultaneously, groundbreaking knowledge will be ever-present at Pharma EXPO and PACK EXPO 2014. Beginning with the Active and Intelligent Packaging World Congress, hosted by the Active and Intelligent Packaging Association, participants will learn new techniques in managing complex supply chains, avoiding waste and stamping out brand counterfeits. During Pharma EXPO, ISPE offers three tracks of educational sessions led by experts in the field to cover a variety of pharmaceutical manufacturing knowledge needs, including: Manufacturing Operations, Compliance Trends, and Pharmaceutical Packaging. One track will be hosted each day at Pharma EXPO. Each day will kick-off with a Keynote Session opened to all attendees. Participants have the opportunity to witness exciting operational advances within the manufacturing and pharmaceutical industry no matter what education track they choose.

Outside the Exhibit Hall in the foyer, the Pharma EXPO Innovation Stage features educational discussions on technology breakthroughs and live presentations of solutions available to assist biopharmaceuticals, nutraceuticals and medical device manufacturers meet today's industry challenges. The Innovation Stage offers not only knowledge, but convenience and will be up and running throughout each day. Up close and personal sessions will be happening in individual booths as well with exhibitors planning to provide in-booth educational demonstrations. Uncover innovative pharmaceutical manufacturing and packaging technology by getting to know the suppliers and new-to-market products to leverage benefits and justify buying decisions. Ask direct questions and hear what things are on your competitors "need to know" list to optimize and analyze your buying decisions.

Continued on page 94.

Pharmaceutical Engineering Announces Finalists of the Article of the Year Award

Pharmaceutical Engineering's "Article of the Year" recognizes the contribution of authors and articles are evaluated by a panel of volunteer reviewers according to a number of criteria including: applicability, timeliness, relevancy, quality of content, and presentation.

The finalists for each "Article of the Year" are chosen from the September/October issue of the previous year, through the July/August issue of the current year. The winner will be announced and recognized at ISPE's 2014 Annual Meeting, 12-15 October in Las Vegas, Nevada USA. The award program was established to express appreciation to all of the authors who submit their work for publication in *Pharmaceutical Engineering*.

We are pleased to announce the finalists of the 2013-2014 Roger F. Sherwood Article of the Year Award:

September/October 2013

A Review of Regulations and Developments in GMP and Supply Chain Integrity of Active Pharmaceutical Ingredients

by Sia Chong Hock, Katherine Loh Kai Xin, Vimal Sachdeva, and Chan Lai Wah

This article presents an overview of the current regulations and developments in good manufacturing practices and supply chain integrity of active pharmaceutical ingredients, and analyzes the challenges faced by regulatory authorities and industry.

November/December 2013

Steam Sterilization Principles

by Marcel Dion and Wayne Parker

This article presents how a good understanding of basic steam sterilization principles can help with avoiding most common mistakes made when using steam autoclaves.

January/February 2014

Evaluation of Controlled Manufacturing Environments following an Air Handling Unit Shutdown

by Catherine E. Anderson and Brian J. Lloyd, PhD

This article provides a methodology to evaluate the environmental impact of an air handling unit shutdown in a GMP manufacturing environment.

Roger F. Sherwood Article of the Year
PHARMACEUTICAL ENGINEERING

March/April 2014

Applying a Consistent, Compliant, and Practical Risk-Based Validation Process for Laboratory Systems

by Anil K. Rattan, PhD and Michael Rubacha

This article presents a consistent, compliant and practical risk-based validation process for laboratory systems.

May/June 2014

A Changing Landscape: Perspectives on Temperature Management for the Distribution of Non-Refrigerated Clinical Supplies Description

by Dr. Nicole Assfalg, Ted Bradley, Tim Brewer, Sébastien Delporte, Kristen DeVito, Bruce Guenter, and Patricia Thomas

This article discusses the shipment of room temperature products from several perspectives: the changing regulatory environment, risk assessment and mitigation, new technologies and budgetary pressures.

July/August 2014

Chemical and Media-Free Pretreatment for Biopharma RO – Electrolysis for Scale Precipitation and UV Dechlorination

by Nissan Cohen and Shlomo Sackstein

This article identifies the issues plaguing water systems with Reverse Osmosis (RO) and defines the proper criteria of operation.

To view the 2015 Editorial Calendar or submit an article, please visit www.pharmaceuticalengineering.org

ISPE's Pharma EXPO Conference Program

Continued from page 92.

Manufacturing Operations – Monday, 3 November

Keynote Speaker: Michael James, Site Leader, SAFC Biosciences, Division of Sigma Aldrich

Session 1: Managing the Design of a Single-Use Facility

Jeff Odum and Thomas Piombino, Integrated Project Services (IPS)

Single-use technology is modernizing traditional manufacturing platforms. Project managers are finding new opportunities through advanced technologies for modernizing design management. Industry professionals recognize an efficient shift requires fresh skillsets and an open-minded expertise to flourish within the next generation of manufacturing facilities. This session will center on several case studies exemplifying the application of modern management in conceptual development, operational analysis, procurement, qualification, and validation planning.

Session 2: Convergence: The Connected Machine

John Kowal, B&R Industrial Automation

This presentation will focus on a practical context of industrial automation and provide straightforward cost justification for machine connectivity and converging functionalities through Human Machine Interface (HMI) access.

Session 3: Automation Project Ishikawa

Chinmoy Roy, Independent Biopharmaceutical Consultant

Regulators recognize the industry's drive toward automated processing and are prepared to meet new challenges with inspectors specializing in modernized manufacturing systems. The speaker will share his personal experiences implementing large-scale automation projects in a non-technical presentation focused on working knowledge without technical complexities. Ishikawa diagrams will assist professionals recognize primary risk factors and secondary root-causes with specific strategies presented to overcome such challenges.

Session 4: ASTM E2500 Approach to Quality Risk Management – Part I

Steve Wisniewski, CAI and Dan Franklin, IPS

The presentation is an overview and introduction to application of an ASTM E2500 approach to the application of Quality Risk Management (QRM) for the Qualification Process (IQ/OQ) to meet the expectations of FDA 2011 Process Validation Guidance, Stage 2A. Two case studies will be discussed to supplement application knowledge and enhance the presentation of leveraging the QRM approach for specific strategies in commercial manufacturing process control.

Session 5: Application in Additive Manufacturing/3-D Printing

Carl Dekker, Met-L-Flo, Inc., Sheku Kamara, Milwaukee School of Engineering, and Terry Kreplin, Baxter Healthcare Corporation

This session is an introduction to additive manufacturing and 3D printing technologies. Discussions will be focused on requirements and application of various processes such as: FDM, SLA, and SLS. Attendees can expect to discover planning strategies as well as cost saving advantages of prototyping and mold making technologies.

Session 6: Chemical and Media-Free Pretreatment for Biopharma RO

Shlomo Sackstein, Biopharmax

This session will focus on identifying issues plaguing water systems with Reverse Osmosis (RO) and defining the proper criteria of operation. The RO membranes commonly have incorporated Polyamide (PA) as a main constituent which is sensitive to oxidation by free chlorine. The reliable and efficient operation of the PA RO membrane is the main focus of this session. A new system for pretreatment of pharmaceutical water systems will be presented that meets the prescribed design criteria with simplicity while providing effective results.

Session 7: EBR Deployment – Part I

Chuck Krumwiede, Malcom Associates

This session presents a simplified migration of Electronic Batch Records (EBR) through document awareness and analysis of actual work flow. Unlike defining user requirements and implementation based on functionality of the software, this strategy will mitigate quality or validation issues and assist with project schedule expectations. Leaning or redesigning the process eliminates redundancy, develops an interface strategy, and validates functional specifications. This simplified strategy identifies potential changes or additions in SOPs and creates an effective road map to implement EBR.

Session 8: ASTM E2500 Approach to Quality Risk Management – Part II

Steve Wisniewski, CAI and Dan Franklin, IPS

The presentation is an overview and introduction to application of an ASTM E2500 approach to the application of Quality Risk Management (QRM) for the Qualification Process (IQ/OQ) to meet the expectations of FDA 2011 Process Validation Guidance, Stage 2A. Two case studies will be discussed to supplement application knowledge and enhance the presentation of leveraging the QRM approach for specific strategies in commercial manufacturing process control.

ISPE's Pharma EXPO Conference Program

Continued.

Session 9: Excellence in Quality and Efficiency

Klaus Thornagel and Fabian Prehn, Fette Compacting

This session presents a report documenting three tablet presses on site. The current status of the processes states an OEE level of 28% (based on shift system). Attendees will learn the assessment of the results, including suggestions for improvement, leading to a demonstration of potential improvements to reach an OEE of 60% (based on shift system).

Session 10: Improving the Compounding Process

Mike Byron and Steve Welsch, Seiberling Associates

This session addresses the conversion of an API process to equal that of a susceptible CIP/SIP operation for sterile biotech processing.

Session 11: EBR Deployment – Part II

Chuck Krumwiede, Malcom Associates

This session presents a simplified migration of EBR through document awareness and analysis of actual work flow. Unlike defining user requirements and implementation based on functionality of the software, this strategy will mitigate quality or validation issues and assist with project schedule expectations. Leaning or redesigning the process eliminates redundancy, develops an interface strategy, and validates functional specifications. This simplified strategy identifies potential changes or additions in SOPs and creates an effective road map to implement EBR.

Compliance Trends – Tuesday, 4 November

Keynote Presentation: Thomas J. Christl, FDA (invited)

Session 12: New Options in Anti-Counterfeiting

Sharon Flank, InfraTrac

This session presents current trends in anti-counterfeiting techniques and vulnerabilities to strategies used in today's markets.

Session 13: Global Approach to Serialization

Dave DeJean, Systech

This session will provide information to implement best

Continued on page 96.

ISPE's Pharma EXPO Conference Program

Continued from page 95.

practices to drive value beyond compliance. Long-term strategies and tools to approach serialization challenges while providing a sense of company significance beyond meeting global compliance requirements will be presented.

Session 14: Eliminating 483s Based on Regulatory Observations

Jan Hickey, Frank Lueddeke, and Kenneth Montano, US Veterans Administration

This session will present training deficiencies ranked in the pharmaceutical industry top10 for FDA 483 observations for the last five years. Regulators and global standards require personnel to demonstrate expected qualifications, applicable competencies, and training effectiveness. A competency program will be presented that demonstrates an employee's knowledge base and ability to understand job tasks. This assessment meets regulatory requirements for competency and assures high standards for performance.

Session 15: Global Serialization Deployment

Marc Puich, Werum

This presentation will discuss the approach of using an independent Level 3 solution globally, how this can work in an environment with MES/EBR, and how it can be integrated into various Level 2 technologies.

René Schwarz, Seidenader Maschinenbau GmbH

A recap of application challenges when implementing level 2 technologies in a global deployment.

Session 16: Managing and Assuring Quality – Part I

Chris Watts, NNE Pharmaplan and Jean-Marie Geoffroy, Hospira

This session will review development and implementation of programs and systems to effectively and efficiently manage product quality. Tools for demonstrating process controls and managing knowledge transfer will be reviewed along with analysis of product and process development through and to routine production. Strategies to identify and bridging any operational gaps in an effective and timely manner will be presented.

Session 17: The Next Big Thing for Nutraceuticals

Rajiv Khatau, Lodaat Pharma

This session will cover the latest in nutraceuticals and new products that are backed by clinical trials and blind placebo controls. Attendees will hear what modern science can learn from complimentary alternative medical treatments and the reasons a 5,000 year old technique is not necessarily mutually exclusive with ICH/GMP guidelines. Finally, this presentation will analyze a unique manufacturing process which integrates pharmaceutical, nutraceutical, and traditional techniques to improve ingredient efficacy.

Par Almhem, ModWave

This session will illustrate some of the challenges, opportunities, and solutions when planning or building a new process line or facility for the production of nutraceuticals.

Session 18: Tools for Successful Serialization Implementation

Elizabeth Weaver and Christopher Washington, Clarke Engineering Services

This session will present innovative solutions for integrating new technology into existing manufacturing structures.

Session 19: Serialization: A Comprehensive Overview

Attilio Bellman, Adept Group LLC

This session will focus on those charged with the responsibility of understanding new serialization requirements and overseeing compliance timelines as they apply to their company. The various complexities and inter-dependencies of serialization and its broad impact to operations and the global supply chain will be presented.

Session 20: Managing and Assuring Quality – Part II

Chris Watts, NNE Pharmaplan and Jon Clark, USP

This session will review development and implementation of programs and systems to effectively and efficiently manage product quality. Tools for demonstrating process controls and managing knowledge transfer will be reviewed along with analysis of product and process development through and to routine production. Strategies to identify and bridging any operational gaps in an effective and timely manner will be presented.

Session 21: Using Technology to Meet FDA Serialization Requirements

Daniel Sanwald, Bosch

This session will present the influences of packaging materials, print and control systems in conjunction with IT systems, and current market demands. Counterfeit drugs pose a threat to both patients and the pharmaceutical industry. To make the pharmaceutical supply chain safer, worldwide laws regulating the serialization and traceability of pharmaceutical packages will become industry standard. Technical solutions and the influence of the technology in regard to serialization requirements and their impact on manufacturing will be presented.

ISPE's Pharma EXPO Conference Program

Continued.

Session 22: Drug Shortages – An ISPE Special Report

Rapid and transparent communication with health authorities is critical to managing a drug shortage situation whether a result from purposeful discontinuation or an unforeseen product interruption. This session will present recommendations from the ISPE Drug Shortages Prevention Plan for managing multiple internal activities required when facing a drug shortage situation.

Pharmaceutical Packaging – Wednesday, 5 November

Keynote Presentation: Dan Balan, Fastraqq, Inc.
Winning the New Innovation Gamp

Session 23: Identification Using 2D Barcode Technology

Gary Parish, Complete Inspection Systems

This presentation will provide a new methodology for incorporating both text and images in a 2D patented proprietary code, called HD barcode. Manufacturers and customers scan the code using a proprietary reading application to acquire comprehensive product details without the need for an Internet connection or reference to data base information. The code can be read using a variety of Smart Phones, off the shelf scanners, or CIS custom camera-based readers.

Session 24: Thermal Imaging Inspection and Detection on High-Speed Production Lines

Robert Hartwig, BTS International LLC

Current seal integrity testing requires either destructive sampling or space, speed, or cost prohibitive methods. This session offers a solution for continuous serialized control of individual packages. A real-time inspection system that is completely non-invasive and unlimited by line speed will be discussed.

Session 25: Package Component Specifications of Consent Decree

Kelley Frank, McNeil Consumer Healthcare

Lessons learned from the packaging perspective of McNeil Consumer Healthcare will provide valuable insights into

Continued on page 98.

ISPE's Pharma EXPO Conference Program

Continued from page 97.

the process of targeting quality standards to be addressed, conducting risk and gap assessments, and designing a plan involving four levels of internal and external audits. Several of the 75 new Quality Standards for McNeil include requirements for package development and specifications. Participate in discussion addressing container closure development, analytical and micro specifications, printed components, shipping qualification, packing validation, and transfer methods.

Session 26: Package Prototyping and Implementing 3D Printing

Michael Storey and Matt Pray, Beckatt Solutions and Jay Beversdorf, Stratasys

Most often, packing begins with the design and testing. This session will include presentations from two leading companies regarding how the application of additive manufacturing /3D printing can lead to packaging improvements. This session will provide practical examples of applying the technology.

Session 27: Transforming the Pharmaceutical Supply Chain

Dan Balan, Fastraqq Inc.

The pharmaceutical industry is characterized by multiple interlocking supply chains. The primary terrain is composed of drug makers, medical device manufacturers, and various supporting entities. In this power-packed presentation, attendees will learn the issues, challenges, conflicts, and objectives of all the stakeholders, how and where the extended supply chain breaks, where erosion of costs, time, and value occurs, the role of information at multiple nodes, and a clear, 10-point analytical framework to drive transformation of your own company.

Session 28: Flexible Isolator Filling Line

Brian Greven, Boehringer-Ingelheim

This presentation will cover the design, construction, and implementation of a new filling facility containing a clinical scale filling line installed inside within an isolator. The filling line has been designed to use one isolator to allow the syringe and vial filler to be interchanged in a unique modular design which reduces change and increases flexibility. The session will also go through the syringe and vial filling line design focusing on introducing ready to use components and filling lines operations.

Session 29: Maximizing Your Productivity and Protecting Vial Integrity

Roger Asselta, Genesis Packaging Technologies and Michael Earling, Garvey Corporation

This session will focus on the benefits of pressureless loop accumulation systems in a pharmaceutical production line. Studies in line analysis will be presented using the theory of constraints giving special consideration to how the machines will interact together. Pressureless loop accumulation systems not only protect the constraint, but also protect glass vials from damage. Common practices that tend to cause glass damage and critical stages where glass is most vulnerable will also be discussed. The information provided in the session assist attendees select material handling equipment that will increase production line efficiency and improve the overall product quality.

Session 30: The Evolution of Visual and Automated Inspection

Wes Maharas, Eli Lilly & Co.

Through a traceable understanding of inspection history and an appreciation to what is possible today, users and suppliers can work together in partnership, providing solutions to meet the needs of the future.

Christian Scherer, Seidenader Inspection Systems

Injectable container integrity problems led to many recalls in the USA. The US pharma industry is forced to take additional measures to increase quality by using different methods of leak detection. The presentation will compare different leak detection technologies.

Session 31: Improving Packaging Line Efficiency with Simulation

Philip Lyman and David Burgos, CRB

This session will present an example process model representing two packaging lines. The assumptions, input data, and a typical model configuration process will be described. Example results will be presented from a recently completed simulation study. This will illustrate how a process model can be used to increase throughput and improve efficiency. Attendees will understand the role of simulation in driving process improvements and lowering costs.

Session 32: Single-Use Final Fill Assembly Implementation

Sue Walker, EMD Millipore

Significant benefits for single use technologies have been well documented, but there are also risks associated with imple-

ISPE's Pharma EXPO Conference Program

Continued.

mentation which could include product loss and questions regarding sterility assurance or product safety. These risks are magnified in the filling operation due to the closeness of the final product in its final form. One step to mitigating this risk is through the design of the single use assembly. By creating a sound initial design with suppliers and end users design can be customized and fit for intended use. This presentation will address assembly design as well as the other practical considerations such as project timing, assembly manufacture and use, and supporting validation documentation.

Dena Flamm and Florian Kauder, Bosch
This session will address trends in aseptic filling, challenges in meeting these trends, considerations for implementation of single use, and how single use systems address's today's challenges.

Session 33: Predictive Condition Monitoring Using Machine Learning

Mike Brooks, Mtell
In this session, technology solutions will be explored providing prominent breakthroughs in reliability and maintenance improvement. The presentation will take a look at how the future of smart machines is unfolding and how today's machine learning technology is is performing "predictive" condition monitoring.

Conclusion

Pharma EXPO is sure to be a multi-media, diverse event providing new educational and product experiences to pharmaceutical industry professionals. ISPE has organized conferences to take place at the McCormick Center 3 to 5 November in Chicago during the entire PACK EXPO and Pharma EXPO packaging event. The conference has daily keynote speakers addressing emerging technology, new solutions, and applicable discussions on best practices to excite and inspire professionals to bring cutting-edge ideas back to their facilities. Be instrumental in advancing your company into the future of pharmaceutical manufacturing. Let ISPE's educational offerings help you!

Global Regulatory News

International

ICH

ICH M7 Guideline Reaches Step 4 of the ICH Process[1]

The ICH M7 Guideline on Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk reached Step 4 of the ICH Process in November 2013 and now enters the implementation period (Step 5).

The purpose of this new ICH Guideline is to offer guidance on analysis of Structure Activity Relationships (SARs) for genotoxicity. Furthermore, it is intended to resolve questions such as whether impurities with similar alerts that potentially have similar mechanism of action should not be combined in calculating a Threshold of Toxicological Concern (TTC) and whether the TTC may differ based on differences in the approved duration of use.

Asia/Pacific Rim

China

China's Vaccine Regulatory System Passes WHO Reassessment[2]

China's national regulatory authority for vaccines has met or passed all the standard requirements of the World Health Organization (WHO). The WHO stipulates only countries with an approved national vaccine regulatory system can receive WHO accreditation and have their vaccines added to the WHO international vaccine purchase list.

Countries which make it through an initial assessment undergo a second inspection after three years. China passed the initial WHO evaluation in March 2011, and the evaluation this year had even higher standards, according to the CFDA.

CFDA also signed a declaration of collaboration with the WHO to further build its capacities regarding the supervision of food safety and medical products.

CFDA Promulgates 120 Industry Standards for Medical Devices[3]

China Food and Drug Administration (CFDA) recently promulgated 120 recommended industry standards for medical devices in the form of No. 30 Announcement of 2014. This is the first batch of industry standards for medical devices promulgated since the implementation of the revised Regulations for the Supervision and Administration of Medical Devices on 1 June 2014. The promulgation of these standards will boost the supervision and management of medical devices and play a positive role in ensuring the safety and effectiveness of medical devices and promoting the sound development of medical device industry.

ISPE Provides Training on "PIC/S QS" for Inspection and Provincial Officers[4]

A training workshop on "PIC/S QS" for Department of Food and Drug Inspection and provincial officers was conducted at the ISPE China meeting. It was organized mainly by Cindy Chen of Roche Shanghai (a former Shanghai FDA senior inspector with assistance from Dr. Vee Revithi and Bob Tribe. The training was given by Helena Baiao, Dr. Revithi, and Bob Tribe.

Europe

European Union

European Medicines Agency Management Board Re-Elects Sir Kent Woods as Chair[5]

The European Medicines Agency's (EMA's) Management Board has re-elected Sir Kent Woods as its Chair for a three-year mandate. Sir Kent, the former Chief Executive of the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom, is one of the longest-serving members on the EMA Management Board. This is his second and final mandate, as the rules of procedure of the Board foresee a maximum of two terms.

Public Consultation Opens on European Medicines Agency's Draft Guide on Monitoring of Medical Literature[6]

The European Medicines Agency has released a draft guide on the monitoring of medical literature and the entry of relevant information into the EudraVigilance database for a two-month public consultation.

All stakeholders are invited to send comments on the draft guidance document to mlm@ema.europa.eu no later than 27 July 2014.

European Medicines Agency Recommends 14 Medicines for use in Animals[7]

Fourteen new veterinary medicines were recommended for marketing authorization by the European Medicines Agency's Committee for Medicinal Products for Veterinary Use (CVMP) in the first half of 2014. This figure exceeds the total number of medicines recommended for marketing authorization during the whole of the previ-

ous year (12). This increase is partly due to the record number of initial marketing-authorization applications submitted in 2013 that have now come to the stage of opinion during 2014, and partly due to the authorization of a related range of vaccines for dogs.

European Medicines Agency Recommends 39 Medicines for Human use for Marketing Authorization[8]

Thirty-nine medicines for human use were recommended for marketing authorization by the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) in the first half of 2014, compared with 44 in first half of 2013 and 33 in first half of 2012.

This figure includes a number of new innovative medicines with the potential to meet unmet medical needs, treat diseases for which no treatments were previously available or bring significant added benefit to patients over existing therapies. Among these medicines are the anticancer medicines Mekinist (trametinib) and Gazyvaro (obinutuzumab), the anti-inflammatory Entyvio (vedolizumab), the anti-infective Daklinza (daclatasvir), as well as Translarna (ataluren) and Sylvant (siltuximab), which are both intended for the treatment of rare conditions.

Management Board Delays Formal Adoption of EMA Publication of Clinical Trial Data Policy to October 2014[9]

The Management Board of the European Medicines Agency (EMA) has postponed formal adoption of the policy on publication of clinical trial data to its 2 October 2014 meeting. Further clarifications on wording and practical arrangements will be discussed by Board members, who have confirmed their general support to the overall aims and objectives of the policy, including the more user-friendly amendments proposed by EMA Executive Director Guido Rasi that would allow data to be downloaded, saved or printed for academic and non-commercial research purposes.

Public Consultation on the Preliminary Opinion "Guidance on the Determination of Potential Health Effects of Nanomaterials Used in Medical Devices"[10]

The European Commission and the Scientific Committee on Emerging Newly Identified Health Risks (SCENIHR) have launched a public consultation on the Preliminary opinion "Guid-

ance on the Determination of Potential Health Effects of Nanomaterials Used in Medical Devices."

The aim of the opinion is to address the use of nanomaterials in medical devices and to provide information for risk assessors regarding specific aspects that need to be considered in the safety evaluation of nanomaterials. In line with the Stakeholder Dialogue Procedures (Annex IV to the Rules of Procedures of the Scientific Committees), the SCENIHR is now seeking feedback from the scientific community and stakeholders on the risk assessment related to the "Guidance on the Determination of Potential Health Effects of Nanomaterials Used in Medical Devices."

All interested parties are invited to submit written comments on the preliminary opinion by 3 October 2014 in view of gathering specific comments, suggestions, explanations or contributions on the scientific basis of the opinion, as well as any other scientific information regarding the questions addressed, to enable Scientific Committees to focus on issues which need to be further investigated.

EMA Requiring Companies to Update, Complete and Improve Quality of Information on Authorized Medicines Submitted to the Agency[11]

The European Medicines Agency now requires marketing-authorization holders to update the information on authorized medicines that they have submitted in accordance with Article 57(2) of the 2010 pharmacovigilance legislation.

This includes completing previously submitted information with additional data elements included in the new data-submission format, bringing medicine information up–to-date, and checking that the quality of the information is in line with the updated reporting requirements. Companies need to complete this process by the end of 2014.

Iceland

Icelandic Medicines Agency Publishes Annual Report 2013[12]

The Yearly Report for 2013 is different from former reports. Instead of the traditional chapters from every Unit, it was decided to have a more informative section on some key responsibilities. The Annual Report is published on IMA's website along with a supplement containing tables and charts.

Ireland

New Name for the Irish Medicines Board[13]

On 1 July 2014, the Irish Medicines Board (IMB) changed its name to the Health Products Regulatory Authority (HPRA).

Denmark

Denmark Publishes Document on Good Laboratory Practice in Non-clinical Trials[14]

Clinical Trials Facilitation Group (CTFG) has prepared a document describing the requirements as to Good Laboratory Practice (GLP) in non-clinical trials. Applicants are reminded that all pivotal non-clinical studies conducted to support submissions for marketing authorization applications and clinical trial applications must be conducted in or inspected by a country that has implemented the OECD Mutual Acceptance of Data system.

Netherlands

Medicines Evaluation Board Annual Report 2013 Available[15]

The English version of the annual report 2013 by the Medicines Evaluation Board (MEB) is available for the first time it is available in full online. The theme of the report is: "50 Years of MEB and Beyond," the same as the theme for the anniversary year.

Through interviews with MEB employees, it illustrates how scientific participation and insights in 2013 have contributed to the execution of MEB tasks. An overview in figures and examples of challenges that the organization encountered in 2013 in executing its task and mission is included. The annual report contains many infographics, including ones about the number of newly authorized products for humans and animals, as well as stimulating quotes.

Poland

Joint Meeting with Polish, Lithuanian, and Korean Medicines Agencies and Pharmaceutical Manufacturers Forum[16]

On 30 June 2014, the Poland, Lithuania and South Korea Forum and the Polish-Lithuanian-Korean Regulators Forum, together with the National Drug Control Agency, organized the Polish Pharmaceuticals, Medical Devices and Biocides Forum. Their ultimate goal was to encourage the parties involved in the forum to engage in drug-agency cooperation, to share experiences, and to enable pharmaceutical companies to develop the sector and develop ties in different countries. Participants included the Polish Deputy Prime Minister and Minister of Economy and Janusz Piechociński, South Korea Food and Drug Safety Minister Chung Seung, South Korean ambassador Ji-in Hong, and representatives from institutions and organizations from other countries.

United Kingdom

MHRA Annual Report and Accounts 2013/14[17]

The Medicines and Healthcare Products Regulatory Agency Annual Report and Accounts 2013/14 were laid in Parliament on 21 July 2014. The Annual Report and Accounts give a selective overview of the events that have had most impact on the agency during the past year. This included the successful merger of the functions of the medicines and medical devices regulatory functions (MHRA) and Clinical Practice Research Datalink (CPRD) with the National Institute for Biological Standards and Control (NIBSC).

New Independent Expert Advisory Group to Be Created as the MHRA Responds to Stephenson Review, an Independent Review Into How the MHRA Can Improve Its Access to Clinical Advice and Engagement With the Clinical Community in Relation to Medical Devices[18]

The Medicines and Healthcare products Regulatory Agency announced that a new independent Devices Expert Advisory Committee (DEAC) will be established before April 2015 and will be responsible for providing independent expert advice that helps the MHRA regulate medical devices such as hips, breast implants and pacemakers. The new DEAC will replace the MHRA's current expert advisory group, the Committee on the Safety of Devices, which has been in operation for 13 years, and will help the agency have stronger links with the wider scientific community to facilitate access to specialist expertise.

North America

United States

Guidance for Industry Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products—Recommended Practices[19]

This draft guidance describes the Food and Drug Administration's current thinking on recommended practices for drug manufacturers and their representatives to follow if they choose to distribute to health care professionals or health care entities scientific or medical journal articles that discuss new risk information for approved prescription drugs marketed in the United States. The recommendations in this draft guidance are intended to address issues specific to the distribution of new information about risks associated with a drug that further characterizes risks identified in the approved labeling.

Guidance for Industry Drug Supply Chain Security Act Implementation: Identification of Suspect Product and Notification[20]

This guidance is intended to aid trading partners (manufacturers, repackagers, wholesale distributors, or dispensers) in identifying a suspect product and terminating notifications regarding illegitimate product. Beginning on 1 January 2015, a trading partner who determines that a product in its possession or control is an illegitimate product must notify the Food and Drug Administration and certain immediate trading partners under section 582 of the Federal Food, Drug, and Cosmetic Act, as added by the Drug Supply Chain Security Act. This guidance identifies specific scenarios that could significantly increase the risk of a suspect product entering the pharmaceutical distribution supply chain; provides recommendations on how trading partners can identify the product and determine whether the product is a suspect product as soon as practicable; and sets forth the process by which trading partners should notify FDA of illegitimate product and how they must terminate the notifications, in consultation with FDA.

Internet/Social Media Platforms: Correcting Independent Third-Party Misinformation About Prescription Drugs and Medical Devices[21]

This draft guidance is intended to describe FDA's current thinking about how manufacturers, packers, and distributors (firms) of prescription human and animal drugs (drugs) and medical devices for human use (devices) should respond to misinformation related to a firm's own FDA-approved or -cleared products when that information is created or disseminated by independent third parties on the Internet or through social media or other techno-

logical venues (Internet/social media), regardless of whether that misinformation appears on a firm's own forum or an independent third-party forum or website. This draft guidance responds to stakeholder requests for specific guidance regarding a firm's voluntary correction of misinformation when that misinformation is created or disseminated by an independent third party.

Internet/Social Media Platforms with Character Space Limitations— Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices[22]

This draft guidance is intended to describe FDA's current thinking on how manufacturers, packers, and distributors (firms) of prescription human and animal drugs (drugs) and medical devices for human use (devices) that choose to present benefit information should present both benefit and risk information within advertising and promotional labeling (sometimes collectively referred to in this guidance document as "promotion") of their FDA-regulated medical products on electronic/digital platforms that are associated with character space limitations—specifically on the Internet and through social media or other technological venues (Internet/social media). Examples of Internet/social media platforms with character space limitations include online microblog messaging (e.g., messages on Twitter or "tweets," which are currently limited to 140 character spaces per tweet) and online paid search (e.g., "sponsored links" on search engines such as Google and Yahoo, which have limited character spaces as well as other platform-imposed considerations). This draft guidance presents considerations to illustrate FDA's thinking on factors that are relevant to the communication of benefit and risk information on Internet/social media platforms with character space limitations.

A Curriculum for Medical Device Progress[23]

In 2011, CDRH embarked on an innovation initiative to help accelerate and reduce the cost of the development and regulatory evaluation of safe and innovative medical devices. Through that and other programs, they learned that the delivery of new therapies to patients can be accelerated if medical device innovators — including entrepreneurs and university students and faculty — understand FDA's regulatory processes. They then established the Medical Device Technology Innovation Partnership, and tasked it with developing an educational program that would explain FDA's standards and procedures for evaluating and approving or clearing medical devices.

The program, called the National Medical Device Curriculum, will provide students at academic institutions and science and technology innovators with the core information about the regulatory pathway to market. This includes an understanding of the expertise needed to design, test and clinically evaluate devices; identify the root causes of adverse events and device malfunctions; develop designs for devices with repetitive functions; and, navigate FDA's regulatory process.

FDA Enhances IT Service Delivery[24]

Since the establishment of the Office of Information Management and Technology seven months ago, the office has fundamentally changed how it supports the Agency's mission — primarily, to increase transparency, and better align functions and resources to achieve more efficient and improved customer support and services. To further these objectives, it has taken the following steps to help transform service to our internal and external stakeholders: reorganized the Office of Information Management; hired the first Chief Health Informatics Officer; requested that the CIO Council, FDA's IT governance board with representation across all of its Centers, focus on opportunities to consolidate IT solutions into capabilities that benefit the agency, eliminating duplication of efforts and creating possibilities for reinvestment; created an IT service cost-allocation model that will include a service catalog and identification of cost drivers for IT services; and restructured the IT portfolio to a service based portfolio.

Guidance for Industry: CGMP — Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act[25]

This interim guidance describes FDA's expectations regarding compliance with CGMP requirements for facilities that compound human drugs and register with FDA as outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Under section 501(a)(2)(B) of the FD&C Act, a drug is deemed to be adulterated if it is not produced in accordance with CGMP. FDA's regulations regarding CGMP requirements for the preparation of drug products have been established in 21 CFR parts 210 and 211.2 26 FDA intends to promulgate more specific CGMP regulations for outsourcing facilities. Until final regulations are promulgated, this guidance describes FDA's expectations regarding outsourcing facilities and the CGMP requirements in 21 CFR parts 210 and 211 during this interim period. This guidance is only applicable to drugs compounded in accordance with section 503B.

Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act[26]

This guidance shows FDA's intention with regard to enforcement of section 503A of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 353a) to regulate entities that compound drugs, now that section

503A has been amended by Congress to remove the advertising and solicitation revisions that were held unconstitutional by the U.S. Supreme Court in 2002. Several parts of section 503A require rulemaking and consultation with a Pharmacy Compounding Advisory Committee to implement. This guidance explains how the provisions will be applied pending those consultations and rulemaking. This guidance also describes some of the possible enforcement actions FDA can bring against individuals or firms that compound drugs in violation of the FD&C Act. This guidance does not apply to registered outsourcing facilities under section 503B of the FD&C Act. Guidance for outsourcing facilities will be issued separately.

US FDA Drafts Strategic Priorities for 2014 – 2018[27]

The FDA Strategic Priorities 2014–2018 document is divided into two main sections:

1. Cross-Cutting Strategic Priorities
2. Core Mission Goals and Objectives

FDA has identified five cross-cutting strategic priorities for the next four years:

1. Regulatory Science
2. Globalization
3. Safety and Quality
4. Smart Regulation
5. Stewardship

FDA's core mission goals and objectives are:

- Goal 1: Enhance Oversight of FDA-Regulated Products
- Goal 2: Improve and Safeguard Access to FDA-Regulated Products to Benefit Health
- Goal 3: Promote Better Informed Decisions about the Use of FDA-Regulated Products
- Goal 4: Strengthen Organizational Excellence and Accountability

FDA Issues Guidance to Support the Responsible Development of Nanotechnology Products[28]

Three final guidances and one draft guidance were issued by the FDA providing greater regulatory clarity for industry on the use of nanotechnology in FDA-regulated products. One final guidance addresses the agency's overall approach for all products that it regulates, while the two additional final guidances and the new draft guidance provide specific guidance for the areas of foods, cosmetics and food for animals, respectively.

References

1. ICH, http://www.ich.org/ichnews/newsroom/read/article/ich-m7-guideline-reaches-step-4-of-the-ich-process.htm.
2. China Food and Drug Administration, http://eng.sfda.gov.cn/WS03/CL0757/102474.html.
3. China Food and Drug Administration, http://eng.sfda.gov.cn/WS03/CL0757/102298.html.
4. ISPE, Meeting Minutes of Regulatory Compliance Committee/Regional Focus Group.
5. European Medicines Agency, http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/06/news_detail_002123.jsp&mid=WC0b01ac058004d5c1.
6. European Medicines Agency, http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/06/news_detail_002118.jsp&mid=WC0b01ac058004d5c1.
7. European Medicines Agency, http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/06/news_detail_002118.jsp&mid=WC0b01ac058004d5c1.
8. European Medicines Agency, http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/07/news_detail_002135.jsp&mid=WC0b01ac058004d5c1.
9. European Medicines Agency, http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/07/news_detail_002138.jsp&mid=WC0b01ac058004d5c1.
10. European Commission, http://ec.europa.eu/health/scientific_committees/consultations/public_consultations/scenihr_consultation_22_en.htm.
11. European Medicines Agency, http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/06/news_detail_002126.jsp&mid=WC0b01ac058004d5c1.
12. Icelandic Medicines Agency, http://www.ima.is/publications/news/nr/4525.
13. Irish Health Products Regulatory Authority, http://www.imb.ie/EN/News/New-Name-for-the-Irish-Medicines-Board-from-1-July-2014.aspx.
14. http://sundhedsstyrelsen.dk/en/news/2014/good-laboratory-practice-in-non-clinical-trials.
15. Dutch Medicines Evaluation Board, http://www.cbg-meb.nl/CBG/en/about/actueel/MEB_Annual_Report_2013_available/default.htm.
16. Lituanian State Drug Control Service. http://www.vvkt.lt/lit/Lenkijoje-vykobendras-Lenkijos-Lietuvos-ir-Korejos-vaistu-agenturu-ir-vaistu-gamintoju-forumas/1152.
17. British Medicines and Healthcare Products Regulatory Agency, http://www.mhra.gov.uk/Publications/Corporate/AnnualReports/CON437731.
18. British Medicines and Healthcare Products Regulatory Agency, http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON437435.
19. US Food and Drug Administration, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM400104.pdf?source=govdelivery&utm_medium=email&utm_source=govdelivery.
20. US Food and Drug Administration, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM400470.pdf.
21. US Food and Drug Administration, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM401079.pdf.
22. US Food and Drug Administration, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM401087.pdf.
23. US Food and Drug Administration, http://blogs.fda.gov/fdavoice/index.php/2014/07/a-curriculum-for-medical-device-progress/?source=govdelivery&utm_medium=email&utm_source=govdelivery#sthash.7g3Vgu6q.dpuf.
24. US Food and Drug Administration, http://blogs.fda.gov/fdavoice/index.php/2014/07/achieving-our-mission-through-enhanced-it-service-delivery/#sthash.695iOHSQ.dpuf.
25. US Food and Drug Administration, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM403496.pdf.
26. US Food and Drug Administration, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377052.pdf.
27. US Food and Drug Administration, http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM403191.pdf.
28. US Food and Drug Administration, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm402499.htm.

Architects, Engineers, Constructors

CRB, 7410 N.W. Tiffany Springs Pkwy., Ste. 100, Kansas City, MO 64153. (816) 880-9800. See our ad in this issue.

EI Associates, 8 Ridgedale Avenue, Cedar Knolls, NJ 07927. (973) 775-7777. See our ad in this issue.

Flad Architects, 644 Science Drive, Madison, WI 53711. (608) 238-2661. See our ad in this issue.

NNE Pharmaplan, Nybrovej 80, 2820 Gentofte, Denmark. +45 4444 7777. See our ad in this issue.

Pharmadule Morimatsu AB, DanvikCenter 28, SE – 13130 Nacka, Sweden. +46 (0)8 587 42 000. See our ad in this issue.

RPA Engineering, 2541 General Armistead Avenue, Suite 100, Norristown, PA 19403. (484) 681-9170. See our ad in this issue.

Stantec, 111 Grant Ave., Suite 201, Endicott, NY 13760. (607) 321-6148. See our ad this issue.

Cleanroom Products

Azbil Telstar Projects S.A., 1504 Grundy's Lane, Bristol, PA 19007 (215) 826-0770. See our ad in this issue.

Dust Collection Systems and Equipment

Camfil Air Pollution Control, 3505 S. Airport Dr., Jonesboro, AR 72401. (870) 933-8048. See our ad in this issue.

Electric Dry Steam Generators

Electropolishing

UltraClean Electropolish, Inc., 1814 Sunny Dr., Houston, TX 77093. (877) 823-7911. See our ad in this issue.

Facilities Design

Dagard Cleanroom, Route Du Stade, Boussac, France 23600. +33 555824027. See our ad in this issue.

Facility Engineering and Maintenance

Valsteam, Rua da Guia, 3105-467, Guia PBL, Portugal, +351 236 959 060. See our ad in this issue.

Filling and Packaging Equipment

Optima Packaging Group GmbH, Steinbeisweg 20, 74523 Schwaebisch Hall, Germany. +49 791 9495-0. See our ad in this issue.

HVAC – Filtration

AAF International, 9920 Corporate Campus Dr., Ste. 2200, Louisville, KY 40223. (502) 637-0320. See our ad in this issue.

Information Technology

COPA-DATA GmbH, Karolingerstrasse 7b, Salzburg, Austria 5020. +43 662 43 10 02-0. See our ad in this issue.

Instrumentation

Bürkert Fluid Control Systems, Christian-Bürkert-Strasse 13-17, D-74653 Ingelfingen, Germany. +49 (0)7940 10 0. See our ad in this issue.

Endress+Hauser, Kägenstrasse 2, 4153 Reinach, Switzerland. +41 61 715 75 75. See our ad in this issue.

Magnetrol, 705 Enterprise Street, Aurora, IL 60504. (800) 624-8765. See our ad in this issue.

Instrumentation (continued)

Particle Measuring Systems Inc., 5475 Airport Blvd., Boulder, CO 80301. (303) 443-7100. See our ad in this issue.

Process Engineering

Sartorius Stedim Biotech (USA), 5 Orville Dr., Suite 200, Bohemia, NY 11716. (800) 635-2906. See our ad in this issue.

Sturtevant, Inc., 348 Circuit St., Hanover, MA 02339. (781) 829-6501. See our ad in this issue.

Process Measurements and Control Systems

Finesse Solutions, LLC, 3501 Leonard Ct., Santa Clara, CA 95054. (408) 570-9000. See our ad in this issue.

Processing and Manufacturing

Freudenberg Process Seals GmbH & Co. KG, Lorsch Straße 13, D-69469, Weinheim. +49 (0) 6201 80 8919-64. See our ad in this issue.

Pumps

Alfa Laval, Inc., 5400 International Trade Dr., Richmond, VA 23231. (804) 222-5300. See our ad in this issue.

Fristam Pumps USA, 2410 Parview Rd., Middleton, WI 53562. (800) 841-5001. See our ad in this issue.

LEWA-Nikkiso America, 132 Hopping Brook Road, Holliston, MA 01746. (508)893-3218. See our ad in this issue.

Software Simulation and Processing Systems

Intelligen, Inc., 2326 Morse Ave., Scotch Plains, NJ 07076. (908) 654-0088. See our ad in this issue.

Tray Systems

Hurst Corporation, P.O. Box 737, Devon, PA 19333. (610) 687-2404. See our ad in this issue.

Validation Services

Azzur Group, LLC, 726 Fitzwatertown Rd., Ste. 6, Willow Grove, PA 19090. (215) 322-8322. See our ad in this issue.

Commissioning Agents, Inc., 652 N. Girls School Rd., Indianapolis, IN 46214. (317) 271-6082. See our ad in this issue.

ProPharma Group, Inc., 10975 Benson Drive., Ste. 330, Corporate Woods Bldg. 12, Overland Park, KS 66210. (913) 661-1662. See our ad in the issue.

Valves/Fittings/Hoses/Tubing

AGRU Kunststofftechnik GmbH, Ing.-Pesendorfer-Strasse 31, A-4540 Bad Hall, Austria. +43 7258 790. See our ad in this issue.

Water/Steam Systems

Biopharmax Ltd, 4 Hasadnaot Street, Herzlia, Israel 46728, +972-9-9716116. See our ad in this issue.

Water Treatment and Purification

ELETTRACQUA Srl, Via Adamoli 513, 16165 Genoa, Italy. +39 010 8300014. See our ad in this issue.

Mar Cor Purification, 160 Stedman Street, Lowell, MA 01851. (978) 453-9600. See our ad in this issue.

Swan Analytical USA, 225 Larkin Drive Unit 4, Wheeling, IL 60090. (847) 229-1290. See our ad in this issue.

Expect more

– from heating and cooling for the pharmaceutical industry

Finding true quality and value means looking beneath the surface. Our tubular heat exchangers and point of use cooler for the pharmaceutical industry have all the features and innovations that make world-class equipment. What's more, they're backed by an unmatched level of service and support to secure lifetime performance. The bottom line: maximum uptime with minimum cost of ownership. With the broadest range in the industry, Alfa Laval can always supply the right heat exchanger for your task.

Scan QR code and learn more.
alfalaval.com/biopharm

ALFA LAVAL