

PHARMACEUTICAL ENGINEERING®

The Official Magazine of ISPE

May-June 2017 | Volume 37, Number 3

Anthony Maddaluna A Matter of Well-Being

Corrosion Investigation
of Pharmaceutical Clean
Steam Systems

A Holistic Approach
to Product Control

Diabetes and the
Internet of Things

SPECIAL REPORT—CONTINUOUS MANUFACTURING

www.PharmaceuticalEngineering.org





“Imperfections? I like them in people. OPTIMA equipment I like to be perfect.”

Birgit Breitmoser

Technical draftswoman
(Machine Engineering)

A filling line from Optima, puts you on the safe side right from the beginning. Because we build complete lines that feature all the advantages: Perfect machine performance made to order, consistent documentation, an ideal software solution including a central contact who is passionate about looking after your smallest concerns. The one thing we refuse to deliver is imperfection. Because we have understood that only perfection translates into absolute customer satisfaction.

OPTIMA
EXCELLENCE IN PHARMA



OPTIMA pharma GmbH | Otto-Hahn-Straße 1 | 74523 Schwaebisch-Hall | Germany
Telefon +49 791 9495-0 | pharma@optima-packaging.com | www.optima-packaging.com/pharma

Member of

PACKAGING VALLEY
Germany

CHANGE IS OPPORTUNITY

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



crbusa.com



THE RELENTLESS PURSUIT OF SUCCESS. **YOURS**™

Biological
OSD
Fill/Finish
Vaccines
API's

Animal Health
Blood Fractionation
Oligonucleo/Peptides
Medical Devices
Nutraceuticals

Engineering | Architecture | Construction | Consulting

PAIRING KNOWLEDGE WITH IMAGINATION



Anna Maria di Giorgio
Editor in chief

*Imagination is more important than knowledge.
Knowledge is limited. Imagination encircles the world.*

—Albert Einstein¹

Albert Einstein's statement captures the innovative spirit that underlies the drive of the 2017 recipients of ISPE's Facility of the Year Awards (FOYA) Program, now in its fourteenth year. This annual program represents the heartbeat of our association, and the breath of its members.

This year's winners, highlighted in the attached 2017 FOYA Supplement, have demonstrated their skill at pairing knowledge with imagination to achieve excellence. They will be honored at the upcoming FOYA Banquet, which will be held during the ISPE/FDA/PQRI Quality Manufacturing Conference, 5–7 June 2017 in Bethesda, Maryland, US.

You can't really talk about manufacturing without invoking quality—that elusive attribute, equal parts quantitative and qualitative, whose whole is infinitely greater than the sum of its parts. It is both a goal and a fundamental characteristic of the medicines and devices we manufacture.

Quality manufacturing will keep drug shortages at bay and produce safe, effective medicines that are available and accessible to those who need them, wherever they are located. To achieve these lofty goals, industry must embrace a quality culture mindset, and adopt the tools needed to instill that mindset in employees and suppliers.

INSPIRATION, INNOVATION, INTELLIGENCE

In this issue, ISPE's Chair Mike Arnold looks at Industry 4.0 and what it augurs for manufacturing. He likens the next wave of changes to the mobile revolution of the 1990s, and draws parallels with our collective effort to make drugs more accessible and affordable to patients.

Our special report looks at continuous manufacturing from the perspective of the organizers and key presenters of ISPE's first Continuous Manufacturing conference in April 2016.

And our cover story pays tribute to an engineer's engineer, who believed in the power of his vision not just for himself, but for the pharmaceutical industry as well.

COUNT ON ISPE

We can't manufacture imagination. Excellence, on the other hand, we can: by training our students and Young Professionals to value it, our middle managers to foster it, and our executives to recognize and reward it. By embracing change and planning for it.

It won't be long before Industry 4.0 has reached beyond manufacturing to change the way patients access and use drugs, or for the pharmaceutical manufacturing industry to reimagine what it means to manufacture drugs and medical devices. And for the drugs themselves to be reinvented by the biopharmaceutical sector.

Industry professionals around the world are conceiving a new architecture of drug manufacturing. We at ISPE are here to support, reward, and recognize it. <>

Anna Maria di Giorgio
Editor in chief



Volume 37, Number 3
Published since 1980

Editor in chief: Anna Maria di Giorgio
Managing editor: Amy Loerch

Editorial Policy

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

Opinions expressed herein do not necessarily reflect the views of ISPE.

Pharmaceutical Engineering is published six times a year by ISPE.

ISPE Headquarters

7200 Wisconsin Ave., Suite 305
Bethesda, MD 20817 US
Tel: +1-301-364-9201
Fax: +1-240-204-6024

ISPE Operations and Training Center

600 N. Westshore Blvd., Suite 900
Tampa, Florida 33609 US
Telephone +1-813-960-2105
Fax +1-813-264-2816

ISSN 0273-8139

US Postmaster

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

Periodicals postage paid at Tampa, Florida, US, and additional post offices

Canada Postmaster

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

Canada Post mail agreement #40012899

All rights reserved. The contents of this publication may not be reproduced in any form without written permission from ISPE.

© 2016 International Society for Pharmaceutical Engineering



Pharmaceutical Engineering Committee

Chair: Roger Nosal, Pfizer Inc.
Peter Werner Christensen, Cook Medical
Nissan Cohen, Start-Up Business Development
Robert Del Ciello, Northshire Associates
Robert Dream, HDR Company LLC
Michelle Gonzalez
Wendy Haines, Mangan, Inc.
Willem Kools, EMD Millipore
George Millili, Genentech
James M. O'Brien, NAMA Industries
Jeff Odum, NNE Pharmaplan
Pietro Perrone, EMD Millipore Corporation
Sundermurti "Tony" Rao, Stantec Consulting Services Inc.
Brian E. Severson, Sage Products, LLC
Pravin Todkar, Dr. Reddy's Laboratories, Ltd.
Chris Smalley, Merck & Co, Inc.
Anders Vidstrup, NNIT A/S

—continued on page 4

1. Viereck, George Sylvester "What Life Means to Einstein." *Saturday Evening Post*, 26 October 1929, p. 117.



12

6 MESSAGE FROM THE CHAIR

What Is "Industry 4.0" and Are We Ready for It?

8 2017 CALENDAR

10 A YP STATE OF MIND

Lessons and Advice from My First Year as a Consulting Engineer

12 COVER

A Matter of Well-Being

17 PEOPLE + EVENTS

26th Annual Aseptic Conference
 Casa Life Sciences Technology Conference
 2017 ISPE Training: July–October
 ISPE GAMP® Guide: Records and Data Integrity
 ISPE Italy, Poised for Leadership
 Matthew Kennedy on Disruptive Innovation
 MECO Vice President Bob Gray Retires After 48 years
 Letter to the Editor



17

32 CAREER Q&A

Prepare. Prepare. Prepare. Repeat.

33 IN YOUR OPINION

Mastering the Art of Supply Chain Management

35 SPECIAL REPORT

Continuous Manufacturing



20

44 TECHNICAL

PRODUCTION STRATEGY

A Holistic Approach to Production Control from Industry 4.0 to Pharma 4.0

Prof. Dr. Christoph Herwig, Christian Wölbeling, and Thomas Zimmer, PhD

FACILITIES AND EQUIPMENT

Corrosion Investigation of Pharmaceutical Clean Steam Systems

Drew C. Coleman and Daryl L. Roll

Extractables and Leachables : Not the Same
Nassrine Lablack, Mathieu Tricot, and Malik Belattar

OPERATIONS MANAGEMENT

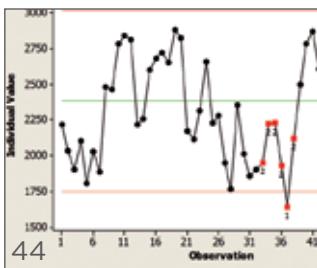
An Introduction to Predictive Maintenance
James Butler and Christopher Smalley

QUALITY SYSTEMS

Embrace Special Cause Variation During CPV
Tara Scherder



35



44

71 INDEX + CLASSIFIEDS

72 POSITION STATEMENT

Diabetes and the Internet of Things

—continued from page 2

Jonathan C. Walker, Tetrphase Pharmaceuticals
 Steven Wisniewski, Commissioning Agents, Inc.
 Christian Woelbeling, Werum IT Solutions
 Joerg Zimmermann, Vetter Pharma-Fertigung GmbH

Pharmaceutical Engineering Reviewers

Joanne Barrick, Eli Lilly & Co.
 Theodore Bradley
 Magali Busquet, Sanofi
 Jose Caraballo, Bayer Healthcare
 Chris Clark, TenTenTen Consulting
 John Connor, SP Scientific
 Mel Crichton
 Steven Davy, NNE Pharmaplan
 Thomas Dine, Dine Consultancy Ltd
 Martin Dueblin, 11 Eleven GmbH
 Paul Egee, IMA North America
 Massimo Eli, MSD Italy Srl / Merck Corp.
 Petter Gallon, Gallon Partners
 Andrew Gee, Boehringer-Ingelheim
 Norman Goldschmidt, Genesis Engineers, Inc.
 Adam Goldstein, Genentech, Inc.
 Diane Hagerty, Genentech, Inc.
 John Hannon, Commissioning Agents Inc.
 Nick Haycocks, Amgen
 Zuwei Jin, Emerson Process Management
 Vijay Kasireddy, Alexion Pharmaceuticals Inc.
 Nigel Lenegan, Energy & Carbon Reduction Solutions Ltd.
 John Lepore, Merck & Co Inc.
 Orlando Lopez
 Joseph Manfredi, GMP Systems Inc.
 Anthony Margetts
 Allan Marinelli, Quality Validation 360 Inc.
 Peter Marshall, AstraZeneca
 Jim McGlade, BHDP Architecture
 Paul Melamud, QPharma
 Donald R. Moore, Jr., Eli Lilly & Co.
 Lars Olsen, NNE Pharmaplan
 Marianne Oth, Eli Lilly & Co.
 Andre Petric, Kraemer US LLC
 James Robinson
 Gregory Ruklic
 Judith Samardelis, AstraZeneca
 Terry Seanard
 Stephen Sirabian, Glatt Air Techniques Inc
 Alan Solomon, Baxter Healthcare Corp.
 David Stokes, Convalido Consulting Limited
 Robert Sussman, SafeBridge Consultants, Inc.
 Andrzej Szarmanski, GMPP Services
 Richard Tessier, Novartis Pharmaceuticals Corp.
 Jenn Walsh, Bristol-Myers Squibb
 Bruce Williams, Williams Process Limited
 Sion Wyn, Conformity Ltd.

Special Report

Guest editors: Theodora Kourti, PhD, and Rapti Madurawe, PhD

Collaborators

Scott Fotheringham, PhD, and James Hale

Advertising and Sales

Neil Boylan: Global Advertising Sales, ISPE and *Pharmaceutical Engineering* magazine
 +1 415-827-2222
 nboylan@ispe.org

Photography

Page 21: Jennifer Hatley, JLH Photography

Stock Photography and Illustration: iStock

Art Direction and Graphic Design

Kaki Design Inc., www.kakidesigngraphique.com

Letters to the editor

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

FLUOR INNOVATES.

FLUOR[®]

www.fluor.com

© 2017 Fluor Corporation. ADOV181001

WHAT IS “INDUSTRY 4.0” AND ARE WE READY FOR IT?



Mike Arnold, Senior Director at Pfizer, and Chair of ISPE's 2016-2017 International Board, Member since 1998

“Industry 4.0” is the networking of information that became possible after several years of disruptive technological innovation. You may have heard related terms such as big data, real-time data, patient data, knowledge management, data analytics, and the Internet of Things—all of these contribute to real-time decision making in this new technological ecosystem.

As stated by Deloitte University Press, “The term Industry 4.0 encompasses a promise of a new industrial revolution—one that marries advanced manufacturing techniques with the Internet of Things to create a digital manufacturing enterprise that is not only interconnected, but communicates, analyzes, and uses information to drive further intelligent action back in the physical world.”¹

There are several industry initiatives in which ISPE has established a lead role that either contributes to or leverages the infrastructure within Industry 4.0: data integrity, drug shortages, quality metrics, quality culture, and facilities of the future, to name just a few.

With the “fourth major upheaval in manufacturing”² hovering overhead, the annual ISPE/PQRI/FDA Quality Manufacturing conference can't come too soon. Hot on the heels of the ISPE Conference on Quality Culture and Quality Metrics and the Data Integrity workshop, the conference promises to tackle the issues that are top of mind for industry leaders across the ranks.

So, what do you do in the face of change that seems foreign, unlike anything you have studied or experienced in your career? You embrace it, just as you have embraced new ideas, processes, and ways of working. You do what we (pharmaceutical professionals) do best: You share knowledge and collaborate. You embrace Industry 4.0.

ISPE members, and indeed all professionals in the pharmaceutical industry, pride themselves on being innovative and quality focused: We continually strive for excellence in an ever-changing world. The changes that are likely to occur as a result of Industry 4.0, therefore, should not come as a surprise, yet I believe they will be more demanding and influential than anything we've seen before. The pharmaceutical manufacturing landscape that is beginning to appear suggests a change similar to the one mobile technology brought about in telecommunications: one that affected not just industry, but lifestyle as well. The idea of an assistant—like Apple's Siri or Amazon's Alexa—to manage daily activities through a mobile device was innovative, and to some, perhaps at first, even heretical. Displaying a name or caller ID on a telephone screen was considered an invasion of

privacy. Once the conversations and debates subsided, however, adoption of both was global.

In the same way, Industry 4.0 technology offers the promise of personalized medicine, tattoos that deliver drugs, and printed 3-D medical devices.

At ISPE, our staff, members, and volunteers stand ready to offer training and professional insight through our conferences and workshops, and to help members enhance current skills and learn new ones. Our guidance documents provide in-depth knowledge that brings together the expertise of members around the world. The pages of this magazine will publish member articles about their experiences with quality culture, quality metrics, and innovative manufacturing opportunities. The annual FOYA supplement (which accompanies this issue) will showcase the best our members have to offer in areas of facility integration, process innovation, sustainability, project execution, and equipment innovation. We are well positioned to support our members as we progress enthusiastically into Industry 4.0.

On a related note, I hope to see you at the FOYA Banquet on 6 June, where we will recognize the achievements of five companies that have earned category awards, and three that have won honorable mentions. This year's winners are exceptional by design. Their winning submissions demonstrated excellence in strategic planning and a clear vision of success, both of which are essential for excellent execution of a mandate.

I invite you to join us as well at the 2017 Annual Meeting in San Diego, where we will announce the 2017 FOYA Overall Winner.

Enjoy your summer. <>

1. Deloitte University Press. “Industry 4.0.” <https://dupress.deloitte.com/dup-us-en/focus/industry-4-0.html>
2. Baur, Cornelius, and Dominik Wee. “Manufacturing's Next Act,” McKinsey & Company, June 2015. <http://www.mckinsey.com/business-functions/operations/our-insights/manufacturings-next-act>



"It proved so successful, we kept the trial unit. The chemist and I wouldn't let it leave. We were able to achieve results that we weren't able to with the old system."

- Therapeutic products manufacturer

PMI Powder Mixer

Modernize Your Mixing

Stop wasting your valuable time and money on outdated, oversized, or underperforming mixing systems. Fristam's Powder Mixer provides quick, high-performance blending and dispersion of wet and dry ingredients into a fluid stream. It produces repeatable results for syrups, inhalers, buffer and media solutions, medicated creams, lotions and shampoos.

The Powder Mixer's proven pump and blender system is fully CIP'able and easy to use and maintain. It is fully customizable and comes with the most comprehensive validation package in the industry.

No-risk trials available. See for yourself.



Fristam
PUMPS®

Engineered For Lasting Performance®

www.fristam.com/PM



2017 CALENDAR

MAY

- 1-3 Australasia Affiliate
Process Validation
Sydney, Australia
- 2-3 Thailand Affiliate
Cleanroom Testing & Certification
Bangkok, Thailand
- 3 Midwest Chapter
Technology & Education Day
Kansas City, Missouri
- San Francisco/Bay Area Chapter
YP Cinco De Mayo Networking Event
Walnut Creek, California
- 4 UK Affiliate
Data Integrity Solution Forum
Oxford, England
- 6-7 San Francisco/Bay Area Chapter
Relay Fundraiser Run
Calistoga, California
- 8 Boston Area Chapter
Spring Golf Tournament
Seekonk, Massachusetts
- Carolina-South Atlantic Chapter
CURLBIO Tour for YPs and Students
Durham, North Carolina
- 8-9 ISPE Pharmaceutical Serialization Workshops
Philadelphia, Pennsylvania
- 9-10 Indonesia Affiliate
Annual Conference
Jakarta, Indonesia
- 9-11 Poland Affiliate
Forum QC
Lodz, Poland
- 10 Delaware Valley Chapter
Statistics for CMC
King of Prussia, Pennsylvania
- Nordic Affiliate
Digitalizing Pharma Industry
YP Network Meeting
Lyngby, Denmark
- 10-11 DACH Affiliate
Containment 2025
Illertissen, Germany
- Netherlands Affiliate
Visit to New TEVA Facility
- San Francisco/Bay Area Chapter
Commuter Conference
San Francisco, California
- 12 Delaware Valley Chapter
Habitat for Humanity Volunteer
Opportunity
- Singapore Affiliate
Process Validation Workshop
Singapore
- 15 New Jersey Chapter
Golf Outing and Winery Tour
Neshanic Station, New Jersey

Please refer to ispe.org/globalcalendar for the most up-to-date event listing and information

- 16 Brazil Affiliate
Biotech Workshop
São Paulo, Brazil
- 17 Belgium Affiliate
Annual Meeting/Networking Event
Brussels, Belgium
- Boston Area Chapter Joint Event with
PDA New England
Validation
Woburn, Massachusetts
- 17-18 Brazil Affiliate
Training: Life Sciences Project Management
São Paulo, Brazil
- Poland Affiliate
YP & SME Process Control and MES Systems
Lodz, Poland
- 18 Greater Los Angeles Chapter
24th Annual Vendor Night Exhibit Show
San Pedro, California
- Nordic Affiliate
Future Pharmaceutical Manufacturing
Hørsholm, Denmark
- 18-19 Japan Affiliate
Annual Meeting
Toyama, Japan
- 19 Greater LA Chapter
Golf Tournament
- 22 Carolina-South Atlantic Chapter
Golf Tournament
Cary, North Carolina
- 22-24 Process Validation (T46)**
ISPE Training Institute
Tampa, Florida
- 25 Ireland Affiliate
Operational Excellence
Limerick, Ireland
- San Diego Chapter
Technical Meeting
San Diego, California
- 30-31 Brazil Affiliate
Regulatory Requirements Calibration Training
São Paulo, Brazil
- 31 Canada Affiliate
24th Annual Toronto Golf Tournament
Hornby, Ontario
- 7-8 Brazil Affiliate
Qualification and Management of TI Training
Sustainability and Cleanrooms Conference
São Paulo, Brazil
- 8 Belgium Affiliate
Young Professionals Event
GAMP/Automation
Huizingen, Belgium
- New Jersey and Delaware Valley Chapters
Joint Meeting
Expedited Shutdown Case Study
Lawrenceville, New Jersey
- 12-14 Basic GAMP 5, Annex 11/ Part 11 (T45)**
Indianapolis, Indiana
- 12-13 Water Generation (T04)**
ISPE Training Institute
Tampa, Florida
- 14 Boston Area Chapter
Brewing, Brettanomyces, and Biotech
Framingham, Massachusetts
- UK Affiliate
NW Summer Conference
Containment and Decontamination
Bracknell, England
- 14-15 Water Storage, Delivery and Qualification (T23)**
ISPE Training Institute
Tampa, Florida
- 15 Belgium Affiliate & A3P Event
Sterilization
Saintes
- France Affiliate
Conference Pharmacie et Procédés Continus
Lyon, France
- GAMP® Americas Regional Steering
Committee and Great Lakes Chapter
Data Integrity Forum
Indianapolis, Indiana
- San Francisco/Bay Area Chapter
Facility Tour
San Francisco, California
- 17 Rocky Mountain Chapter
Member Appreciation Party
Lafayette, Colorado
- 17-18 Singapore Affiliate
YGen Challenge
Singapore
- 19-20 GAMP 5 GxP Compliance (T21)**
ISPE Training Institute
Tampa, Florida
- 20 Brazil Affiliate
Management of Risks in Quality Systems
Training
São Paulo, Brazil
- 20-21 Philippines Affiliate
Seminar on Microbiology and Cleaning
Validation
Quezon City, Philippines
- 21 Greater Los Angeles Chapter
Joint Meeting with LCI Operations Excellence
Los Angeles, California
- Italy Affiliate
Serializzazione: Stato dell'Arte e Prospettive
Milan, Italy

JUNE

- 1-2 Turning QbD Into a Practical Reality (T43)**
ISPE Training Institute
Tampa, Florida
- 4 2017 ISPE Data Integrity Workshop
Crystal Gateway Marriott
Arlington, Virginia
- Nordic Affiliate
CoP Biotech Network Meeting
Lund, Sweden
- 5-7 2017 ISPE/FDA/PQRI Quality
Manufacturing Conference
Crystal Gateway Marriott
Arlington, Virginia
- 6 Belgium Affiliate
GAMP COP Benelux Event
Data Integrity
Zwijndrecht, Belgium

- 22 San Diego Chapter
Social Event
San Diego, California
- 27 Brazil Affiliate
Technologies in Insulators and RABS Training
São Paulo, Brazil
- 28 Boston Area Chapter
Summer Social and Volunteer Appreciation
Luau
Quincy, Massachusetts
- 28-29 DACH Affiliate
Workshop Pharma 4.0: Digitalisierung in
Pharma
Karlsruhe, Germany
- 29 France Affiliate
Atelier de Réflexion Annexe 15
Paris, France

JULY

- 3-5 Brazil Affiliate
GAMP 5 Training
São Paulo, Brazil
- 5-6 DACH Affiliate
Die Containment-Schnittstellen im
Productfluss
Illertissen, Germany
- 6 Singapore Affiliate
Introduction to Biosafety Workshop
Thirsty Thursday!
Singapore
- 10-12 HVAC (T14)
ISPE Training Institute
Tampa, Florida
- 11 Italy Affiliate
25th Anniversary Celebration
Milan, Italy
- 12 Greater Los Angeles Chapter
Technical Meeting
Los Angeles, California
- 13 San Diego Chapter
Therapeutic Thursday
San Diego, California
- 13-14 OSD (T10)
ISPE Training Institute
Tampa, Florida
- 19 Brazil Affiliate
Good Engineering Practice Day
São Paulo
- 19-20 Brazil Affiliate
Commissioning and Qualification Training
São Paulo, Brazil
- 20 San Francisco/Bay Area Chapter
Fun Day
Napa, California
- 27 Brazil Affiliate
Signatures & Electronic Registers Training
São Paulo, Brazil
- Pacific Northwest Chapter
Annual Golf Tournament
Mukilteo, Washington
- San Diego Chapter
Facility Tour or Technical Meeting
San Diego, California

TRAINING

High-Quality, In-Depth Skill Development



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

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



ISPE Training Institute

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

ISPE eLearning

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

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

**Industry's Trusted Source
of Knowledge**

eLearning

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

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

Onsite training

Bring customized ISPE training courses to your company.

Topics include:

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



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



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

MY FIRST YEAR AS A CONSULTING ENGINEER



Emily Welker is a recent graduate of the University of Georgia with a degree in biomedical engineering. She has been with CRB for over a year, working as a consulting Process Engineer focusing mainly on detailed design work and start-up activities. She has been a member of ISPE and the Carolina-South Atlantic Chapter since 2016.

Leaving the familiarity of a college environment, and beginning your career can be both exciting and intimidating. It's a time when you are expected to put your years of education into practical use. However, even with a degree in hand, you still face a huge learning curve when establishing yourself at the beginning of a career.

As I look back on my first year as a consulting engineer, there is a lot that I wish I had known prior to this venture. I experienced challenges, but also learned key methods and strategies that helped me find success.

ASK QUESTIONS

This is the number one tactic that catalyzes success! When I began my career as a process engineer, I worried that I was expected to know everything right off the bat, and that if I asked questions, people would perceive me as unqualified.

This is not the right mindset. Just as your professors didn't expect you to be an expert at the beginning of each semester, neither do your colleagues at the new job. However, it is your responsibility to learn. Do not be afraid to ask why things are done the way they are. Senior engineers know you are new to the field, and they are happy to help. I was pleasantly surprised to see how many people appreciated my inquisitive nature. Processes are always changing and advancing, so learning how to ask good questions is a skill that successful professionals should master.

LOOK FOR NEW ANSWERS

An old saying advises, "If it ain't broke, don't fix it," but engineers like to tinker and improve. Challenge others to think differently about a process or practice, and ask why things are done a certain way. If the answer is, "That's how we have always done it," maybe it's time to test the answer. Fortunately, as engineers, we work in an industry that welcomes the streamlining or improving of existing processes and sees the value a fresh set of eyes can bring to a project.

FIND YOUR NICHE

I discovered that this is essential. Search for an area or aspect of your job that you are passionate about, and become the best at it. Grab opportunities when they present themselves; don't wait for them to come to you. Constantly look for ways to improve upon current standards, and do your best to stand out.

BE ACCOUNTABLE

As a young engineer, it's easy to rely on more experienced individuals to own tasks rather than take ownership yourself, but remember that

AS A NEW ENGINEER, YOUR POTENTIAL FOR GROWTH AND SUCCESS IS UNLIMITED

failure or success depends on you. Work is not like college. You are not constantly given feedback or told what needs to be improved, so it is important that you hold yourself accountable for the work you do and the actions you take.

FIND A MENTOR

Find someone you admire and respect, and try to develop a relationship. I found this advice extremely valuable, and personally rewarding. Not only will you gain invaluable insight, but you will also establish a direct line of contact whenever you have questions—be they technical or general questions about your work environment. By establishing a mentor relationship, you are also showing your interest, and investing in becoming a valuable worker.

CHOOSE THE RIGHT CULTURE

Choose a company with a culture that fits your values and needs. Your attitude and happiness affects your quality of work, and culture plays a significant role in determining whether you enjoy coming into work every day. A culture of open communication and a genuine concern for your continued learning is vital in creating a positive work environment.

Finding success and happiness in your career does not have to be stressful. As a new engineer, your potential for growth and success is unlimited, especially when you interact with experienced colleagues. Personal success in the workplace is not reflected by a GPA or grade scaling, but by what you contribute as an individual. Taking charge of your career, and being proactive, offering new ideas, sharing fresh perspectives and adopting the right attitude can make all the difference during your first year in the workplace.

I hope this advice can help others just beginning their careers make a smooth and successful transition to the workplace. ◆

WE DON'T JUST **FIND** SOLUTIONS, WE **ENGINEER** THEM.



Inventive design is the best way to get an excellent result. This is why advanced engineering is the pillar of our process. We go beyond machine manufacturing: we focus on the development and production of performing solutions to provide tangible added value to customers looking for strong specificity combined to consistent quality. Our standard and robotic portfolio covers the following:

- Washing and decontaminating
- Depyrogenating
- Filling, closing and capping
- Isolators

interpack
PACKAGING AND PROCESSING
LEADING TRADE FAIR

4-10 May 2017 - Hall 16, Booth B10

 **Steriline**
ASEPTIC PROCESSING
PERFORMING SOLUTIONS

STERILINE Srl - Via Tentorio 30 - 22100 Como - Italy
www.steriline.it | [LinkedIn](#)

A MATTER OF WELL-BEING

A Profile of Anthony Maddaluna



Maintaining a robust supply of high-quality medicine is neither easy nor inexpensive. It depends on reliable processes, a secure supply chain, and a skilled workforce. Yet even when good medicines exist to treat an illness, delivery of these drugs could be disrupted by quality challenges, breaks in the supply of active pharmaceutical ingredients (APIs), or corporate decisions about where and when to allocate resources.

There are few who understand this as well as Anthony Maddaluna, whose career at Pfizer Inc. spanned four decades. He announced his retirement in December 2016, when he stepped down as executive vice president of Pfizer; his transition will be complete at the end of June.

THE WELL-BEING INDUSTRY

In 1975, when Maddaluna started his career as a chemical engineer with Pfizer in East St. Louis, Missouri, Wozniak and Jobs had just developed the Apple 1 prototype, the Vietnam War had ended, and disco, Rubik's Cubes, and pet rocks were the latest fads. He worked in the company's minerals, pigments, and metals division before holding engineering positions at a plant in Adams, Massachusetts. He moved into the pharmaceuticals division in 1983, and stayed.

Maddaluna spent time considering what his life's purpose was. It was founded on his desire to persistently make a profound positive difference, in both his personal and professional lives.

"Once I did that exercise, I realized that by being a part of the industry, I could make a real difference in people's lives. I enjoyed my work, found it fulfilling, and feel that I was able to contribute positively because what I was doing aligned and resonated with my purpose."

A well-functioning society depends on what Maddaluna likes to call "the well-being industry." "All of us at some point rely on the pharmaceutical industry," said Maddaluna. "If we're not doing our job, it means you're not getting to work, you're not getting to the grocery store, you're not driving your children to school. We are fundamental to society."

EARLY CAREER

Maddaluna received his BS in chemical engineering from Northeastern University, and earned an MBA in management and organization development from Southern Illinois University. He had co-op assignments at the US Environmental Protection Agency and Johnson & Johnson prior to joining Pfizer.

Despite his academic training as a chemical engineer—an education he recommends for the way it teaches problem-solving skills—he knew early on that he wanted to move into management, and work directly with people. This was reinforced when he learned a valuable lesson as a co-op student



MADDALUNA HELPED CHANGE THE WAY PFIZER APPROACHED ITS BASIC SUPPLY CHAIN ORGANIZATIONAL STRUCTURE

at Johnson & Johnson during his last plant rotation as a maintenance supervisor in the Band-Aid production area. Beyond the technology and the costing he learned, he saw that the key to a plant's success lay in its people and their relationships.

"I quickly discovered that the most important people were those who were packing Band-Aids by hand and operating the machines, because they were closest to the process and first to identify a problem," he remembered. "They were the real experts."

It showed him that quality and reliable supply stem from nurturing good relationships with people; this knowledge has had a lasting impact on the way he has worked ever since.

After East St. Louis and Adams, he moved on to what was supposed to be a three-month assignment at a plant in Terre Haute, Indiana, working on a plant start-up. It turned into an 11-year assignment during which he met his wife Brenda. Maddaluna became the plant manager in 1991. He was also instrumental in crafting the values of the plant, which focused on people, relationships, and internal culture. These became the basis for the values and vision that Pfizer Manufacturing developed in the 1990s.

In 1994, he moved to Puerto Rico as the general manager of Pfizer's fully integrated high-volume Barceloneta plant, which produced APIs as well as finished drug and packaged drug products, and shipped them to the United States. It was the company's largest factory, responsible for end-to-end production of products that helped grow the company—including Procardia XL, Norvasc, Diflucan, Zithromax, Zolof, and Viagra.

AN EVOLVING SUPPLY CHAIN

Maddaluna has seen incredible changes in the industry over the course of his career, perhaps nowhere greater than in the supply chain he has overseen since his time as general manager in Puerto Rico. Since the 1990s Pfizer has grown from three plants in the United States and a few in Europe to its current slate of more than 60 plants around the world, with the greatest footprint in the United States.

"We now have around 30,000 SKUs," he said. "Different products have different supply chains, but they are global, unlike in Puerto Rico, where everything was made from beginning to end."

The push for low-cost generic products like anti-infectives globalized manufacturing and drove the decision to outsource. "Virtually all of the anti-infective API manufacturing is done outside of the United States. That part of the industry was pushed out because the products became competitive, the supply chain became more complex, and regulatory requirements drove investments that could not be justified."

Difficulties of a complex supply chain included supplier issues, and the challenges of being efficient. Despite this, the fact that a lot of products are now derived from a combination of internal and external supply offers an opportunity for innovations in supply chain design.

MANAGING COMPLEX SUPPLY CHAINS

Maddaluna helped change the way Pfizer approached its basic supply chain organizational structure. Previously, some plants combined operational units with customer-facing roles. Over the last several years, Maddaluna oversaw the separation of the two. Within the customer interface, the company added a product portfolio management group with an end-to-end view of products.

"We've taken the supply chain piece and rolled it into Pfizer Global Supply where before it wasn't fully integrated," he explained. His team also enacted a corporate initiative to institute an enterprise resource planning system, which provides a common database for data pulled from different levels. Pfizer Global Supply does demand planning for all the businesses and has market representatives in 78 countries.

"If you look at the supply chain, there's planning the products, the demand planning, the scheduling, all the flow of information through the supply chain, and matching up this information with the flow of the manufacturing process," he said. This means managers are now able to take an end-to-end view of the entire supply chain process, and incorporate activities that used to be done at plants into the overall network. Control towers manage distribution from plants to its distribution centers. Now the company is creating designated supply hubs around the world instead of doing supply planning in all of its operations.

"We're aiming for a tracking system similar to what big retailers have," Maddaluna said. "Imagine the ultimate result: A doctor pulls a vaccine out of a fridge, and a smart unit sends a signal to us via the internet telling us we need to replace that product."

SERIALIZATION AND SECURITY

Currently, high-volume older products such as statins and blood pressure meds can be tracked with the systems that are in place. It's the low-volume personalized products such as gene therapies and biologics for which delivery must evolve.

Pfizer piloted radio-frequency identification (RFID) of products eight years ago in partnership with the US FDA and others, placing an RFID antenna on each bottle of Viagra. They found the cost and robustness problematic, however.

"The technology behind the RFID labels wasn't quite there," he said. "I'm not saying it won't come back, maybe [it will] with impregnated chips, but as an industry, we decided that the 2D bar code was the way we wanted to go."

This serialization is now either in place or being mandated by regulators around the world. Two examples are the US Drug Supply Chain Security Act, which requires the creation of an electronic system to identify and trace drugs to the level of individual packages,¹ and the European Union's Falsified Medicines Directive 2011/62/EU, which will require a track-and-trace system with 2D bar codes and anti-tampering devices on all products by February 2019.²

"With track and trace, every product is now serialized with a 2D bar code," he said. "We can match any unit with the case and the pallet it came from."

This move to serialization is fundamental, not only to maximize the efficiency of global supply chain logistics, but to prevent falsified medicines and theft. "With serialization in place, if a product comes out of the supply chain, it won't get back in," Maddaluna said. "This includes product that has been sent to a distributor or a pharmacy or has been stolen."

Other technology changes that will affect the supply chain include the block chain, which can act as a secure electronic ledger of a product's movements; the Internet of Things, which connects equipment across a firm's network of facilities and, probably, individual product packages; robots to automate production and delivery; drones used in delivery; and 3D printing.³ All of these increase security vulnerabilities.

SUPPLY CHAIN AND DRUG SHORTAGES

Drug shortages are an ongoing problem, particularly for generic injectables and a significant number of chemotherapeutics; there were 120 new occurrences in the first three quarters of 2016.⁴ ISPE conducted a survey of its membership and found that compliance, together with manufacturing and product quality issues, represented the single most important factor leading to drug shortages.⁵⁻⁶

The Pew Charitable Trusts and ISPE recently published findings from a survey of manufacturers of sterile injectables in the United States; the survey explored factors other than quality that lead to drug shortages.⁶ One of these factors is supply chain management, which includes inventory, demand planning, and forecasting to match predicted demand with projected inventory.

The study found that while companies use "business continuity elements" (e.g., safety stock of raw materials and finished goods, and more than one supplier for a product), they did not use them across their product lines. Instead, manufacturers based their contingency plans on the type of product, taking into account the investment required, the effect of shortages on patients, and the complexity of the manufacturing process.⁶

Maddaluna noted that there are products for which it's hard to make a good business case—antibiotics is one example. Historically, these were low-cost products; when many firms entered the market, businesses



“MOST TIMES THE BEST COURSE OF ACTION IS TO SLOW DOWN THE CONVERSATION, GET THE BIG PICTURE, AND REALLY UNDERSTAND BEFORE YOU DO ANYTHING.”

couldn't survive because world prices went down. "To address this issue in light of the fact there are only one or two players making APIs for a particular anti-infective outside the United States, you need to sustain an investment in equipment and process of these older products," he said.

He said Pfizer has been approached at times by the FDA, asking if it could make a product it no longer does. "We've brought products that are on the supply shortage list back because it's good for patients, and it's good for the business."

Maddaluna believes the public should be reminded of this kind of activity. "Think of all the advances we've made. I believe that cancer, for my kids' or grandkids' generation, will be treated like a chronic disease. It is this type of difference that ties back to my purpose."

A PASSION FOR EXCELLENCE

Maddaluna is most proud of the last job he had, setting up Pfizer Global Supply Transformation. It has seven work streams, including digital, supply chain, and organizational efficiency, each with its own metrics. The program is the embodiment of what he believes is required for an organization that aspires to become world class.

"'World class' to me means that we're doing things impeccably," he said. "It means our customer gets the product, that there are no shortages. It works because of where we're making it and how we're costing production." Maddaluna knows that "world class" is not easy to measure, despite the metrics, "but you know when you achieve it."

He is gratified with the transformation underway, and not only because it fosters a self-sustaining organization that will continue to help patients.

He believes he and his group draw upon a strong history of manufacturing expertise on which the Pfizer executive team and entire organization can build upon as new businesses are integrated into the company's supply chain network.

"This transformation effort is for our patients, certainly, and it's for the organization. But where it's most important, to me at least, is for our 30,000 colleagues. As you move towards becoming world class, it becomes easier for them to get their work done. They get it right the first time. You're more engaged, you feel ownership. That resonates if we show our colleagues the material results and how it affects them."

Although Kirsten Lund-Jurgensen succeeds Maddaluna, he will remain active in the pharmaceutical industry as a member of the board of directors of Albany Molecular Research Inc. He also represents Pfizer on the National Association of Manufacturers (NAM) and is a member of the NAM executive committee.

In addition, he has some parting advice for young leaders in his industry: "Most times the best course of action is to slow down the conversation, get the big picture, and really understand before you do anything. When you're younger, you're prone to action and want to solve problems."

Maddaluna leaves Pfizer knowing that his focus has always been on harmonizing the values of the company with his personal values, which revolve around his relationships with his colleagues and delivering helpful products to patients.

"No matter how automated you get, I don't think robots are going to

replace personal and corporate values," he said. "Our colleagues understanding the importance of what they do each and every day and the relationships within our network and industry are key to delivering to patients and to the well-being industry we are in." ♦

—Scott Fotheringham, PhD

References

1. US Food and Drug Administration. "Drug Supply Chain Security Act (DSCSA)." <http://www.fda.gov/Drugs/DrugSafety/DrugIntegrityandSupplyChainSecurity/DrugSupplyChainSecurityAct/default.htm>
2. European Commission. "Medicinal Products for Human Use." https://ec.europa.eu/health/human-use/falsified_medicines_en
3. PwC. Health Research Institute. "Top Health Industry Issues of 2017." <http://www.pwc.com/us/en/health-industries/top-health-industry-issues.html>
4. Fotheringham, S. "The Catastrophe of Drug Shortages in Pediatric Oncology." *Pharmaceutical Engineering* 37, no. 1 (January-February 2017): 33–34. <http://blog.ispe.org/drug-shortages-pediatric-oncology>
5. US Food and Drug Administration. Drug Shortages. "Frequently Asked Questions about Drug Shortages." <http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050796.htm#q2>
6. The Pew Charitable Trusts. "Drug Shortages." January 10, 2017. <http://www.pewtrusts.org/en/research-and-analysis/reports/2017/01/drug-shortages>



Overachiever.

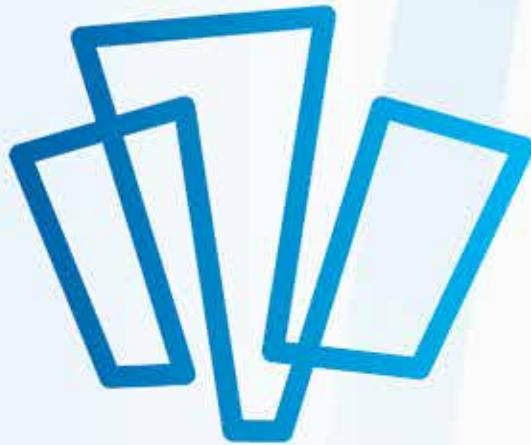
Analytical performance at pilot and production scale. And more.

LEWA EcoPrime® LPLC achieves accuracy and precision better than 99% with linear gradients from 5 to 95%. Add to that the versatility of our on-board buffer in-line dilution system, and you've got all the makings of a real chromatography wunderkind.

www.lewapt.com



LEWA
Creating Fluid Solutions



FOYA | 2018

Facility of the Year Awards

It's an exciting time in our industry. Thanks to your innovative designs, we're changing the way we work and deliver quality medicines to the people who need them.

Does your company or supplier have a new exciting project that could be a winner? If so, submit a proposal for the Facility of the Year awards. Learn more about the categories at:

www.FacilityOfTheYear.org/SubmitYourFacility

**SUBMIT YOUR
PROPOSAL TODAY.**

2018 Deadline: 20 November 2017

Innovation.
By Design.

www.FacilityOfTheYear.org





Also in this section

- 20 Casa 24th Annual Life Sciences Technology Conference
ISPE Training: July–October 2017
- 26 ISPE GAMP® Guide: Records and Data Integrity
- 28 ISPE Italy, Poised for Leadership
- 29 Matthew Kennedy on Disruptive Innovation
- 30 MECO Vice President Bob Gray Retires After 48 years
Letter to the Editor

26TH ANNUAL ASEPTIC CONFERENCE

Already in its 26th year, ISPE's annual Aseptic Conference continues to be the place to go to for the latest and greatest in barrier/isolation technology, small- and large scale aseptic manufacturing, and disposables. The conference presents fantastic opportunities to interact with industry leaders, experts, and regulatory agencies. This year's gathering, held at the Hyatt in Reston, Virginia, US, was no exception.

Keynote speeches, education tracks, and panel discussions attracted over 300 attendees from 17 countries in North America, Europe, Asia-Pacific, Africa, and the Middle East. The feedback from speakers, regulators, vendors, and participants was very positive: "Really nice conference and really nice people. I wish all conferences were that friendly!" was a typical remark.

Thomas Arista, Investigator and National Expert Pharmaceutical/Biotechnology, FDA, kicked off the conference with his entertaining and thought-provoking keynote: "What I Learned as Regulator through Years of Assessing Pharmaceutical Manufacturers." Attendees were able to directly see what is expected in audits and inspections.

The industry panel, held for the second straight year, was entitled "How to Reach the Point of Fill: Introduction Techniques into the Aseptic Core Area." A broad variety of technologies was discussed, ranging from e-Beam external decontamination of syringe tubs and rapid transfer chambers using H₂O₂ to traditional technologies like steam sterilization into

the core area. Panelists and audience members engaged in a lively discussion on the qualification and practical aspects of these methods.

The second keynote presentation was given by Frances Zipp, President and CEO, Lachman Consultant Services and ISPE Board member, on "Pew Charitable Trusts—ISPE Joint Research Project on Drug Shortages." This study has identified the various causes and interdependencies of drug shortages. As patients and health care providers struggle with the consequences, it was of utmost importance for the manufacturers of sterile dosage forms to see where the industry needs to improve to prevent these shortages.

The workshop sessions in which attendees and speakers interact, and work in small groups, remain very popular. Discussions centered around topics like "Leachables and Extractables Are Not the Same" (see page 60), "Glove Management," "Isolator Environmental Monitoring and Process Monitoring," "Pioneering Designs of Multi-Product Facilities to Optimize Capital Assets and Product Segrega-



Jörg Zimmermann, Vice President of Vetter Development Services, Vetter Pharma Fertigung GmbH & Co. KG, and member of the ISPE Board of Directors

tion," and "Flexible Combi-Filling Lines Using Disposable Components."

The pinnacle of the conference was, as always, the regulatory panel. FDA representatives answered questions from their respective departments' perspective. New this year was an anonymous poll with questions that the regulators asked the audience. Results were shown and discussed as part of the panel forum.

And of course, in addition to the packed education sessions, there was also enough time to network with peers and visit the exhibit hall. Preparations for next year's edition are already under way. Conference dates are 6–7 March 2018 at the same Hyatt in Reston. Watch this space for more information!

**THE PINNACLE
OF THE
CONFERENCE
WAS, AS
ALWAYS, THE
REGULATORY
PANEL**

FDA Panel Q&A

Disclaimer: This is an abridged, unofficial summary of FDA regulator's responses during a panel dialogue at a conference that has not been vetted by the agency. The responses below are an informal and brief synopsis of the panel's views, and do not represent official guidance or policy of the FDA.

In an effort to disseminate the information shared during the regulatory Q&A session, ISPE is making strides to publish the discussions. These comments are considered opinions only, and cannot be viewed as statements by the FDA; they do, however, provide insight into current directions and risk points to be considered when operating aseptic facilities.

An annual highlight of the ISPE Aseptic Conference is the regulatory discussion panel. Attendees can submit questions to the regulators in advance via the ISPE website; there is also an open microphone option for those brave enough to ask their questions directly.

This year's FDA representatives were:

- Thomas Arista, Consumer Safety Officer, FDA/ORA/ORO/DMPTO
- Rebecca Dombrowski, Facility Reviewer, FDA/CDER/OPQ
- Lynne Ensor, Division Director (Acting), FDA/CDER/OPQ/OPF/DMA
- Richard Friedman, Deputy Director, Science and Regulatory Policy, FDA/CDER/OC/OMQ
- Robert Sausville, Director, Div. Case Management, FDA/CBER/OMPT/OCBQ
- Jeremy Wally, CDR, PhD, US Public Health Service, Director, Regulatory Operations Officer, FDA/CBER/DMPQ

How do regulators review process design and what are the critical stage parameters that should be considered in designing an advanced aseptic process?

- On the review side, two internal groups (OPF's Division of Process Assessment and Division of Microbiology Assessment) determine whether a good manufacturing design concept will ensure that the products meet specifications.
- If applications are vague, then the agency asks the owner for clarification, but many times the owner cannot clarify.
- For advanced aseptic processing, a meeting

with the agency beforehand is highly recommended—especially if the approach is novel—to verify that the firm is on the right track.

- Our inspections and reviews are also interested in things like pressure differentials, transfer points, and other elements that can increase or decrease sterility assurance. On the inspection side, we evaluate procedures and controls as well as air patterns.
- During PAI [preapproval inspection], we will also refer back to the application to verify that you are doing what you said you would.

What are the agency's expectations on the management of glove holes? Does the agency think a robust inspection process is better than using a glove tester? Are the expectations for interventions performed during media fills different for isolator vs. a cleanroom line (i.e., do we need to simulate every intervention in an isolator media fill)?

- The two potential weak points of an isolator have always been 1) glove holes, and 2) transfer ports.
- Both glove testing and visual inspection are important. As you heard in the conference, automatic testers can identify circa 30–70 µm breaches, while the eye can detect breaches around 300 µm.
- Expectations are clear in the FDA's 2004 aseptic guidance: (<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf>). We expect you to look at gloves each day of use (preferably observing the gloves anytime you go into them), as well as via a routine automated/mechanical test.
- The whole point of preventive maintenance is to avoid making the difficult decision of what to do after finding holes in your gloves. So these expectations are basic to quality assurance. Prevention is better than detection. GMPs, quality engineering, and QA all say same thing: Build in quality by prevention, not by reaction.

Is there an expectation that interventions and operator proficiency in performing interventions are challenged in a media fill in the same frequency and manner as in a conventional filling line?

- Along with same aseptic technique, whether

you call it a media fill or a process simulation, the point is it's a simulation. The same aseptic technique is expected in an isolator as in a conventional cleanroom.

- Yes, you should simulate planned and unplanned interventions that can occur.
- Plan your media fill to represent what you will see and do in production. FDA always compares the simulation with production.
- If done right, you might be able to compress things (shifts) on isolators, so two shifts might be simulated in one semiannual media fill (instead of two). This is because isolators are not as vulnerable to shift changes as are less protected processes. This guidance, however, does not apply to RABS [restricted barrier access systems]. A RABS process should still be simulated using two media fills per shift for each line each year. See the FDA website for Q&A guidance.

What is considered an acceptable practice for the handling holes in RABS gloves? Is there a recommended frequency for challenging the gloves? Is a standalone qualitative visual inspection an acceptable practice? What frequency is expected for resterilizing gloves?

- Sterilize and install gloves for every batch or campaign. If you campaign (anything more than one day) any aspect of your RABS operation (e.g., hoppers), it should be only a few days, never as long as for an isolator.
- If you encounter problems, response is similar to the situation with isolator (see Q2).
- Like an isolator, gloves should be visually inspected and subjected to automated testing. If you are going to campaign, you should use an automated test during the campaign.
- For RABS, it is critical to disinfect installed gloves during a campaign (after open-door interventions) as well.
- We recommend automated testers. The same concepts apply for either RABS or isolators. The principle is that the doors/walls provide a barrier for sterility assurance; to the extent the barrier is compromised, then nonintegral gloves are a tough situation.
- Need an understanding how often gloves could be resterilized, how much wear and tear they could take. You must sterilize RABS gloves before a campaign. You must know the maximum n times that gloves may be sterilized.

- The other way to compromise a RABS is by opening a door. See discussion of open and closed RABS in FDA's Compliance Program Guidance Manual 7356.002a: "Sterile Drug Process Inspections."
- If you have holes, then you must investigate the deviation and address the problem. If you open the doors even to the Grade A/HEPA filtered air outside the RABS, then you must disinfect gloves frequently, same as a conventional cleanroom. You must use testers for RABS, same as for isolators.

How far are we from the world that requires isolators only for aseptic filling? For how long is there room for closed-door RABS with glove ports and rapid transfer ports? What are the expectations?

- We are all proponents of 1) isolators and 2) RABS. There are circumstances in which isolators may not be possible, so well-designed RABS are fine. The main point is GMP—we will hold you to that!
- There are opportunities where even those companies can move to next level. We are encountering the conventional equipment less and less. So such firms can move to glove boxes and RABS, rather than using the old paradigm of a hood or a processing line with limited barriers.
- More advancement in protective technologies should help shorten inspections! RABS/isolators are incentivized because you are likely to have more reliable performance and lower scrutiny. There is no set date to require isolators.
- For years many conventional cleanrooms have operated on the edge of failure, so overall, we do expect some sort of barrier technology for aseptic processing (e.g., glove boxes, RABS, isolators) in nearly all cases. See the cGMP documents on the FDA website.
- The bottom line is that advanced aseptic technology means at least RABS, and particularly RABS with no open-door interventions.
- It really depends upon circumstances of the product and production.

Do you support the use of RMM [rapid microbial monitoring] for EM inside an isolator? If used appropriately, do you feel it could have the potential to reduce the frequency and num-

ber of points during isolator EM [environmental monitoring]?

- The methods we know about for EM are continuous monitoring devices. We were a little puzzled in the question about less frequency, etc. You are going to get a lot of data points. It's difficult to answer except to say there are going to be fewer classic surface samples in an isolator just by design due to sampling at the end of a campaign, so you have some savings there. RMM includes lots of data and continuous monitoring that provides valuable insight into state of control of the process environment—that is great! Two different concepts are being conflated: RMM vs EM.
- Continuous monitoring with RMM can be a valuable method in conjunction with appropriate routine EM methods to detect any microbes that might be present.
- Re: the number of points—if they are the validated locations that are important to monitor, how do you conclude that you no longer need to sample those locations? Why? If you have justified valid locations for EM, then how could RMM eliminate the need for monitoring?

Should the room for an aseptic isolator for highly potent product (sterile powder handling, liquid, or freeze-dry processing) be pressurized positive or negative?

- This is tough, right? You don't have to use a negative pressure isolator—we have seen companies have difficulties with them. You could use a closed positive-pressure isolator, or you could use open positive pressure and control egress points. The operator could use PPE [personal protective equipment] (done classically before there was a negative-pressure isolator).
- Those options and others are all there before you go to negative-pressure isolator.
- If you decide a negative-pressure isolator then you would have an antechamber, surrounding room, and an airlock into the room.
- The bottom line: negative-pressure isolators should likely be your last choice, but they could work if other preferred options are not suitable.



Acknowledgments

Many thanks to the following members of the program committee for their invaluable help and collaboration: Hite Baker, Principal Process Engineer, DME; Michael Faia, Associate Director, Facilities and Engineering, AstraZeneca; Klaus Ullherr, Product Manager, Robert Bosch GmbH; and Matthew VonEsch, CPIP, Senior Director, Manufacturing and Facilities, Exelead BioPharma. ♦

*Jörg Zimmermann, Vice President
Vetter Pharma-Fertigung GmbH & Co.*

CASA LIFE SCIENCES TECHNOLOGY CONFERENCE

Amy Lineberry, CPIP, Validation Engineer II, Mangan Biopharm, and CaSA Chapter Tech Conference Chair



The ISPE Carolina–South Atlantic Chapter celebrated its twenty-fifth anniversary in style, hosting its Life Sciences Technology Conference at the Raleigh Convention Center in downtown Raleigh, North Carolina, on 14 March 2017. The event drew a record 1,000 attendees and almost 200 exhibitors, including eight manufacturing companies—Merck, Novo Nordisk, FujiFilm Diosynth, Seqirus, Biogen, BioTechnique, Catalent Pharma Solutions, and Pfizer—that were highlighted in the CaSA Pavilion with the corporate sponsors.

The annual conference, which has become a premier life sciences education event for the Southeastern United States, featured presentations by top industry speakers on topics such as serialization, information management, cleaning, engineering, and project management. The Investigational Products Community of Practice hosted an education track, as did the new Women in Pharma Initiative and the NC BioProcessing Development Group. New for 2017 was a breakfast for honoring the Chapter's Past Presidents, who were also recognized during the keynote session.

Each year the conference also hosts a track for the students and Young Professionals to provide them with career development advice and increase their knowledge of the industry. Students and YPs also help by volunteering at the conference. The undergraduate student poster winner was Morgan Caudill from North Carolina State University; graduate student poster winner was Yen-Cheng Chen from Georgia Tech. Both will advance to the ISPE International Student Poster Competition at the ISPE Annual Meeting in San Diego, California, 29 October–1 November 2017. The Jane Brown Scholarship Award winner was Amanda Kaufman from North Carolina State University.

As in years past, the conference partnered with a local nonprofit for fund-raising. This year's honoree was The V Foundation for Cancer Research. Founded in 1993 by basketball coach and broadcaster Jim Valvano, the organization has donated over \$170 million in cancer research grants nationwide. Conference raffle ticket and silent auction purchases raised nearly \$6,000 for the foundation.

The conference wrapped up with a wonderful networking reception in the ballroom lobby—a

great time to catch up with colleagues and co-workers—followed by the ever-popular “casino night.”

I want to thank all the conference speakers for sharing their insights and knowledge, the dedicated volunteers on the Technology Conference Committee for helping the conference grow and succeed, and the ISPE CaSA Executive Board and FirstPoint Management Resources for their guidance and help. Most of all, I want to extend very special thanks to our sponsors for the support they give to ISPE and our Chapter each year. Without them, this conference would not happen.

The twenty-fifth Annual Life Sciences Technology Conference is set for 13 March 2018. Pre-registration for exhibit space is available until 15 August 2017. Visit ispe-casa.org for more information. ♦

2017 ISPE TRAINING JULY–OCTOBER

EUROPE

Cleaning Validation (T17)

25–26 September

Amsterdam, Netherlands

Can you establish, manage, and maintain a scientifically sound cleaning validation program?

With the US FDA's risk-based regulatory initiatives focusing new attention on the risks of cross-contamination, understanding lifecycle management techniques for an effective cleaning validation program is paramount. *Cleaning Validation* course topics include: a risk-based approach to cleaning development and verification; risk analysis, control, review, and communication; procedures and evaluation tools including FMEA/FEMCA; master planning; PAT; periodic assessment and monitoring; selection of analytical and sampling methods; determination of residues to be targeted and appropriate limits in various pharmaceutical and biotechnology processes; and establishment of scientific rationales acceptable to regulatory inspectors. For mature cleaning validation programs, concepts such as understanding process control, capability, learning to effectively self-audit a



cleaning validation program and documentation will be essential takeaways.

Biotechnology Manufacturing Facility Design (T31)

25–26 September

Amsterdam, Netherlands

Do you know the regulatory requirements for biopharmaceutical facilities?

Using case studies and exercises the *Applying the Biopharmaceutical Manufacturing Facilities Baseline® Guide Principles* course in facility design provides an overview of the concepts utilized in the development and renovation of sound designs for facilities that manufacture biopharmaceutical products. The course includes a review of facility design and regulatory issues important in the US and Europe that involve industry trends and changing regulatory policy. Participants will discuss current case studies on a wide array of facility topics, and complete class exercises that involve developing facility scope of work and deliverables to meet corporate economic goals and regulatory requirements.

Basic GAMP 5, Annex 11/ Part 11 (T45) – Updated 25–27 September

Amsterdam, Netherlands

Are you leveraging a risk-based approach when validating your GxP computerized systems?

The *Basic Principles of Computerized Systems Compliance using GAMP® 5, Including Revised Annex 11 and Part 11* course explores tried, tested, and internationally recognized methods and provides a pragmatic and effective framework for achieving computerized systems that are fit for intended use and meet current regulatory requirements. Course updates include: applying the GAMP categories in practice; infrastructure qualification; cloud service providers; maintaining compliance during the operational phase; legacy systems; testing; how to meet FDA 21 CFR Part 11 requirements in practical and effective way, and European and international requirements for electronic records and signatures.

Sterile Pharmaceutical Facilities (T12)

27–28 September

Amsterdam, Netherlands

Do you know the key requirements and GMPs for sterile manufacturing facilities?

Through lectures and group exercises the *Sterile Product Manufacturing Facilities: Applying the ISPE Baseline® Guide and FDA Guidance*

principles to Design and Operation course will review regulatory philosophy; aseptic process and equipment considerations, aseptic clean room design and operation, differential pressure requirements, airlocks, basic utility system monitoring, US and European HVAC considerations, C&Q issues, and a brief introduction to barrier isolation technology. An exercise in the layout of an aseptic filling facility will be used to demonstrate how to use process flow diagrams and an accommodation schedule to thoroughly define facility requirements before advancing to the floor plan layout stage. Additional topics include the use of RABS and isolator systems, plus methods for contamination control.

GAMP 5 Process Control (T21)

27–28 September

Amsterdam, Netherlands

Are your process control systems fit for use?

Using a lifecycle approach for the development and management of process control systems, *A Risk-Based Approach to GxP Process Control Systems—Applying the GAMP® Good Practice Guide: A Risk-Based Approach to GxP Process Control Systems (2nd Edition)* course demonstrates how the principles and concepts of GAMP 5 may be practically applied. The course covers both regulated company and supplier quality management systems and the full system lifecycle from concept to retirement. You will learn how appropriate QRM and specification and verification activities should be an integral part of the normal system lifecycle and how to leverage supplier documentation and activities to avoid unnecessary duplication, cost and waste.

C&Q (T40)

27–28 September

Amsterdam, Netherlands

Is your equipment and facility “fit for use” as defined by current global regulatory authorities?

Guidance on the transition of an organization's approach to C&Q to one that incorporates a science and risk-based approach is the basis for our *Science and Risk-Based Commissioning and Qualification—Applying the ISPE Good Practice Guide: Applied Risk Management for Commissioning and Qualification* training course. A detailed review of the principles and activities that constitute an efficient and acceptable approach to demonstrating facility and equipment fitness, improving the ability to meet documented process requirements, controlling risks

Gericke

CONTINUOUS MANUFACTURING OF ORAL SOLID DOSAGES BY GERICKE



Gericke Continuous Feeding-Mixing-Modules supply mixtures from 5 to 1000 kg/h for:

- Direct compression of API and up to 5 excipients
- Dry and Wet Granulation
- Hot Melt Extrusion
- Sachet and Capsule Filling

Our Continuous Manufacturing Modules combine high precision loss in weight feeders with scientific designed compact mixer and integrated PAT solutions.

Switzerland:
T +41 44 871 36 36
gericke.ch@gericke.net

Gericke USA, Inc.:
T +1 855 888 0088
gericke.us@gericke.net

gericke.net

within the manufacturing process, producing high quality products and consistent operation to meet product user requirements will be explored. Additional emphasis will be placed on a review of ICH documents Q8 (R2), Q9, and Q10, and ASTM E2500.

UNITED STATES

HVAC (T14) – Updated

10–12 July

ISPE Training Institute

Tampa, Florida

Are you able to resolve common HVAC issues for bio, bulk, laboratory, packaging, OSD, sterile, and warehousing operations?

The HVAC course will include risk-focused discussions about change rate frequency, facility classification, cross-contamination, system, or individual component qualifying; common issues and problems in the operation of a facility; and maintaining readiness for cGMP inspection. Course content has been updated to include an update of changes and common interpretations for ISO 14644-1 and 2. Topics include control system alarm management, common system construction deficiencies, cGMP documentation, how to maintain an “inspection-ready” state, frequency of testing and balancing, airflow visualization, and air change rate reduction. A thorough review of global cGMP regulations and their common interpretations and how they can apply to your facility.

OSD (T10) – Updated

13–14 July

ISPE Training Institute

Tampa, Florida

Do you understand the latest issues associated with oral solid dosage forms?

The newly updated *OSD: Operations, Quality, Equipment and Technology* course, which utilizes the *ISPE Baseline® Guide: Oral Solid Dosage Forms, 3rd Edition*, examines current technology, provides scenario-based exercises for system troubleshooting and investigational events for process deviations, discusses quality management and GMP inspection preparation, and provides guidance on advanced asset life-cycle management strategy. Using a process and production video simulation for unit ops, including mixing, blending, drying, sizing, tabletting, encapsulating, and coating provides a

visual demonstration of current manufacturing and engineering practices. The simulation will vividly present real time experiences for identifying and analyzing the problem, identify the root cause, and present solutions.

Clean in Place (T03)

7–8 August

ISPE Training Institute

Tampa, Florida

Do you have the tools to design, build, and implement a cleaning process and identify cleaning solutions to complex cleaning processes?

The *Clean in Place Fundamentals* course will provide an overview of clean-in-place (CIP) systems including design, integration, and selection of cleaning chemicals. Participants will discuss engineering concepts, principles, and integration of CIP systems, clean-out-of-place (COP) systems, or immersion parts washers. While there will be some discussion of manual cleaning practices, cleaning principles will be primarily introduced as they relate to the dynamics of CIP and COP technologies, with an emphasis on selecting the right cleaning chemistries for specific soil residues. Additional topics include a CIP technology review, including examples of various pharmaceutical processes that illustrate how CIP technologies and hygienic design can improve cleanability. Other topics include CIP spray device selection criteria and dynamics of integrating CIP process piping into a pharmaceutical process. A dynamic hands-on workshop will allow participants to work in groups to design, build, and implement a cleaning process for a pharmaceutical application.

C&Q: Applied Risk Management (T40)

7–8 September

ISPE Training Institute

Tampa, Florida

Is your equipment and facility “fit for use” as defined by current global regulatory authorities?

Guidance on the transition of an organization’s approach to one that incorporates a science and risk-based approach is the basis for our *Science- and Risk-Based Commissioning and Qualification—Applying the ISPE Good Practice Guide: Applied Risk Management for Commissioning and Qualification* training course. A detailed review of the principles and activities that constitute an efficient and acceptable approach to demonstrating facility and equipment fitness, improving the ability to meet

documented process requirements, controlling risks within the manufacturing process, producing high quality products and consistent operation to meet product user requirements will be explored. Additional emphasis will be placed on a review of ICH documents Q8 (R2), Q9, and Q10, and ASTM E2500.

GAMP® Data Integrity (T50) – Updated

11–13 September

ISPE Training Institute

Tampa, Florida

Can your data integrity process stand up to regulatory scrutiny?

Data integrity is currently one of the highest cited areas in regulatory observations. It’s also a topic of great interest both within the industry and for regulatory agencies that are reevaluating their industry guidance and enforcement strategies. The *GAMP Approach to Data Integrity, Electronic Records and Signatures, and Operation of GxP Computerized Systems* utilizes the newly published *ISPE GAMP Guide: Records and Data Integrity*, covers data integrity, electronic records and signatures, and the compliant operation of GxP Computerized Systems to provide the tools and techniques to implement proper controls for data to ensure the integrity and validity of information throughout the data lifecycle.

Process Validation in Biotechnology Manufacturing (T32)

14–15 September

ISPE Training Institute

Tampa, Florida

Can you successfully develop and validate your bioprocess?

The inherent complexity and uncertainty of biotechnology makes developing and validating bioprocesses for manufacturing proteins and biopharmaceuticals very difficult. Understanding and using the US FDA’s Process Validation Guideline is critical to establishing and maintaining control of complex processes, as well as achieving regulatory approval of new products. The *Process Validation in Biotechnology Manufacturing* course is designed to provide a clear understanding of the regulatory, scientific, and engineering tools required to successfully develop and validate bioprocesses. Course topics includes a long list of activities required to validate biopharmaceutical processes, a comprehensive strategy to process validation, a review of important biotechnology manufacturing pro-

cesses, and the regulatory requirements for their validation. In addition to classroom lectures, participants will take part in several interactive exercises, solve group problems, and participate in class discussions to understand the underlying principles behind process validation.

QRM (T42) – Updated

18–20 September

ISPE Training Institute
Tampa, Florida

Do you have the tools to manage risk?

Through interactive workshops, this course will help you apply the key principles of QRM programs that need to include quality system elements (ICH Q10) within the product/system lifecycle. Topics include focusing on drug development; method development and transfers; validations, deviations, investigations and manufacturing; utilizing tools like FMEA, fishbone analysis, and preliminary hazard analysis (PHA) for an understanding of the philosophy and application of a holistic QRM process through the development of a QRM plan; developing and implementing a risk decision tree and the appropriate use of risk assessment tools; applying risk management methodologies through design and verification phases; the importance, format, and maintenance of a risk dashboard and a summary of the US/EU/CFDA and WHO regulatory requirements, citations, and expectations that may influence the implementation.

Process Validation (T46) – Updated

25–27 September

ISPE Training Institute
Tampa, Florida

Do you need a practical understanding of PV principles and expectations in the US and EU?

The *Practical Implementation of Process Validation Lifecycle Approach* three-day course includes a blend of presentation of concepts and details, followed by related practice application scenarios/exercises that will define the requirements for preparation, planning, and execution of validation/process validation and how to maintain a state of control. Course content has been expanded to include a discussion of the number of lots for several product families and dosages, and a detailed review for setting up a CVP program correctly. It explores the three stages of the validation product lifecycle, including process design, equipment and utility qualification, establishing and implementing process performance qualification (United States) or Process Validation (Europe) requirements, and putting in place an ongoing/continued process verification program.

Overview Biotechnology Manufacturing Processes Training Course (T24) – Updated

2–3 October

ISPE Training Institute
Tampa, Florida

Can you effectively evaluate and compare various process alternatives for manufacturing biotech products?

An *Overview of Biopharmaceutical Manufacturing Processes* covers the principles and unique challenges of biotech manufacturing pro-

GEMÜ®

VALVES, MEASUREMENT AND
CONTROL SYSTEMS

Safe and automation-capable: GEMÜ SUMONDO® Single-Use Diaphragm Valve



The first diaphragm valve for precise control of single-use plant:

- Proven, reliable actuator design
- Mechanically stable and gamma-sterilisable valve body material
- Hermetic sealing between valve body and actuator



www.gemu-group.com

cesses. Topics include: identifying important operating parameters for each unit operation and how they impact process performance, parameters for process validation, critical factors for developing a viable commercial manufacturing process, process/facility relationships, options for single-use technologies, cell culture and fermentation, harvest and recovery, viral removal and inactivation, tangential flow filtration, centrifugation, size exclusion, and adsorptive chromatography. Additional content will review current regulatory guidance affecting process development and execution, compare various process aspects of upstream and downstream operation, technology transfer, and trends and future biomanufacturing developments.

Technology Transfer (T19)

5–6 October

ISPE Training Institute

Tampa, Florida

Does your technology transfer reflect an enhanced approach to current best practices?

Technology Transfer (T19) includes knowledge transfer, science- and risk-based principles including ICH Q8, Q9, Q10, Q11, and efficient processes to meet evolving business needs. As the industry continues to experience changes, technology transfer for APIs, finished dosage forms and analytical methods between development and manufacturing sites and contract manufacturing organizations (CMOs) has become increasingly important. The Practical Application of Technology Transfer course uses current industry challenges and real-world examples as tools for industry and regulators to use when conducting and evaluating technology-transfer activities.

GAMP 5 GxP Process Control (T21)

12–13 October

ISPE Training Institute

Tampa, Florida

Are your process control systems fit for use?

Using a lifecycle approach for the development and management of process control systems, *A Risk-Based Approach to GxP Process Control Systems—Applying the GAMP® Good Practice Guide: A Risk-Based Approach to GxP Process Control Systems (2nd Edition)* course demonstrates how the principles and concepts of GAMP 5 may be practically applied. The course covers both regulated company and supplier quality management systems and the full sys-

tem lifecycle from concept to retirement. You will learn how appropriate QRM and specification and verification activities should be an integral part of the normal system lifecycle and how to leverage supplier documentation and activities to avoid unnecessary duplication, cost, and waste.

Water Generation (T04) – Updated

23–24 October

Boston, Massachusetts

Are you able to differentiate regulatory requirements from regulatory myths for water treatment, storage, and distribution?

Using the USP, EP, JP Monograph, USFDA “Guide to Inspections of High Purity Water Systems,” current FDA views, and cGMP requirements, the *Pharmaceutical Water Generation* course will provide a sound regulatory framework to understand common water system myths. Updated content includes discussion of the upcoming European Pharmacopoeia regulatory change allowing alternative WFI production methods in addition to distillation. The change will align EP requirements closely with USP WFI production methods opening opportunities for membrane-based systems. The course will also include material from the new *ISPE Good Practice Guide: Sampling for Pharmaceutical Water, Steam, and Process Gases* and will review optimizing sampling plans to significantly reduce operational costs. A variety of practical system designs will be evaluated for compliance, as well as their advantages and disadvantages. Particular attention will be paid to microbial control, laboratory water, key design philosophies, systems and component sanitization procedures, operation, testing and maintenance of equipment, and systems for water generation. Attendees will examine methods for proper water quality selection as well as study compendial and noncompendial water, fundamentals of basic water chemistry, and information on common unit operations (deionization, reverse osmosis, and distillation). Pretreatment systems, detailed guidance for selection of construction materials, and operation issues related to pharmaceutical water-generation systems will also be discussed.

Biotechnology Manufacturing Facilities (T31)

23–24 October

Boston, Massachusetts

Do you know the regulatory requirements for new or for renovating biopharmaceutical facilities?

Using case studies and exercises the *Apply-*

ing the Biopharmaceutical Manufacturing Facilities Baseline Guide Principles course in facility design provides an overview of the concepts utilized in the development and renovation of sound designs for facilities that manufacture biopharmaceutical products. The course includes a review of facility design and regulatory issues important in the US and Europe that involve industry trends and changing regulatory policy. Participants will discuss current case studies on a wide array of facility topics, and complete class exercises that involve developing facility scope of work and deliverables to meet corporate economic goals and regulatory requirements.

Cleaning Validation (T17)

23–24 October

Boston, Massachusetts

Can you establish, manage, and maintain a scientifically sound cleaning validation program?

With the US FDA’s risk-based regulatory initiatives focusing new attention on the risks of cross-contamination, understanding lifecycle management techniques for an effective cleaning validation program is paramount. *Cleaning Validation* course topics include: risk-based approach to cleaning development and verification; risk analysis, control, review and communication; procedures and evaluation tools including FMEA/FEMCA; master planning; PAT; periodic assessment and monitoring; selection of analytical and sampling methods; determination of residues to be targeted and appropriate limits in various pharmaceutical and biotechnology processes; and establishment of scientific rationales acceptable to regulatory inspectors. For mature cleaning validation programs, concepts such as understanding process control, capability, learning to effectively self-audit a cleaning validation program, and documentation will be essential takeaways.

HVAC (T14) – Updated

24–26 October

Boston, Massachusetts

Are you able to resolve common HVAC issues for bio, bulk, laboratory, packaging, OSD, sterile, and warehousing operations?

The *HVAC* course will include risk-focused discussions about change rate frequency, facility classification, cross-contamination, system or individual component qualifying, common issues and problems in the operation of a facility, and maintaining readiness for cGMP inspection.

Course content has been updated to include an update of changes and common interpretations for ISO 14644-1 and 2. Topics include control system alarm management, common system construction deficiencies, cGMP documentation, how to maintain an “inspection ready” state, frequency of testing and balancing, airflow visualization, and air change rate reduction. A thorough review of global cGMP regulations and their common interpretations and how they can apply to your facility.

Facility Project Management (T26)*

25–26 October

Boston, Massachusetts

Do you have the tools for successful project delivery?

The interactive *Facility Project Management in the Regulated Pharmaceutical Environment* course provides more than the usual project basics. It develops the concept of project lifecycle from initiation through delivery of business benefits, along with tools to manage all project resources. It is specifically targeted to the needs of facility projects within the regulated pharma-

ceutical industry and demonstrates the value inherent in the use of “good practice” project management. Trends in regulatory compliance, environmental, health and safety legislations, project delivery methodologies, and product speed-to-market expectations all affect how pharmaceutical facility projects are managed. Each course module introduces key project management concepts and tools as well as methodologies that specifically support successful project delivery.

Water Storage, Delivery, and Qualification (T23) – Updated

25–26 October

Boston, Massachusetts

Can you establish, manage, and maintain a scientifically sound cleaning validation program?

With the US FDA’s risk-based regulatory initiatives focusing new attention on the risks of cross-contamination, understanding lifecycle management techniques for an effective cleaning validation program is paramount. *Cleaning Validation* course topics include: risk-based approach to cleaning development and verifica-

tion; risk analysis, control, review and communication; procedures and evaluation tools including FMEA/FEMCA; master planning; PAT; periodic assessment and monitoring; selection of analytical and sampling methods; determination of residues to be targeted and appropriate limits in various pharmaceutical and biotechnology processes; and establishment of scientific rationales acceptable to regulatory inspectors. For mature cleaning validation programs, concepts such as understanding process control, capability, learning to effectively self-audit a cleaning validation program, and documentation will be essential takeaways. <>

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

SCALABLE
Fluid path solutions
 We can work with you at every process step

Our scalable technology with constant contact materials minimizes validation. We deliver repeatable, consistent and accurate performance.

Peristaltic pumps • High purity tubing • Liquid filling • Fluid path components.
 Weirless Radial diaphragm valves • Sanitary gaskets • Reinforced silicone hoses

wmftg.com/biopharm
 800-282-8823

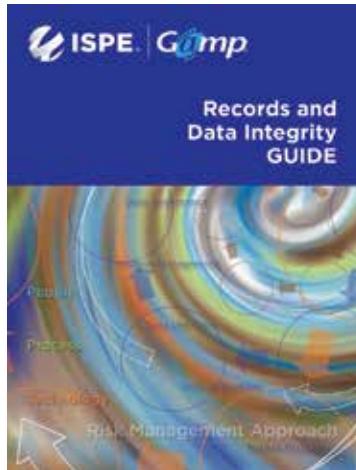
WATSON MARLOW
 Fluid Technology Group

ISPE GAMP® GUIDE: RECORDS AND DATA INTEGRITY

The importance of ensuring data integrity is reflected in guidance, citations, and public comments of regulators and health agencies. A number of companies have suffered serious regulatory and financial consequences as a result of unacceptable pharmaceutical data integrity practices. The *ISPE GAMP® Guide: Records and Data Integrity* provides principles and practical guidance on meeting current expectations for the management of GxP-regulated records and data, ensuring that they are complete, consistent, secure, accurate, and available throughout their life cycle. This approach is intended to encourage innovation and technological advancement while avoiding unacceptable risk to product quality, patient safety, and public health.

The *ISPE GAMP Guide: Records and Data Integrity* is intended as a stand-alone ISPE GAMP Guide aligned with the *ISPE GAMP 5: A Risk-Based Approach to Compliant GxP Computerized Systems*. It has been designed so that it may be used in parallel with guidance provided in ISPE GAMP 5 and other ISPE GAMP Good Practice Guides. It replaces the previous *ISPE GAMP Good Practice Guide: A Risk-Based Approach to Compliant Electronic Records and Signatures*.

This Guide has been developed by ISPE's GAMP Community of Practice (CoP), a worldwide community of practitioners and subject matter experts who over



25 years have been developing internationally accepted guidance on risk-based approaches to safeguard patient safety, product quality, and data integrity. This Guide has been produced with significant input and review from regulators worldwide, including key specialists from leading regulatory authorities (MHRA and WHO) working in this area.

The *ISPE GAMP Guide: Records and Data Integrity* is intended to be a complete and comprehensive single point

of reference covering the requirements, expectations, and principles of pharmaceutical data integrity. Topics covered include regulatory focus areas, the data governance framework, the data life cycle, culture and human factors, and the application of quality risk management to data integrity. As such, it is of great interest to anyone with a responsibility for ensuring data integrity, including:

- Executives and managers
- Process and data owners and data stewards
- Technical system owners
- System developers, maintainers, and users
- Quality assurance and quality control
- Clinical, manufacturing, and laboratory personnel
- Validation and compliance specialists
- Suppliers of systems and services
- IT and engineering professionals

Readers will gain an invaluable insight into the pressing hot topic of pharmaceutical data integrity, gaining an in-depth understanding of the key requirements and principles, as well as learn about practical approaches and techniques to effectively address data integrity challenges. The *ISPE GAMP Guide: Records and Data Integrity* will assist regulated companies and their suppliers to achieve the high level of data integrity expected by regulatory authorities worldwide. Please visit <http://www.ispe.org/gamp-guide/records-pharmaceutical-data-integrity> to purchase the Guide.

ISPE also offers a new two-day training course using the Guide, *A GAMP Approach to Data Integrity, Electronic Records and Signatures, and Operation GxP Computerized Systems (T50)* in San Diego, California, US; Copenhagen, Denmark; Tampa, Florida, US; and Manchester, England, UK. This course provides the tools and techniques to implement proper controls for data to ensure the integrity and validity of the information throughout the data life cycle. Please visit <http://www.ispe.org/training/classroom/gamp-data-integrity> for more information and to register for this training course. ◊

PROCESSES MANUFACTURED IN PORTUGAL

High purity systems require high quality products.
That's what Adca Pure is all about.

**PURE CONTROL
CLEAN EFFICIENCY
TOTAL RELIABILITY**

ADCA Pure
Pharma, Food, Chemical & Cosmetic

STEAM TRAPS | SAMPLE COOLERS | HUMIDITY SEPARATORS
CONTROL VALVES | PRESSURE REDUCING VALVES | PRESSURE SUSTAINING VALVES

Zorla Industrial da Guia | Pav. 14 - Brega | 3150 - 467 Guia PBL | Portugal
+351 236 999 060 | adca@valsteam.pt | www.valsteam.com



JUST PUBLISHED!

**PURCHASE
TODAY**
and receive your
electronic copy in
your inbox in
minutes!

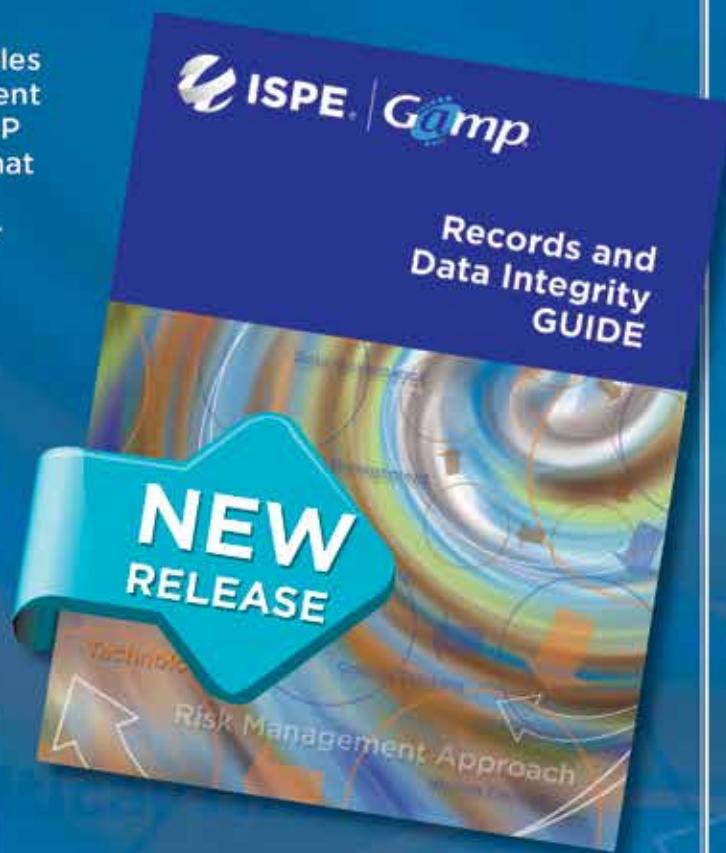
ISPE GAMP® Guide: Records and Data Integrity

The ISPE GAMP® Guide: *Records and Data Integrity* provides you with principles and practical guidance on meeting current expectations for the management of GxP regulated records and data—ensuring that they are complete, consistent, secure, accurate, and available throughout their life cycle.

This guide addresses the integrity of GxP records and data used within the regulated life science industries including pharmaceutical, biological, and medical devices. The guidance is intended for regulated companies and suppliers of systems, products, or services in this area, as well as providing a useful reference for regulators.

Key concepts that you can take away from this guide include:

- Risk Management Approach
- Data Governance
- Data Life Cycle
- Key Concepts Summarized by ALCOA and ALCOA+
- GxP Computerized System Life Cycle



Member Price: \$200/€185
Nonmember Price: \$395/€360

**Available in book and
PDF format**

Purchase your copy today at
www.ISPE.org/Gamp-Guide/Records-Pharmaceutical-Data-Integrity

ISPE ITALY POISED FOR LEADERSHIP

A country best known for its artists, food, and fashion designers, Italy is also home to a thriving pharmaceutical industry. Along the country roads that stretch from Milan to Bologna, Florence, deep into Rome and Naples, idyllic hillsides are dotted with the facilities of life sciences companies both big and small, as well as those of satellite industries like medical devices and packaging equipment. In fact, Italy is Europe's second-largest producer of pharmaceutical products (Germany ranks first), exporting 73% of its pharmaceutical manufacturing industry production through some 200 production sites, and employing 65,000 people!

"It's our best-kept national secret," said Teresa Minero, Founder and CEO of LifeBee, a management and IT consulting firm for the life sciences industry, and President of ISPE Italy, a position she has held since May 2016, following a term as Vice President from 2014 to 2016. An ISPE member since 1992, she is also Vice Chair



Minero began her career on the IT side in 1984, working for a multinational consulting firm. It was in 1993 that she began working in the pharmaceutical industry. When the firm decided to sell its Italian subsidiary, Minero saw an opportunity to strike out on her own. She founded LifeBee, a company with a focus on "digitalizing life sciences."

ITALY IS EUROPE'S SECOND-LARGEST PRODUCER OF PHARMACEUTICAL PRODUCTS

of ISPE's European Leadership Council. "I believe that Italy has great potential to become a true European hub," she explained. With reasonable production costs, state of the art production technology and highly qualified professionals—about 224,000 employees work in the pharmaceutical supply chain!—Minero thinks Italy may well become an even stronger player in Europe's pharmaceutical manufacturing space.

ISPE Italy has 400 members. Roughly half come from industry, regulatory agencies, and academia; the other half represent from satellite industries and services. "We are Italy's largest and most popular international association dedicated to life sciences," said Minero, "and our members come from across the spectrum: engineering, manufacturing, automation, IT, validation, and quality assurance, and also from laboratories, logistics, and regulatory agencies." This broader definition is one that matters to Minero. She believes it will help boost membership and promote ISPE as an inclusive association that is about more than just engineering and pharma, as it used to be and sometimes (at least in Italy) still perceived to be. "Life sciences counts almost four times as many people working in it [than pharma]," she said, "and it is important we reach out to the entire supply chain: the sector

is bound by similar regulations and guidelines, by similar opportunities and challenges, and, ultimately is devoted to the same customer, the patient."

Based in Milan, Italy's industrial capital, Minero concedes ISPE Italy has had its membership issues. "The economic downturn of the last couple of years has had an impact," she said, "yet through our public relations activities, we are hoping to reignite interest and demonstrate value." The Affiliate's board has begun outreach efforts at the local level. "We're more active in northern Italy simply because all our Board members, save one, are from the north," she stated. The life sciences sector is most active in northern Italy, and in the center of Italy. "This, too, is a challenge, as it isn't always possible to travel from one end of the country to the other, either for Board members or Affiliate members."

Each Board member has been assigned one of the Affiliate's 2016–2018 strategic objectives; these include development of local communities of practice on topics such as powder-handling safety, GAMP® data integrity, activities with other associations and European affiliates, and building a Young Professional (YP) community. The current Board has 10 members, seven of whom are women. Other executives include Vice President Guia Bertuzzi, Treasurer Corinna Carganico and Secretary Cristian Musazzi; remaining Board members are Fernanda Ferrazin, regulatory relations and ISPE RCC representative; Francesca Maienza, operational support; Alessandro Villa, local community of practice coordinator; Fabiana Stoppa, YP coordinator; Anna Lidia Vignoli, GAMP Italy relations; and Saverio Cornacchia, membership. ISPE Italy's accomplishments were recognized in 2015 when it was named ISPE's Affiliate of The Year. "We're still beaming," said Minero, "and it is an honor we promote when positioning ISPE at trade shows and other association events."

Celebrating its twenty-fifth anniversary this year, the Affiliate has planned events both social and professional to highlight its member contributions, including the new Operations Management Good Practice Guide, which boasts two Italian leaders: Giuseppe Ravizzini of Recordati and Marzio Mercuri of Polpharma. The Board is planning and organizing events based in Milan, Bologna, and Rome on a variety of subjects, such as Industry 4.0 and operational excellence, data integrity, serialization and track & trace, elemental impurities, new information and communi-

Pharmaceutical industry portrait²

63,500

employees, of whom

6,100 are researchers

€30 billion in production,

of which 73% is exported

€2.6 billion in investments

€1.4 billion in R&D

€1.2 billion in production

Did you know?

Population

61,680,122 people

23rd largest country in the world, by population

Area

301,340 square kilometers

72nd largest country, by area

Languages spoken

Italian (official)

German
(Trentino-Alto Adige region)

French
(Valle d'Aosta region)

Slovene
(Trieste and Gorizia)

sponsibility of sharing knowledge. “Our Board members are passionate about ISPE Italy—they always have been,” she said. “They want things to work well, and for us to create even stronger ties with members, both current and future.

“The view that the pharma industry needs to redeem its reputation is a matter of fact. The sciences sector has improved the quality of many lives, and it continues to achieve new and important goals, even if sometimes it is forgotten by media and social networks. We have to remind colleagues within the pharma industry, but especially to everybody outside it, that people are the end of our supply chain. Our children, our mothers, and our friends—they are affected by the work we do every day; their better health is what drives our professional community. This is our value, and the message we need to get across.” 

—Anna Maria di Giorgio

References

1. Farindustria
2. Farindustria: Imprese del farmaco e ricerca

MATTHEW KENNEDY ON DISRUPTIVE INNOVATION



Matthew Kennedy is a Bioprocess Specialist and Senior Associate at CRB in Philadelphia, Pennsylvania, US

Manufacturing therapeutic proteins such as monoclonal antibodies, while potentially lucrative, is fraught with uncertainty. A company can have a number of biologics in the pipe-

line, each requiring an estimate of future need for a variety of indications, a different competitive landscape, and none with a guarantee of regulatory approval.

“It can be extremely challenging for companies to estimate manufacturing capacity to support their market projections,” said Matthew Kennedy, a bioprocess specialist and senior associate at CRB in Philadelphia, Pennsylvania, US, and an ISPE member since 2001. “They have to invest in manufacturing capability long before they know the definitive outcome of clinical trials.”

This is a challenge Kennedy loves to meet. He is a champion of applying innovations in facility and equipment design—namely continuous, closed processing and single-use technology—to the facility of the near future. The benefits include a reduced footprint, lower capital and ongoing utility costs, greater speed to market, and the capability to scale up or scale out from clinical production through launch capacity.

In 2015 Kennedy was named a “Top 20 under 40” award winner for the *Engineering News Record* Mid-Atlantic Chapter for his work in design and construction. He studied chemical engineering at the University of Delaware, US. After graduating, he worked at Biokinetics, where he first got exposure to the design, construction, and validation of equipment used in biopharmaceutical manufacturing. He continues to build on that experience at CRB, where he focuses on holistic design to align the investment in the manufacturing facility with the business objectives of the company.

Kennedy sees continuous closed processing as key to dealing with demand uncertainty and, when combined with single-use technology, to transforming the biologics industry.

“Combining single-use, closed, and continuous manufacturing dramatically compounds the effects of each of these innovations,” he said. “While each holds the potential to reduce the footprint, when you have all three, the size of the facility collapses. Single-use technology eliminates or reduces process utility systems, while the process closure reduces the number and size of air handlers, and thereby the demand for chilled water, steam, and electricity. Continuous processing then amplifies these effects and reduces the cost of consumables making a dramatic impact on the cost of goods.”

This end-to-end manufacturing connects upstream and downstream processes, both of which have seen enhanced efficiency in the past decade.

cations technology trends in good practices, powder-handling safety, and nutraceuticals.

Promoting the ISPE Italy brand and its message of knowledge-sharing and collaboration ranks high on Minero’s list of objectives for 2017. In addition to “making room” for members outside of traditional pharma, “like Brazil and San Diego are doing on nutraceuticals,” Minero and the Board want the affiliate to be more present at other association conferences and trade shows, for example. “It felt great to deliver a speech as an ISPE representative last spring at the Paperless Lab Academy in Barcelona,” she recalled. Her presentation, “Paperless and Data Integrity: Different Paths, Same Goal,” was also an opportunity to promote ISPE, GAMP, and the benefits of membership. “We need to be more visible, to create and participate in working groups, write articles and make everybody aware of ISPE’s great body of knowledge,” said Minero. “If knowledge sharing and networking are our true values, we need to ‘live’ them,” she added.

On a personal and professional level, Minero tries to stay true to her values. She believes in the power and passion of groups, and the re-

“As we get up to higher cell densities and higher protein expression rates upstream, then single-use manufacturing becomes attractive for large-scale protein production,” Kennedy said. “Instead of a \$1 billion, 60,000-liter bioreactor facility, you can make the same quantity of a therapeutic protein using much smaller, simpler pieces of equipment like 2,000-liter single-use bioreactors operating in intensified batch or perfusion mode. The process becomes cheaper, faster, and better.”

This pushes the bottleneck downstream to harvesting cells and the desired proteins they express. But here, too, innovations such as multicolumn chromatography have improved productivity, coupling high-yield protein production upstream with an efficient purification process. It is now possible to purchase one train of equipment that has a bioreactor operating in a perfusion mode, couple it to continuous purification, and make it all single use.

“This overcomes a downside of single-use technology which, despite a low capital cost, is expensive in the long run. When you couple single-use technology with continuous manufacturing, connecting upstream and downstream processes, you reap the benefits of both innovations. The cost incurred from frequent and rapid changeover usually associated with batch-based single-use systems goes away.

“If you need to switch to another product, you can simply reconfigure some tube sets, swap out a series of chromatography resins and filters, and quickly change the suite to begin production of another protein. Not only can you produce a large amount of protein with a well-architected platform of manufacturing technology, you can change the protein you’re making with a modest changeover time. If you need to double production, you can quickly scale out by adding a second set of equipment.

“Innovation can be beneficial while being disruptive.” ◊

—Scott Fotheringham, PhD

RETIREMENT NEWS

After 48 years of service, MECO Vice President Robert “Bob” Gray is retiring.



He joined MECO as a sales rep in 1968, after a 23-year career in the US Marine Corps. He became an integral part of the company’s expansion through the 1970s, selling MECO’s first pharmaceutical unit.

During his tenure, Bob traveled the world, building relationships with people whose requirement for pure water is critical to their processes and operations. He engineered industry-specific solutions and designed new technologies, including the “BG Special”—a transportable vapor compression unit that defense forces could airlift to any location by helicopter. He became an active member of ISPE in 1981, serving on conference and vendor committees for over 20 years.

Bob Gray earned the trust and respect of his colleagues, clients, and fellow ISPE members. His fame rests securely on the strength of his character and the quality of his contributions to the industry. ◊

LETTER TO THE EDITOR

Dear editors:

I noticed that there is a mistake in the article “Understanding Cleanliness Classification for Life Science Facilities,” which was published in the March-April 2017 issue of *Pharmaceutical Engineering*.

The error is on page 39, in the first paragraph:

ISO 14644-1:1999 (superseded): This standard defined classes of cleanliness by airborne particle count concentration following a decimal system.... The relationship between ISO class number, particle number concentration, and reference particle size is defined in the standard by the formula $C_n = 10N \times (0.1/D)^{2.08}$, where C_n is the particle count, N is the ISO class, and D is the particle mean diameter in millimeters.

The unit for D must be micrometers; the 0.1 should also be defined as a constant measured in micrometers.

*Christian Klose, Managing Director, PiQuP AG
Neuhausen am Rheinfall, Switzerland
christian.klose@piqup.ch*

Dear Christian:

Good catch! Thanks for pointing that out—we appreciate the correction. The sentence should read:

... reference particle size is defined in the standard by the formula $C_n = 10N \times (0.1 \mu\text{m}/D)^{2.08}$, where C_n is the particle count, N is the ISO class, and D is the particle mean diameter in μm .

*Norman Goldschmidt, President,
Genesis Engineers
Plymouth Meeting, Pennsylvania, US
ngoldschmidt@geieng.com*

*Gordon Farquharson, Principal Consultant
and Managing Director
Critical Systems, Ltd., Guildford, Surrey, UK
gjf@critical-systems.co.uk*



ISPE/FDA/PQRI Quality Manufacturing Conference

5th Annual ISPE/FDA/PQRI Quality Manufacturing Conference

Align Your Company Strategies with Regulatory Priorities

Focus on 2017 Regulatory and Industry Priorities

- **Clinical Relevance**
- **Emerging Technology and Innovation**
- **Facility and Life Cycle Quality Management**
- **Quality Metrics**

Exhibit and Sponsorship Opportunities Available:

For more information or to secure your exhibit space and sponsorship, contact Alisa Pachella at apachella@ispe.org

Register at: ISPE.org/2017-Quality-Manufacturing-Conference

Keynote Speakers



Michael Kopcha, PhD, RPh
Director, Office of Pharmaceutical Quality, FDA/CDER
Office of Pharmaceutical Quality Progress Update



François Sallans, PharmD
Vice President, Quality and Compliance, Chief Quality Officer
Johnson & Johnson



Thomas Cosgrove, JD
Director, Office of Manufacturing Quality
FDA/CDER/OC



Roger Nosal, PhD
Vice President and Head of Global Chemistry, Manufacturing and Controls
Pfizer Inc.



Helen Saccone, CDR, PharmD
Associate Director, Global Regulatory Policy
FDA/OC/OGROP

Brian Boyd
Vice President, Global Facilities Management
Johnson & Johnson

5 - 7 June • Crystal Gateway Marriott • Arlington, VA

PREPARE. PREPARE. PREPARE. REPEAT.

Hi David, I've had several interviews, but have yet to receive an offer. What could I be doing wrong?

Interviewing repeatedly without receiving an offer can be humbling. Let's walk through some questions to assess where you might be able to improve.

WERE YOU PREPARED?

The most important thing you bring to an interview is confidence, and that's a product of preparation. Interviewers expect you to have done your research. Did you visit the company website? Did you find out as much as you could about the people you'd meet? Did you review their LinkedIn pages to understand what they do and the role they play in relation to the position?

Having the right materials handy also demonstrates organizational skills and your interest in the position. Did you have copies of your resume, a list of references, and appropriate supporting documents (such as a recommendation letter)? Did you bring a copy of the interview agenda—including the names and titles of people you'd meet? Did you print a copy of the job description? How about something for taking notes, or a list of prepared questions?

WHAT DID YOU SAY WITHOUT SPEAKING?

Your interview starts the moment you arrive on site. Did you park in the appropriate location? Did you show up on time with enough leeway to check in with security or the receptionist? Did you greet each person you met with a smile and respect? The first impression you make can greatly influence the hiring decision.

In a face-to-face interview, nonverbal communication is critical. Did you greet each interviewer with a good handshake and a smile? Did your posture, style, eye contact, and body language reflect your enthusiasm for the job? Using a positive tone, uncrossing your arms, maintaining good eye contact, and leaning toward the speaker all demonstrate engagement.

Your appearance is the first thing people notice about you, and the way you dress shows respect for the opportunity, interviewer, and organization. Proper attire says that you're eager to make a good impression and fit within the company culture.

DID YOU PROVIDE GOOD ANSWERS?

The content of your resume is usually what leads to an interview, and most interviewers use it to formulate questions. Did you think about questions that might be asked about your work history (employment gaps, reasons for changing jobs, etc.)? Were you prepared to provide detailed answers about your accomplishments and results? Were you able to discuss the scope and depth of expertise for the skills you listed?

Behavioral-based questions open the door for candidates to share how they work with others, handle adversity, and adapt to challenges. Were you too negative about a current or previous employer or colleagues? Did you talk about what you learned from experiences and discuss actions you took to produce a better outcome, or were you more focused on the others' faults?



David G. Smith is Principle Recruiting Partner for Biogen's manufacturing, manufacturing sciences and quality organizations in the United States.

Not fully listening to questions is a sure way to miss context and the desired answer. Did you allow the interviewer to complete a question before planning what you were going to say? Interrupting or hijacking the conversation is another common problem for many candidates and a frequent area of frustration for interviewers.

Trust is a key factor in deciding which candidate to hire, and to establish trust you must be authentic. Did your responses give the interviewer a good sense of who you are? Did you say what you thought he or she wanted to hear or what you really believe? Interviewers can usually spot a canned answer, which can make them wonder what you are holding back. Think about how your answers can be less cookie-cutter and more representative of your true beliefs.

WHAT YOU SHOULD DO NEXT?

Interviewing is a learned skill. The more you practice, the more skilled you will become and better prepared you will be. Rehearse with a friend or colleague who can give you real, objective feedback. Reviewing possible questions, conducting mock interviews, and learning more about the organization are also good strategies.

As you conduct post-interview evaluations your confidence will grow, your verbal and nonverbal communication skills will improve, and you will understand your value to potential employers. By learning from your mistakes and successes, you will be more prepared the next time. <

THE MOST IMPORTANT THING YOU BRING TO AN INTERVIEW IS CONFIDENCE, AND THAT'S A PRODUCT OF PREPARATION

Thank you once again for your questions. I hope you will find this guidance helpful. If you are curious about other topics, please email me at david.g.smith@biogen.com, and I will likely answer in a future column.

MASTERING THE ART OF SUPPLY CHAIN MANAGEMENT



Michael Schmitz is Vice President, Planning and Logistics, of Vetter Pharma-Fertigung GmbH & Co. KG. In this position he is focused on logistics operations, production resources, OEE measures and customer service levels, and inventory management.

Supply chain management. Three simple words, perhaps, but together they constitute an entire process, one that is critical to a contract development and manufacturing organization (CDMO) and its customers. In today's market, increased regulation, cost pressures, intensifying competition, and globalization present complex challenges to proper management of the pharmaceutical supply chain and are forecast to increase. If drug manufacturers are to deal with these complex dynamics successfully, mastering the process of supply chain management is essential. They must also maintain flexibility, however, and be prepared to react to changes in demand, maintain a secure supply chain, and produce a consistently high level of quality.

A rapidly changing market environment has also affected CDMO operations, where customer demands increasingly require the manufacture of drugs in smaller volumes. Customers expect that their CDMO will make every effort to continuously increase service levels and reduce lead times. These constantly evolving requirements are expected elements of a rapidly changing market. Successful service providers are able to modify their services accordingly, reaching the highest machine utilization in regard to capacity/filling possible, and achieving effective overall equipment efficiency.

S&OP

A well-managed supply chain requires coordination and cooperation. Establishing open communication of expectations between the customer, the CDMO, and other stakeholders (such as suppliers) is essential to prevent disruption in operations. To help, companies are relying on the sales and operations planning process, commonly referred to as S&OP, which involves ongoing business reviews and consul-

tative meetings that align expectations early in the process.

The maintenance of a nimble demand and supply chain that can adapt and maximize the highest level of machine usage also requires quick decision-making. This is why monthly reviews and the incorporation of S&OP as a key supply chain process to iron out any conflicts and achieve the highest possible level of customer service are important.

FLEXIBILITY

Being flexible to market changes is a key component in the formula for successful supply chain management. The allocation of resources means anticipating situations and reacting to them accordingly. Cleanroom capacity utilization, for example, must be considered well before beginning production. A reference for high flexibility in the supply chain is the use of multi-product lines that feature modular equipment.

When security of supply is absolutely crucial, or when a second supply site does not exist, many (bio)pharmaceutical customers prefer to qualify two different cleanrooms at the same service provider. Preestablished and validated equipment and processes offer an advantage to manufacturing one product on different lines.

INVENTORY AND STORAGE

While there has been significant growth in the number of APIs and final products that require deep-freezing or storage temperatures between 2°–8°C, it is subject to extreme fluctuations in demand. This has a strong effect on the storage capacities of CDMOs who must maintain the cold chain throughout the entire production process. Because shelf life is crucial to customers, CDMOs must provide extensive storage capacity in-house. This includes storage with varying temperatures that will meet

the needs of all APIs, ingredients, and final drug products. In this manner, the changing demands can also be more easily managed.

The ability of production to react to unforeseen demand changes with inventory in the short term is one of the key differences that distinguish (bio)pharmaceutical companies from other industries. In the area of fill and finish of injectables, for example, API, primary and secondary packaging materials, glass barrels, stoppers and cardboard packaging are available in storage for production.

FINAL THOUGHTS

Changes in the global market will continue to provide new opportunities and challenges for (bio)pharmaceutical companies and their strategic partners. Being prepared to face these challenges is critical to remaining successful. Processes like S&OP help achieve open communication and flexibility while maintaining the highest possible quality and safety standards. Thus, a well-conceived supply chain management plan and advance preparation is the key to an agile supply chain. ♦

Have an opinion you'd like to share?
Let yourself be heard! Send your submission to
amdigiorgio@ispe.org.

Cooperation for pharmaceutical process automation

We call that teamwork: The collaboration between Siemens and Bürkert resulted in the Type 8647 AirLINE SP valve island, which is compatible with the Siemens I/O system SIMATIC ET 200SP. It is designed not only for fast installation, but also features numerous safety functions for pharmaceutical processes, such as the new LCD with real-time status display of diagnosis data or check valves to prevent mixing of different media. Together with maximum system availability, the result is a solution for outstanding process reliability.

AirLINE SP Type 8647:
Better process reliability is hardly possible.

We make ideas flow.
www.burkert.com



bürkert
FLUID CONTROL SYSTEMS

www.burkert.com

ISPE 2016
CONTINUOUS
MANUFACTURING
CONFERENCE
HIGHLIGHTS



Conference co-chairs Theodora Kourti, PhD • Rapti Madurawe, PhD | **Regulators** Kurt Brorson, PhD • David Doleski • Dolores Hernán Pérez de la Ossa, PhD • Jean Hu-Primmer | **Industry** Christian Airiau, PhD • Gretchen A. Allison • Richard D. Braatz, PhD • Yanxi Tan Cain, PhD • Lawrence de Belder • Steve Hammond • Jun Huang, PhD • Christopher Hwang, PhD • Gordon (Randy) Lambertus, PhD • Catherine MacConnell • Steve Miller • Christine M. V. Moore, PhD • David Pappa • Wyatt Roth, PhD • Vidya Swaminathan, PhD • Kelly Swinney, PhD • Kelly Tolton • Andre Walker

CONTINUOUS MANUFACTURING

A summary from the ISPE Continuous Manufacturing Conference

This paper discusses the findings and outcome of the ISPE Continuous Manufacturing Conference held 20–21 April 2016 in Baltimore, Maryland. While the ideas captured below reflect presentations and discussions both during the main conference and in breakout sessions, they are not necessarily the views of the authors or their organizations.

Continuous manufacturing (CM) can offer significant quality and cost advantages over batch manufacturing of active pharmaceutical ingredients (APIs) and drug products. Benefits are delivered through design for high-quality product and manufacturability—these include safety from reduced human intervention, smaller manufacturing footprint, higher process efficiencies through fewer process steps, and reduction in post-manufacture testing for release. CM also allows for end-to-end manufacturing where drug substance and drug product operations are connected without drug substance isolation and release.

While these benefits are recognized by industry and regulators, barriers and challenges to the adoption and implementation of CM remain. Notably, the existence of facilities with depreciated batch manufacturing equipment assets may be a barrier to new capital investment. There are also technical and regulatory risks in coupling an untried manufacturing technology with new product development and registration—possibly more acute in accelerated development scenarios. One approved product manufactured via CM, however, is designated as breakthrough therapy, which implies that the perceived risks are manageable.

Successful implementation of CM requires an organizational commitment to the CM paradigm, a long-term strategy, and a well-defined im-

plementation plan for either new product development or a batch-to-CM switch of already approved products. Advancement of CM requires an investment in infrastructure and capabilities, a comprehensive product quality management mindset, development of a CM framework and practice, new skillsets and expertise, and continued investment in CM platforms.

BUSINESS BENEFITS

Business cases for CM in the pharmaceutical industry can be grouped as development, technology transfer, and commercial benefits, each with its own set of assumptions. For senior leaders to support these assumptions, they must trust in the team charged with implementing CM—trust that is built with data and implementation success stories. Sharing data, discussing lessons learned, and seeking ways to collaborate can help the team grow the critical mass of knowledge needed to speed up the initial deployment phase of this technology. The initial investment in CM must be understood and supported throughout the organization from development to manufacturing; the business case may vary for each organization.

Initially, investments in effort and resources are needed to grow learning for parallel development of process analytical technology (PAT) and analytical methods. Because these costs are often difficult to estimate, it may be beneficial to keep learning cost separate from the business case. Reducing technology-transfer time only improves speed to market for some accelerated launch products, typically for Phase 3 data when it is on the critical path. Equipment should be designed with business case drivers in mind and transition towards modularity and standardization, and equipment design must also consider robustness and preventive maintenance to minimize failure/deviation risks during operation.

To ensure that development products are successfully transferred to commercial line, probability of success and comprehensive risk assessment/mitigation should be estimated; a backup transfer plan should also be in place, if required.





REGULATORY CONSIDERATIONS

Regulators are aligned with industry's goal of delivering high-quality medicines to patients. Most can see the potential that pharmaceutical CM offers for quality and cost advantages, thereby benefitting industry, patients, and regulators. By improving the consistency of drug manufacture and adjusting production to meet demand, faster response to shortages and emergencies can be enabled.

At the conference, some points to consider were further discussed by US Food and Drug Administration (FDA) regulators:

- Connected unit operations and continuous material addition, processing, and product formation introduce unique challenges compared to batch manufacture.
- Defining batch size in a flexible way is warranted in a continuous process.
- A sound control strategy is built upon the knowledge of residence time distributions at the desired mass throughput rate or range and the system dynamics of connected unit operations. In continuous bioprocessing, this may trigger the need for short-term hold vessels when volumetric throughputs of sequential steps differ, for example.
- Further, the output of some continuous processing steps like periodic countercurrent chromatography can be viewed as a continuing series of small batch operations, rather than a constant stream.

This knowledge can be used to develop plans for material traceability, rejection of potentially nonconforming material, and sampling. Identification of the potential sources of variability and their control ensure that products are made under a state of control and the process is robust. Characterization and control of input material attributes for CM, a process monitoring and control system to maintain the process within acceptable operating ranges, and an appropriate in-process sampling scheme are some key elements of a successful control strategy. Process models may also be used to enable real time release approaches.

Representatives from the European Medicines Agency (EMA) further elaborated that dossiers must be self-comprehensive for the regulators to understand how the product and process have been developed and to discern the sponsor's intentions for future manufacturing process control. The level of detail in the regulatory submissions should be commensurate with the significance of the outcome to the commercial manufacturing process and the control strategy.

Considerations around development (e.g., evaluation of raw material specifications and lot-to-lot variability, process dynamics, potential interactions between design spaces for different steps); manufacture and control strategy (e.g., batch definition, PAT tools, use of models and their roles,

feedback and feedforward loops, sampling plan, justifications for IPCs, handling of nonconforming material, real time release testing [RTRT], and process validation strategy); and equipment (e.g., potential for fouling) were also discussed.

Since both industry and regulators have limited experience, EMA and FDA encourage early dialogue when innovative technologies/approaches are being used. Advice from EMA can proceed through the Committee for Medicinal Products for Human Use scientific advice/protocol assistance,¹ or early discussion meetings with the PAT team, established in 2003.² Although currently EMA provides no specific guideline on CM, it was indicated that this approach fits well within existing guidance—e.g., the EMA guideline on process validation for finished products, which introduces the concept of continuous process verification.³

Early dialogue with FDA should greatly facilitate acceptance of such processes. FDA can be expected to support the implementation of CM in cases where it is justified by a science- and risk-based approach. Industry should recognize that it is important to address how regulatory aspects can affect the decision of when to implement new technology—early in the development process, midstream, approval, or licensure. Each may trigger different levels of risk considerations by regulatory authorities.

To help address issues such as these, the FDA's Emerging Technology Team (ETT) was formed in 2014. ETT draws membership from all Center for Drug Evaluation and Research quality review, research, and inspection functions, including the Office of Biotechnology Products. The ETT provides a primary point of contact for external inquiries regarding emerging technology in pharmaceutical and biotechnology manufacturing and quality control. The ETT will partner with review offices in a cross-functional manner to identify regulatory strategy and resolve roadblocks to implementation of new technologies relating to existing guidance, policy, or practice related to review or inspection. The team's initial focus will be innovative products, manufacturing processes, or testing technologies or processes to be submitted in an Investigational New Drug Application, Biologics License Application, New Drug Application, or Abbreviated New Drug Application.

CGMP CONSIDERATIONS

Current good manufacturing practice (CGMP) considerations for CM include:

- An effective pharmaceutical quality system (PQS)
- Appropriately validated facilities and software
- Determining a state of control
- Dealing with deviations in real time
- Managing segregation of "potentially nonconforming" materials (Note that for consistency with ICH Q7, "nonconforming" should only be used to describe material that does not meet appropriate specifications)

or standards; segregated material can be referred to as “potentially nonconforming” until its disposition is determined)

GMP regulatory considerations for CM should consider if any modifications are needed to the existing PQS. In general, the structure of an effective quality assurance unit should be flexible enough to cover CM, although processes and definitions may need revisions. For example, the definition of a “lot” or “batch” should be consistent for its use in the continuous operation. Batch record review should consider the timelines for RTRT operations, the quantity of information reviewed, and the sequence of batch record review vs. the production run. Further quality considerations include how the PQS deals with process upsets. Material traceability should be understood and process events should be evaluated for their potential impact to other segments or batches.

Considerations for equipment are similar to traditional manufacturing and include decisions related to the choice of dedicated vs. multi-product and single-use vs. reusable equipment. The ability to verify cleaning of the equipment is important, including observability of accumulated material within the system. Additionally, the materials of construction should be durable and not have leachable impurities. Finally, it is essential that the equipment operates reliably over the desired length of a manufacturing run or campaign.

For automation, the level of software validation depends on the associated risks. Requirements for functionality should be documented. There should be clarity on automated actions vs. operator actions and adequate training of the operators to use software. A clear procedure for resolution of alarms is expected, and resolution of the issues should incorporate an understanding of the impact on product quality.

Determining a state of control should be based on defined operating ranges and historical experience to deliver product with adequate assurances of quality, strength, identity, and purity. Understanding the process and the system dynamics is essential to support CGMP-related decisions. CM control strategies typically allow for adjustment of drifts. Deviations can include both process (true) deviations and sensor deviations; alarms are not necessarily deviations. Action limits should indicate when to segregate potentially nonconforming material. It is essential that procedures be in place that predefine how and where material segregation will occur. Considerations for segregation of potentially nonconforming material include the location of product diversion, preestablished diversion criteria, expected response to expected and unexpected events, and persons accountable for making the diversion decisions. Additionally, the data required to support decisions on product collection or diversion should be defined for start-up, pause, and shutdown operations.

CM IN DRUG SUBSTANCE, DRUG PRODUCT, AND END-TO-END MANUFACTURING

As of April 2016, CM was approved by the US FDA for a new chemical entity for Vertex Pharmaceuticals—which was developed as a CM process—and for a Janssen legacy product converted from batch to continuous. Although a case of approval for end-to-end CM of drug substance is not known, several companies have had single continuous drug substance reaction or purification steps approved.¹⁴

Manufacturing equipment for drug substance is highly flexible and variable in the number and complexity of unit operations. As such, the online

analytical equipment required to support a process control strategy should be highly adaptable, provide representative sampling with minimum fouling, and be robust over extended periods of use without sacrificing accuracy or precision relative to traditional quality control lab counterparts.

Development organizations can leverage the data-rich analytics provided by online spectroscopies and chromatography to build process understanding. As experience is gained in manufacturing, then opportunity exists to reevaluate and, when possible, simplify the analytical instrumentation for long-term installations. As the industry gains familiarity and experience with these processes and measurements, online analytics may soon be commonly used for in-process controls of drug substance manufacturing.

CM for drug product has been adopted by a number of companies. Pfizer, G-Con, and GEA have formed an “open innovation” consortium as cofounders, with GSK as a member. This consortium is focused on development and deployment of a “portable, continuous, modular, miniaturized” (PCMM) and flexible continuous solid dose manufacturing train contained in a “POD.” The POD concept can provide local manufacturing through rapid deployment of manufacturing capability. POD is capable of being disassembled, shipped to another location (country), reassembled, and commissioned in a few months. Version one of the manufacturing train includes both direct compression and wet granulation. Version two will include coating operations. The system has a “smart manufacturing” architecture that includes PAT, advanced process control, and data integration. This system won the ISPE 2016 Facility of the Year Award for Equipment Innovation.⁸

A continuous-flow process that produces active pharmaceutical ingredient and the drug product in one integrated system is referred to as end-to-end CM. A four-step approach for the design of end-to-end continuous pharmaceutical manufacturing process control uses first-principles models:

1. Select the strategy for assurance of each critical quality attribute (CQA) specification
2. Build first-principles dynamic models and control systems for each unit operation
3. Place unit operation models and controls into a plant-wide simulation
4. Design plant-wide control strategy based on plant-wide simulation

Four strategies were described for the first step:

1. Direct measurement of the CQA
2. Prediction of the CQA based on a first-principles model that is fed measurements of related variables
3. Prediction of the CQA based on an empirical or semiempirical model
4. Operation of the critical process parameters (CPPs) to lie within a design space—that is, some specified set shown in offline studies to provide assurance.¹¹

The control systems in the second step are designed to suppress the effects of local uncertainties and disturbances.¹² For the third step, design procedures were described for optimization of start-up and real time diversion of off-spec material procedures, and for the justification of RTRT. The plant-wide control strategy in the fourth step is designed to suppress effects of remaining uncertainties and disturbances on the final product CQAs.²

PAT AND MSPC

Several approaches have been taken for the design and implementation of PAT in CM.

PAT has been employed as part of an automated commercial control strategy for in-process control and RTRT. Equipment capability, process complexity, segregation, and the need for real time decision making were considered in the implementation of the control strategy. Sampling plans and associated statistical sampling plan justifications were developed and implemented in a manner to ensure real time compliance.

For the Pfizer PCMM, PAT applications and their interfaces were designed to match the low retained mass and low mean residence time of the primary mixer. PAT measurements of multiple properties take place after each unit operation in the continuous system. Measurements can be taken post-mixing, post-granulation, post-drying and milling, and in the feedframe before compression. The speed of the measurement systems in the PCMM continuous processing equipment has been shown to be timely in relation to the speed of the process and movement of material through the equipment train.

Multivariate statistical process control (MSPC) can be used in CM for process monitoring. Examples exist from other industries where MSPC is being used to monitor not only steady-state operations but also to guarantee reproducible and optimum start-ups and shutdowns.⁷ Use of lagged variables, residence time distributions, and frequency of sampling should be considered in such models. Model maintenance is an integral part of MSPC.

CONTROL STRATEGY, PAT, AND SOFT SENSORS

The choice between using PAT instrumentation to infer a property or soft sensors (where the property is calculated from process parameters) depends on the applications, taking into account many factors such as method accuracy, robustness, maintenance, cost, etc. Business cases, management support, and knowledge transfer for lifecycle management are all topics of great interest and ongoing debate. Many questions still exist related to process validation, measurement redundancy, and gaps due likely to lack of experience in the manufacturing implementation of PAT and soft sensor-based control strategies industry wide.

Only a few pharmaceutical companies have developed and implemented control strategies integrating PAT or soft sensor-based advanced process control for CM, proposing, for example, a soft sensor model to predict dissolution of core tablets. Specific concerns exist regarding the lack of skillset currently in place in the pharmaceutical industry to support advanced process control methodologies and to some extended PAT-based applications when used as a core component of the control strategy. However, the need for and interest in these technologies are growing rapidly, with a desire for a continued push forward in the use of soft sensors, PAT in control strategy for CM of pharmaceutical products.

PAT equipment and model maintenance

During the product lifecycle, there will be changes in the analyzers due to reasons like age-related equipment drift, nonroutine maintenance repair, replacement, and upgrades for improved functionality or additional functionality. There will also be process changes related to aging equipment, changes in equipment, continual improvement, process adjustments, and movement within the design space.

There will also, of course, be raw material variability related to new suppliers, changes in raw material manufacturing process, or changes in raw material bulk properties or grade. All these changes may require updating the PAT models.

Customized Solutions for Full-Scale Operations

- ◆ C&Q Planning & Execution
- ◆ Cleaning & Process Validation
- ◆ Automation & Tech Transfer
- ◆ Program Management
- ◆ Asset Management & Reliability
- ◆ Operational Excellence
- ◆ Human Performance
- ◆ Paperless Execution Solutions



WHEN YOU NEED TO MEET A HIGHER STANDARD

Continuous manufacturing drivers

Commercial

- Improved cost of goods: significant reduction of capital expenditure (CAPEX), less direct and indirect effort (labor, materials, consumables), less energy and water consumption, better yields
- Higher supply chain flexibility: flexible campaign size
- Better process understanding with PAT
- Potentially more consistent product quality and fewer rejected batches: only partial rejected, depending on circumstances
- Lower inventory for finished goods and work in progress
- If driven by capacity increase, cost avoidance of additional equipment or additional facilities can play an important role to create a good net present value
- If the equipment can be fully loaded, high throughput equipment often decreases equipment down time and maximizes capacity utilization

Development and technology transfer

- Faster and cheaper development: fast design of experiments, less development material
- Faster development can help speed to market
- More robust formulations if API availability is a constraint
- More products developed as direct compression vs. wet granulation
- Less material and effort needed to scale up from development to clinical and to commercial processes

From a regulatory perspective, models can be categorized based on intended use as high, medium, and low impact.⁹⁻¹⁰ The expectations for model maintenance and subsequent variations related to post approval updates are category dependent.

It is suggested that users discuss criticality in advance with the regulatory agencies to help determine requirements for post-approval changes. It may be possible that a post-approval change management plan can be filed and used for model maintenance. In that case, models can be maintained with some greater flexibility within a company's quality system (e.g., flexibility with preprocessing condition, number of principal components). It may be possible that redundancy of control can help keep the process running while models are being updated.

SAMPLING

CM offers a wealth of process information that should be able to be used in lieu of traditional release testing. Concerns related to sampling for release testing for continuous drug product manufacturing include potential for traditional release testing expectations by some health authorities. The intended purpose of the sampling plan (e.g., confirmatory testing of in-process data vs. ability to detect process disturbances) should be clearly defined and the sampling strategy should be based on product specific CQAs and risk assessments. Using an RTRT approach, rather than measuring end product attributes, it is possible to infer them based on process data, such as a relevant combination of measured CQAs of process intermediates and process controls. Several gaps currently exist in equipment offerings

for sampling and testing. Automated, high frequency sampling/labeling equipment and technologies that enable monitoring of low detectability CQAs are critical unmet needs for CM.

VALIDATION

Process and cleaning validation have some unique considerations for CM. Stage 1 development data may require:

- How to evaluate raw material/excipient variability impact, process conditions defining end of start-up and start of normal process conditions (e.g., product flow, process residence time, residence time distribution)
- Time constraints, including coping with interruptions
- Maximum/minimum run time considerations
- Comparability between development CM equipment/scale and commercial equipment/scale may be needed if different or relocated, which may require requalification due to variability in operators, sizes, and utilities

Stage 2 production of initial process validation batches should ensure that control and monitoring systems can take measurements at a frequency correlated to dynamic response time of the critical parameter/attributes. A commonly held opinion is that real time monitoring of each CPP/CQA (i.e., continuous process verification as described by ICH Q8) is more relevant than traditional batch testing. If online real time monitoring is not possible or available, a risk-based approach could potentially be used.

Important considerations include start-up/shutdown activities along with demonstrating the ability of the system to maintain intended process conditions over time. The number of Stage 2 "batches" may depend on the knowledge accumulated in Stage 1, as well as the control/monitoring strategy utilized (e.g., online real time monitoring, or offline testing). Stage 3 ongoing verification strategy would also depend upon the control and monitoring strategy used. Cleaning validation would be required for nondedicated CM equipment. The cleaning limits would depend upon how "batch size" was determined. Cleaning frequency, campaign length, and hold time considerations are considered the same or similar to traditional batch manufacturing.

POST-LAUNCH EXPERIENCE WITH CM

Commercial/shared filing and launch experience with CM includes the following:

- The small-scale nature of CM equipment facilitates streamlined quality by design process development on commercial-scale equipment early in development, making CM ideally suited for accelerated development programs (i.e., breakthrough therapies)
- Redundant in-process control methods were implemented as a business-driven strategy to increase operational efficiency, the availability of batch data, and manufacturing resiliency
- Real time release testing was also implemented to improve operational efficiency while providing increased assurance of product quality
- The anticipated hurdles related to developing and filing a CM process were manageable through early and frequent engagement with regulatory agencies



CM IN BIOTECH

Regulatory considerations

CM and PAT concepts have been adopted in many cases initially by the small-molecule industry; the progress in biotech is likely to be incremental and gradual, but the future is promising. To some extent, a hybrid form of CM has already been embraced. For example, individual unit operations like cell culture have been run in continuous mode for certain products since the 1990s. The output from these culture feed into more traditional batch processing. The next logical step is to adapt and link these continuous cultures to downstream CM unit operations. Addressing issues such as viral clearance and microbial control will be a challenge, but not an insurmountable one. One distinct advantage for CM over batch is that it minimizes the time labile intermediates are held between processing steps, an important advantage for the production of enzyme and clotting factor products.

Implementation of CM will likely require advanced PAT tools. Various existing or novel analytical tools for measurements during, rather than at the end of, a process (PAT) can provide more information about the process and allow control in real time. With biopharmaceuticals, process intermediates and APIs are highly complex; and even when using the most current technology, not everything can be tested. Further, the API may be a minor species in the process intermediate in the upstream part of the process. However, targeted research and development may eventually evolve PAT approaches even for complex protein properties such as secondary structure and glycosylation patterns. PAT has been evolving from real time measurement of operational parameters to measurement and control of the actual product or raw material critical quality attributes. Achievement of full control by PAT will require surmounting significant technology barriers through intense and purposeful R&D, multivariate analyses, and data analytics.

CM and PAT have the capacity to revolutionize the biopharmaceutical industry, but only if the opportunity is seized. The development and implementation of such technological advances have, and will continue to receive, strong support from the FDA. To speed up CM and PAT implementation, it is vital that success stories be shared.

Industrial perspective

Over the past 5 years, there has been significant progress made by the biopharmaceutical/biotechnology industries, academia, and suppliers in applying CM to production of biologics. The drivers for the biopharmaceutical industry to adopt continuous technologies are the same as for other industries: increased productivity and flexibility, reduced cost and cycle time, enhanced process control, and product quality.

Many companies have been successful in intensifying their operations through perfusion cell culture processes, developing and implementing continuous chromatography systems suitable for manufacturing, integrating various unit operations to eliminate non-value-added steps, and streamlining production process while achieving state of process and product attribute control. Some have demonstrated proof-of-concept of fully continuous process (bioreactor to formulated drug substance), while others have successfully scaled integrated processes to commercial scale. As the industry drives toward continuous commercial operation, there are increasing efforts to develop and implement robust PAT, process monitoring, and automation while addressing remaining key technology gap, such as continuous virus inactivation, virus filtration, and buffer exchange. With continued strong support and active engagement with health authorities, it is envisioned that a continuous architecture will emerge and become established as a very competitive, universal platform for the production of biologics.

The willingness of regulators to support innovations provides a positive backdrop for CM, although challenges for end-to-end biologics manufacturing process are substantial. A created inventory of existing or desired technologies with considerations for equipment, measurements, process knowledge, and regulatory challenges for each unit operation could be helpful in progressing adoption. Continuous cell culture and harvesting is already quite common in the industry, and although long-term sterility can be a significant challenge, proven operation is possible with good design and operating principles. Continuous chromatography technologies have been demonstrated by cleverly configuring multiple “batch” column processes so that the process stream flows without interruption.

Although bioreactor integration with continuous product capture has been demonstrated at bench and production scale, key technology gaps remain before the entire production process can be made fully continuous; these challenges includes continuous unit operations for viral inactivation, viral filtration, ultrafiltration/diafiltration, and fill/finish. Smartly designed automation as well as online/inline PAT to monitor product attributes are additional key enablers that will need to be developed and fully tested in the pilot/production environment, along with optimized operational practices and comprehensive risk assessment/mitigation, before end-to-end CM and real time release can be implemented and fully realized in biomanufacturing.

Lastly, although there are many important strategic advantages of CM over conventional batch processing, it will be very helpful to fully assess the impact of CM on cost reduction (operating expense and CAPEX), which will help to support business case.

CONCLUDING REMARKS

Although the benefits of CM seem obvious and significant, large-scale deployment in the commercial environment is still in its infancy. Many companies are either in the exploratory or wait-and-see stages for adoption of these new technologies. At the time of this publication, there exist two known approvals by the US FDA using CM for tablet manufacturing; one of these is also approved in Europe. Scattered examples of approved CM for single-unit operations exist for small-molecule and biotechnology drug substances.

The regulatory interest in adoption of CM is substantial. Health authorities from several regions have formed special teams to aid in the adoption of this and other emerging technology. FDA has posted that “continuous manufacturing has a strong impact on drug quality,”¹⁶ making a clear statement of encouragement. FDA and the US Biomedical Advanced Research and Development Authority also have ongoing opportunities for innovations in medical countermeasure CM.⁵ Additionally, in April 2016, the Executive Office of the President, White House National Science and Technology Council, declared CM in pharmaceuticals as a manufacturing area of “emerging priority,”¹⁴ and specific funding for CM was provided in the 21st Century Cures Act, which was adopted at the end of 2016.¹³

With a framework being laid by regulators in many regions, the onus is now on industry to deliver the new technology. With its enhanced assurance of quality and availability of supply, CM is expected to have positive impact for industry, regulators and patients. <>

References

- European Medicines Agency. Scientific Advice and Protocol Assistance. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000049.jsp&mid=WC0b01ac05800229b9
- . Quality by Design. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000162.jsp&mid=WC0b01ac058076ed73
- . Process Validation for Finished Products—Information and Data to be Provided in Regulatory Submissions. Revision 1. 28 February 2014. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000729.jsp&mid=WC0b01ac0580028e8b
- Executive Office of the President of the United States. Subcommittee for Advanced Manufacturing of the National Science and Technology Council. “Advanced Manufacturing: A Snapshot of Priority Technology Areas across the Federal Government.” <https://www.whitehouse.gov/sites/whitehouse.gov/files/images/Blog/NSTC%20SAM%20technology%20areas%20snapshot.pdf>
- FedBizOpps.gov. “Innovations in Medical Countermeasure Continuous Manufacturing.” Solicitation Number: FDA-RFI-1148971. https://www.fbo.gov/?s=opportunity&mode=form&id=33786084313fe44c63e23c2c15d10fce&tab=core_&cvview=0
- US Food and Drug Administration. “Continuous Manufacturing has a strong impact on Quality.” *FDA Voice*, 12 April 2016. <http://blogs.fda.gov/foodvoice/index.php/2016/04/continuous-manufacturing-has-a-strong-impact-on-drug-quality>
- Kourti, T. “Multivariate Dynamic Data Modelling for Analysis and Statistical Process Control of Batch Processes, Start-Ups and Grade Transitions.” *Journal of Chemometrics* 17, no. 1 (January 2003): 93–109.
- International Society for Pharmaceutical Engineering. Facility of the Year Awards. 2016 Category Winner for Equipment Innovation. <http://www.facilityoftheyear.org/winners/2016-equipment-innovation>
- Kourti, T., et al. “Scientific and Regulatory Considerations for Implementing Mathematical Models in the Quality by Design (QbD) Framework.” *Pharmaceutical Engineering* 35, no. 3 (May–June 2015): 80–88.
- Kourti, T., et al. “Scientific and Regulatory Considerations for Implementing Mathematical Models in the Quality by Design (QbD) Framework, Part 2.” *Pharmaceutical Engineering* 35, no. 4 (August 2015): 38–51.
- Myerson, A. S., et al. “Control Systems Engineering in Continuous Pharmaceutical Processing.” *Journal of Pharmaceutical Sciences* 104, no. 3 (March 2015): 832–839.
- Lakerveld, R., et al. “The Application of an Automated Control Strategy for an Integrated Continuous Pharmaceutical Pilot Plant.” *Organic Process Research & Development* 19, no. 9 (2015): 1088–1100.
- US Congress. 21st Century Cures Act. <https://www.congress.gov/114/bills/hr34/BILLS-114hr34enr.pdf>
- Yu, Lawrence. “Continuous Manufacturing Has a Strong Impact on Drug Quality.” *FDA Voice*, 12 April 2016. <https://blogs.fda.gov/foodvoice/index.php/2016/04/continuous-manufacturing-has-a-strong-impact-on-drug-quality>

Authors

Conference co-chairs

Theodora Kourti, PhD, Senior Vice President, Global Regulatory Affairs, ISPE, United States

Rapti Madurawe, PhD, Division Director, Office of Process and Facilities, FDA/CDER/OPQ, United States

Regulators

Kurt Bronson, PhD, Lab Chief (Acting), FDA/CDER/OPQ/OBP/DBRRIL, United States

David Doleski, Deputy Director (Acting), Office of Process and Facilities, FDA/CDER/OPQ, United States

Dolores Hernán Pérez de la Ossa, PhD, Quality Specialist, Quality Office, Specialised Scientific Disciplines Department, EMA, United Kingdom

Jean Hu-Primmer, Interdisciplinary Scientist and Senior Advisor for CBRN and Pandemic Influenza, FDA/OC/OCET, United States

Industry

Christian Airiau, PhD, Team Manager, Process Analytical Technologies, R&D GlaxoSmithKline

Gretchen A. Allison, Senior Director, Team Lead Validation, Pfizer Inc., United States

Richard D. Braatz, PhD, Edwin R. Gilliland Professor of Chemical Engineering, Novartis-MIT Center for Continuous Manufacturing, Massachusetts Institute of Technology, United States

Yanxi Tan Cain, PhD, Executive Director, Global Quality Assurance, Merck & Co., Inc., United States

Lawrence de Belder, Senior Principal Engineer, Johnson & Johnson, Belgium

Steve Hammond, Senior Director/Team Leader, Process Analytical Sciences Group, Pfizer Inc., United States

Jun Huang, PhD, Senior Manager, Advanced Manufacturing Technology, Pfizer Inc., United States

Christopher Hwang, PhD, Senior Director, Continuous Manufacturing Skill Center, Sanofi Genzyme, United States. Currently Executive VP of Process and Product Development, JUST Biotherapeutics Co., Hangzhou, China

Gordon (Randy) Lambertus, PhD, Senior Research Scientist, Process Design and Development, Eli Lilly & Co., United States

Catherine MacConnell, Engineering Specialist, Pharmaceutical Commercialization Technology, Merck & Co., Inc., United States

Steve Miller, Director, MedImmune/AstraZeneca, Global Engineering, United States

Christine M. V. Moore, PhD, Global Head and Executive Director, Merck & Co., Inc., Kenilworth, New Jersey, United States

David Pappa, Director—Technical Services & Manufacturing Science, Indianapolis Dry Products, Eli Lilly & Company, United States

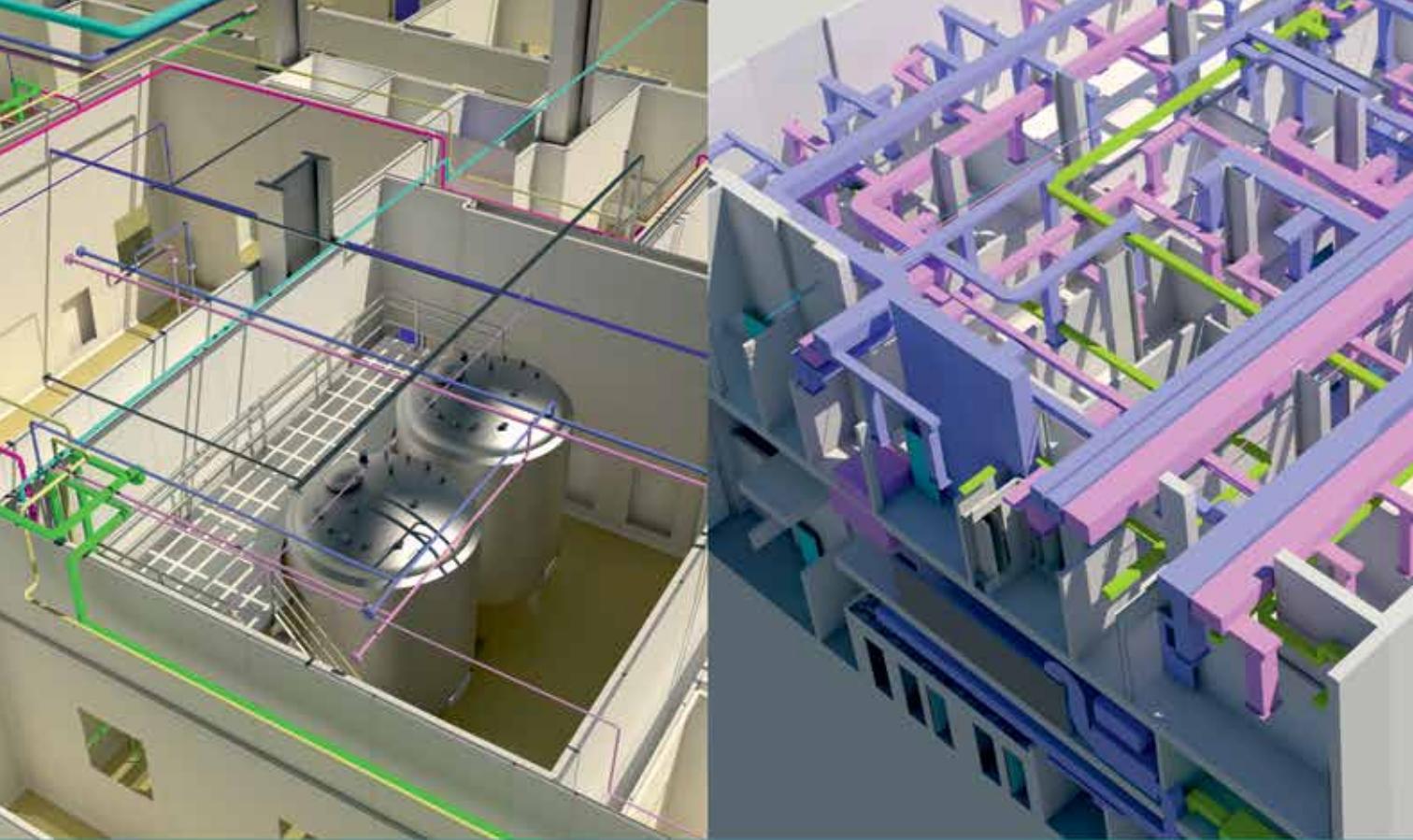
Wyatt Roth, PhD, Senior Research Scientist, Eli Lilly & Co., United States

Vidya Swaminathan, PhD, Director—Global Manufacturing & Supply, Bristol-Myers Squibb, United States

Kelly Swinney, PhD, Senior Director, Drug Product Continuous Manufacturing Lead & Process Analytical Technology (API & DP), Vertex Pharmaceuticals, Inc., United States

Kelly Toltan, Senior Director, Technical Operations, Vertex Pharmaceuticals, Inc., United States

Andre Walker, Andre Walker Consulting, Greater Boston Area, Massachusetts, United States



Put your planning in safe hands FOR TURNKEY PHARMACEUTICAL SOLUTIONS

*The numbers
speak for themselves*

63 PROJECTS

75 INDUSTRY VETERANS

250+ GLOBAL SUPPLIERS

35+ VENDOR BASE COUNTRIES

268 MEMBER STRONG EXECUTION TEAM

Call : +91 22 4031 3888 or Email : sales@pharmaaccess.net

www.pharmaaccess.net

411 / 413, Dilkap Chambers, Off Veera Desai Rd.,
Andheri (W), Mumbai 400 058, Maharashtra, India.



A HOLISTIC APPROACH TO PRODUCTION CONTROL FROM INDUSTRY 4.0 TO PHARMA 4.0

Prof. Dr. Christoph Herwig, Christian Wölbeling, and Thomas Zimmer, PhD

This article presents the work of the newly formed ISPE Holistic Production Control Strategy Working Group, which has identified and summarized the need for a redefined control strategy implementation methodology.

PROBLEM STATEMENT

The current submission-based control strategy plays a key role in ensuring that critical quality attributes (CQAs) are met, and the quality target product profile (QTPP) is realized. It does not, however, consider GMP, facilities, utilities, equipment and other production-specific controls to mitigate risk and ensure an effective, reliable, and stable production process. In addition, the effect of unknown process parameters, raw material attributes, and impurities usually are not sufficiently addressed in the control strategy lifecycle management—it is often impossible to predict such variations for a production lifecycle already in development.

Transforming today’s development-based control strategy to commercial manufacturing by technology transfer and scale requires a best practice methodology that would change the current control strategy into a holistic production control strategy (HPCS).

This would create a flexible and robust production process with well-documented lifecycle management that could be applied to existing production operations as well as facilities of the future, from design concept to detailed design, and from implementation up to commissioning, qualification, and daily operations.

Speaking at the ISPE EU Annual Conference in Frankfurt in March 2016, Ian Thrussell, Expert Inspector at the World Health Organization, identified additional requirements: “The transformation in the design

and the execution of the control strategy has to follow a ‘data integrity by design’ approach.”

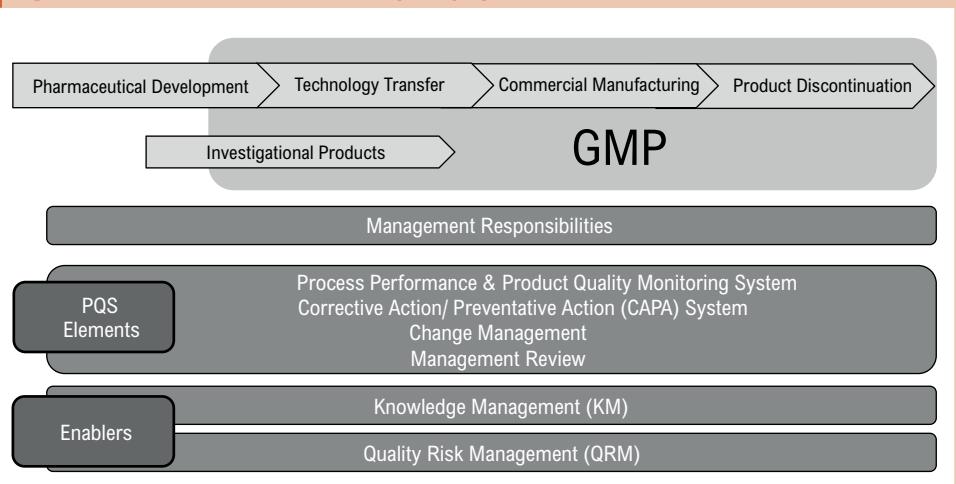
Data integrity by design is a structured risk-based approach that applies critical thinking to create process maps, process data maps, and data flows to design the production process in a flexible and robust manner. Professionals miss an opportunity for success when they don’t apply two key cross-functional factors: a process-oriented approach, and communication skills. Additionally, business process descriptions or process charts/maps and process data maps are not always developed and applied properly.

Critical thinking during the design, creation, and execution of the shop floor production process ensures repeatable, robust, and right-first-time execution of the commercial production process. The parameter space must be adapted throughout the product lifecycle, beyond the original design space and the submission-based control strategy.

ICH is currently drafting the Q12, “Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management” Guideline, which will specify the post-approval change management of the product control strategy, and enable the application of new, robust, and flexible product and production-process monitoring plans and controls like continuous process verification (CPV).

All these concepts are currently isolated from each other, however. A new “holistic” production control strategy could be based on existing ICH-defined concepts, incorporate new elements and enablers that ad-

Figure 1: ICH Q10—Pharmaceutical quality system



dress challenges from digitalization and big data management, and include all activities throughout the value chain and the product lifecycle.

THE CHALLENGE: IMPLEMENTING ICH Q10 IN PRODUCTION

This information was presented at the 2016 Facilities of the Future Conference, 14–15 November 2016, Bethesda, Maryland, US

The proposed approach is based on the ICH Q10 view of the PQS product lifecycle and control strategy.

Figure 1 shows the original ICH Q10 visualization of the PQS. This concept is based on key principles (enablers) and control strategy design tools (elements) used throughout the pharmaceutical production lifecycle. ICH Q10 states that: “these elements should be applied appropriately and proportionally to each lifecycle stage recognizing opportunities to identify areas for continual improvement.”

Using this as a basis, the HPCS working group developed a concrete and practical corresponding picture to detail this approach in production.

Figure 2 shows enablers and elements, which are critical success factors for designing and executing a stable yet flexible and robust HPCS in commercial manufacturing.

The physical and operational design of the pharmaceutical equipment, facilities, logistics, and operational concepts (including work instructions, automation, and equipment) shall be based on business process descriptions, process maps, process data maps reflecting production experience, and best practices. Early collaboration from all pharmaceutical departments—quality assurance, quality control, process development, manufacturing operations, engineering, automation, and information technology (IT)—is required to design a robust, flexible, right-first-time facility that operates at the expected quality level to ensure that the CQAs are met and the QTPP is realized. A data integrity by design principle can also be implemented by applying a risk-based approach based on critical thinking.

While current ICH Q8 and Q10 definitions of control strategy remain valid, facilities of the future will have a high level of automation applying the newest technologies. Pharmaceutical production based on Industry 4.0* factory design will become “Pharma 4.0” when applied to GMP

Holistic Production Control Strategy

- Is a set of enablers and elements that provides a holistic view of production to ensure a flexible, agile, sustainable, and reliable pharmaceutical production that mitigates the risk to patients, products, processes, and the business.
- Covers products and materials designed for fully automated processes. It requires an educated workforce to manage integrated processes and data flows as well as modern platforms, machines, and facilities designed for digitalization and automation.
- Supports business processes with integrated GxP IT systems along the supply chain.
- Requires management to establish and foster an adequate framework and organizational culture for Pharma 4.0.

compliance, validation, and GAMP® requirements. HPCS encompasses best practice design methodology from the submission control strategy documentation to the master production control record, up to and including Pharma 4.0 documentation and requirements. This leverages the benefits from the new operational excellence opportunities of Pharma 4.0. A new “Workforce 4.0” will also be required to interact with the complex and intelligent equipment.

APPROACHING THE PROBLEM

Control strategy best practice methodology is outlined in the ISPE PQLI® Guides. HPCS implementation requires a cross-divisional approach and methodology that includes product and production data lifecycle management. This is not yet completely well established in all organizations.

HPCS enablers

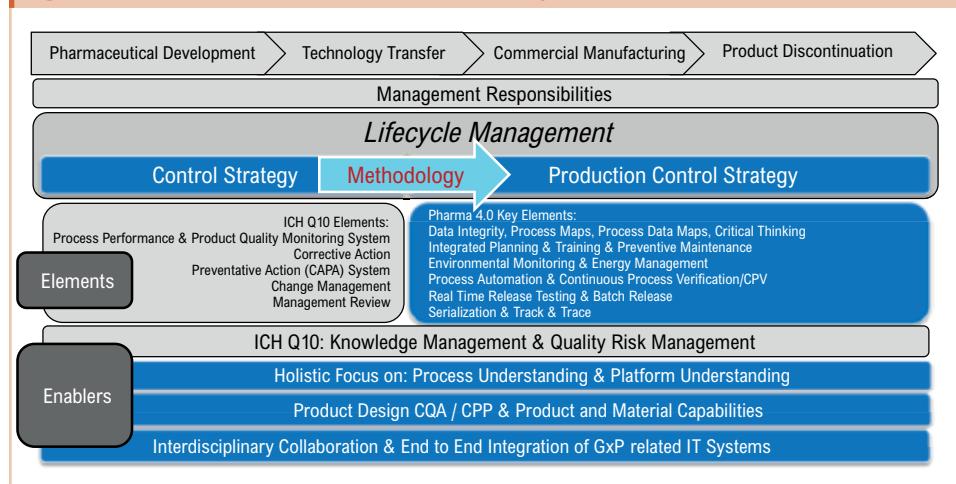
ICH Q10 identifies knowledge management and quality risk management as two major enablers throughout the pharmaceutical lifecycle and the bases for HPCS design and execution. Product design—including identifi-

cation of CQAs, critical process parameters (CPPs), and critical material attributes—is another key enabler for product and material capabilities.

Holistic process and platform understanding needs cross-organizational interdisciplinary collaboration from all departments and stakeholders combined with integration of all GxP-related IT systems to enable data

* Often called the fourth industrial revolution, Industry 4.0 is the digitization of manufacturing, including “big data,” connectivity, analytics, the Industrial Internet of Things, and digital-to-physical transfer.

Figure 2: From ICH Q10 to Pharma 4.0—holistic production control



integrity. Enhanced data science approaches in production must become the foundation for decision-making to operate in automated environments, implement process analytical technology (PAT) in its holistic definition, and allow modern advanced technologies like continuous manufacturing.

HPCS elements

By applying a design process based on process maps and underlying process data maps, Pharma 4.0 will ensure data integrity by design.

Data integrity is much more than ensuring a good audit trail: It is about quality of data, the right content, and respecting the ALCOA+ principles.¹ Auxiliary materials and excipients, for example, could have the same name and quality-specific reference number across the global network of a company to avoid mix-ups and misunderstandings. Critical thinking is needed to design a robust, repeatable, but still flexible production process. This includes thorough data science approaches and architectures. When establishing a quality risk map using ICH Q 9, for example, one of the most important steps is risk identification, which requires experience, a balanced

view on risk, and the ability to imagine what can go wrong. Hence, prior knowledge should be available in a structured form.

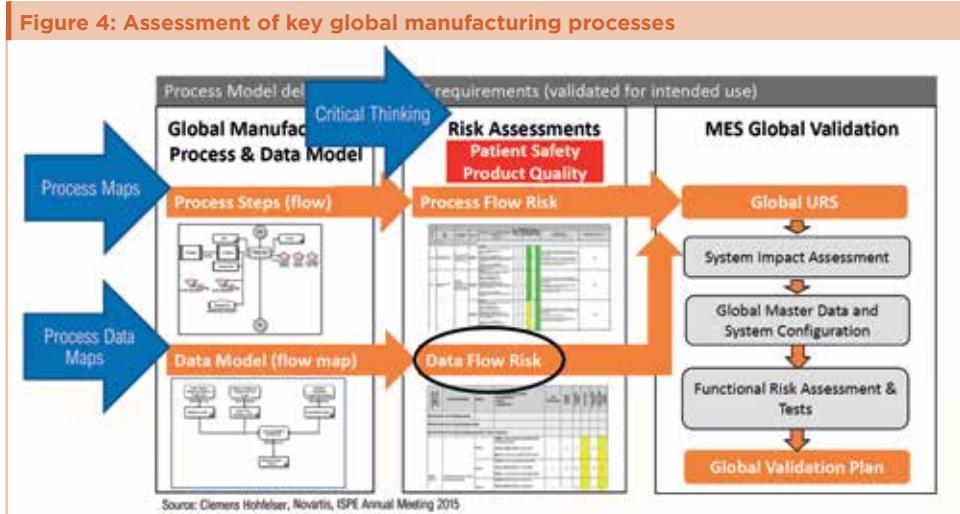
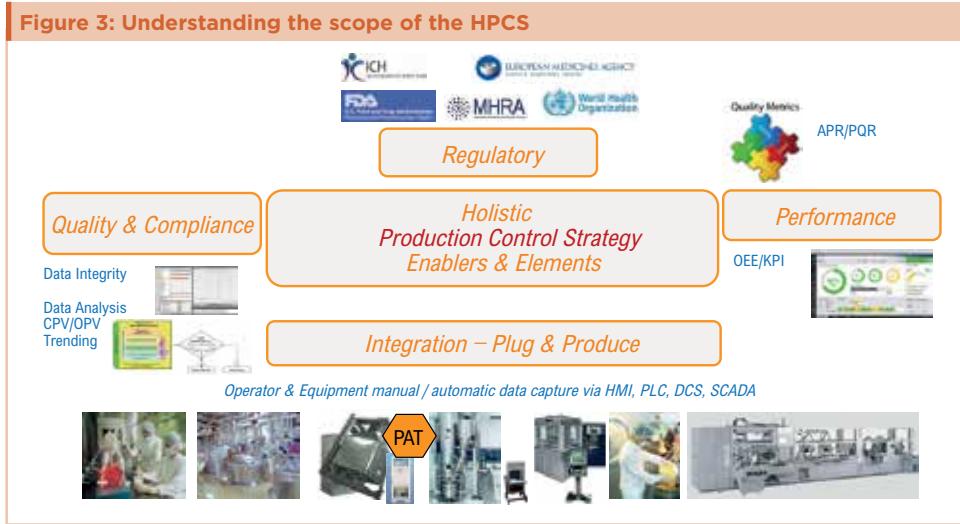
Integration of all supporting computerized systems is key, both vertically and horizontally across systems, as well as throughout the product lifecycle and the value chain. This includes physical data interfaces, process automation to support CPV (by applying modern technologies like PAT), and predictive process controls to establish real time release testing (RTRT). Big pharma companies that recognize this need have started to establish a one-source “data lake” for system integration, plus fast real-time and ad hoc reporting for management decisions.

Preventive maintenance to enhance performance and minimize downtimes could be integrated into a process planning procedure that optimizes the collaboration of all production-related equipment, operators, and their training, as well as environmental monitoring, including energy consumption. A “ready-to-run” visual shows all conditions required to start production:

Is the employee qualified? Has he/she undergone updated SOP training? Has the machine, room, and equipment clearance been done? Are all maintenance cycles in compliance with internal SOPs? Has the product dossier been updated with the latest corrective/preventive actions and change management?

Environmental monitoring and energy management are similar to preventive maintenance, and should be integral parts of a release to start production. Integrated energy management will ensure that all processes have sufficient electricity and backup. Even seconds of downtime can destroy a batch. All other infrastructure system malfunctions could be defined as relevant for quality and compliance, and integrated into the supervision process.

Automation and CPV usually apply only to their bespoke products. Products more than 10 years old are often not suitable for automated processes, as they depend largely on unwritten operator knowledge of both the process and the interaction between equipment and environmental conditions. The strategic target of a development project, therefore, could



Source: Clemens Hohfleser, “Data Integrity in Manufacturing Execution ... A Process Oriented Approach.” Presented at the ISPE 2015 Annual Meeting, 8–11 November 2015, Philadelphia, Pennsylvania, US. Reprinted with permission.

¹ See Special Report on Data Integrity, *Pharmaceutical Engineering* 36, no. 2 (March–April 2016): 39–67.

be pharmaceutical processes with automated PAT-related controls when CPV is applied.

Real-time and batch releases in a Pharma 4.0 world would be harmonized so that batch and document release are synchronized; this would prevent holding the real-time release of a process until all documents had been reviewed.

Other commercial and regulatory requirements like mass serialization and track and trace against counterfeit products are also key elements of HPCS. As the product code and security number are now considered compliance relevant they must be an integral part of the whole supply chain; this also prevents false positives. Even a high-quality product can hold up the supply chain if its serialization numbers are not correct.

These are all generic key elements of Industry 4.0 applied specifically as Pharma 4.0. In general, all GxP-related IT systems such as enterprise resource planning, enterprise content/documents management, and enterprise quality management could be integrated in one enterprise manufacturing intelligence system.

PHARMA 4.0: HPCS

The holistic view of the production control strategy consists of four key areas where enablers and elements are applied. Regulatory requirements and guidelines provide overall governance (Figure 3):

1. Manufacturing process work instructions

The master production control record is still the key regulatory element for the description of the manufacturing process. Processes that follow the paradigm of a flexible execution need a flexible control strategy. In addition, the elements of preventive maintenance and optimized process planning influence the production process flow.

2. Quality and Compliance

ICH and FDA process validation guidelines help establish flexible production processes, including the CPV and ongoing process verification; these enable close monitoring and control of CQAs and CPPs. Combining data integrity and data lifecycle management approaches with practical knowledge management processes is still a challenge in the industry.

In a Pharma 4.0 world, however, the concept of quality assurance must be adapted to cross-functional business processes and must redefine the tasks and responsibilities of systems, cross-functional process owners, and content owners in the various business functions.

3. Performance

To ensure a cost-efficient production process, data must be evaluated, analyzed, and used to optimize the process. Quality metrics will be applied to measure the efficiency of the overall production process. Enabling flexible processes can also shorten production lead time.

In a Pharma 4.0 world, operational excellence goals should be redefined. If targets continue to be “solo-ed” the total optimum will never be reached. This management challenge is supported by knowledge from senior experts and knowledge management tools.

GEMÜ®
VALVES, MEASUREMENT AND CONTROL SYSTEMS

**GEMÜ Quality Products...
GEMÜ Quality Service**

4212 & 4242 Automation features:

- Class 1 DIV 2, UL & CSA
- Multiple control options: 24 VDC, AS-I, DeviceNet
- Super bright LEDs indicate valve position

Multiport Diaphragm Valve features:

- Thousands of block designs to solve process challenges
- Minimize dead leg and hold up volume for optimal process efficiency

Globe Valve features:

- High cycle life
- Variety of end connections, materials of construction and actuation

4212 Switch

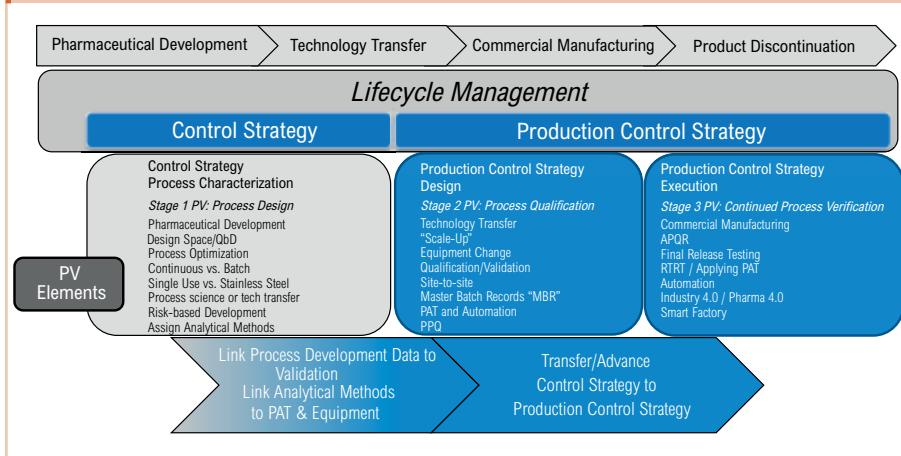
550 Globe valve with 1434 positioner

650 Diaphragm valve with 4242

Multiport

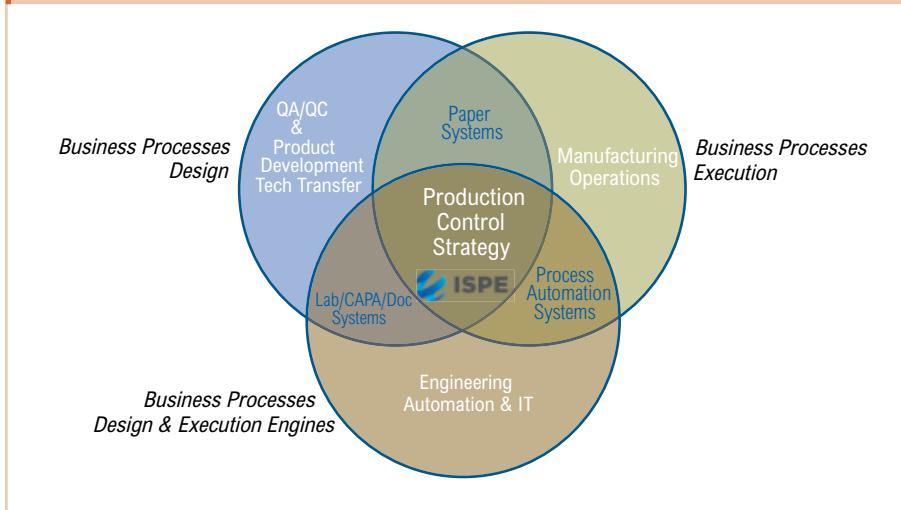
3800 Camp Creek Parkway • Building 2600 • Suite 120
Atlanta, GA 30331 • info@gemu.com • Tel: 678-553-3400
www.gemu.com

Figure 5: Three-stage Pharma 4.0 process validation



Source: ISPE Biotech Special Interest Group

Figure 6: Interdisciplinary collaboration



4. Integration: Plug and produce

The HPCS-enabled smart factory will be integrated horizontally and vertically by standard interfaces, which will ease integration of prequalified equipment. This is already established in the semiconductor and other industries. Integration for plug-in compatibility should also comply with data integrity requirements (such as audit trail); data security; seamless integration of on-line, inline, and at-line PAT instrumentation process control; and RTRT or packaging serialization and track and trace. Future integration concepts should follow this plug-and-produce concept to reduce costs and enable flexible production solutions and provide a cost-efficient lifecycle management interface.

In Pharma 4.0 the industry needs globally defined technical standards such as GAMP or ISO as well as standards for product quality profiles and technical suitability for automated processes. Some materials should be removed from developer material lists as unsuitable for technical processes (e.g., for high physicochemical variability).

Products made for small batches and personalized medicine need other standards than a mass product for large populations.

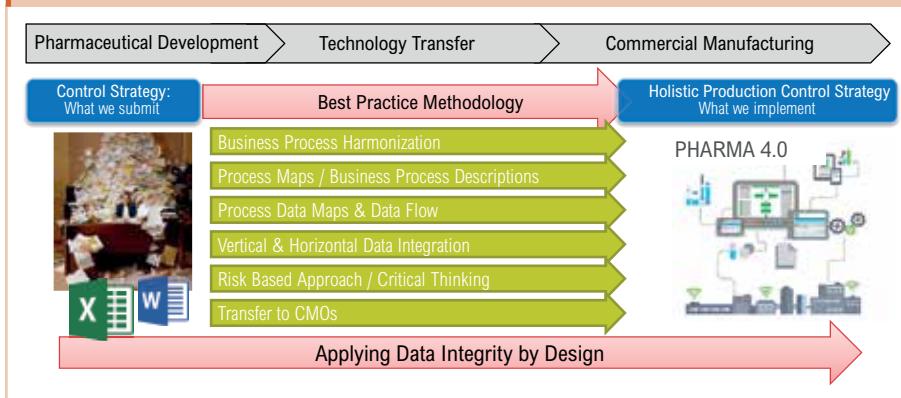
HPCS IN PROCESS VALIDATION

The ISPE Process Science Working Group, part of the Biotech Special Interest Group (SIG), enhanced the ICH PQS lifecycle picture and applied it to the three stages of process validation (Figure 5). This shows the evolution of the control strategy to the HPCS across the three process validation stages.

WORKFORCE 4.0

An HPCS needs interdisciplinary collaboration of all organizational business units responsible for the production process, technology, and quality. Per ICH Q10, this also includes management, since they are responsible for quality and HPCS compliance. We call this Workforce 4.0.

Figure 7: HPCS best practice implementation



HPCS in a Nutshell

Potential cost savings are enormous. Regulatory guidelines are in place to leverage this potential, but examples to put them into practice are still missing. At the same time, regulatory authorities and inspectors increasingly apply requirements for quality risk management and safe production for pharmaceutical products. The trend to megadigitization—the Industrial Internet of Things or Industry 4.0—offers the opportunity to realize these potentials. This is more than just the next wave of hot topics; it will lead to one of history's biggest paradigm changes for pharmaceutical manufacturing.

To create a successful cross-functional approach to these new concepts, the pharmaceutical industry must align with its main stakeholders: regulators, investors, manufacturing leaders, and key suppliers. An ISPE SIG is studying how best to transition commercial manufacturing from current control strategies to an HPCS using a Pharma 4.0 framework.

Three main areas need attention:

Leadership: Senior management understanding, ownership, and responsibility for cross-functional stakeholder management.

Capabilities: Cross-divisional knowledge, understanding, and collaboration.

Toolbox: Identify, implement, and train methods and best practices to implement an advanced HPCS.

SUMMARY

There is a huge potential in applying Industry 4.0 technologies along the end-to-end supply chain. Regulatory prerequisites for this approach are already in place. While the industry may still be hesitant to implement these technologies and change well-established, qualified, and validated production processes, development of the ICH Q12 "Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management" Guideline will enhance the regulatory basis for this approach.

The goal of the Pharma 4.0 SIG and its Holistic Production Control Strategy and Plug and Produce Subgroups is to provide best practice implementation methodologies, approaches, and practical examples on how to apply the technologies and integration approaches and to improve quality by well-understood and -controlled processes. With these in place, data integrity, quality, compliance, and predictive production processes will be the reward. ◊

Acknowledgments

ISPE Germany, Austria, and Switzerland (DACH) Affiliate:

Pharma 4.0 Special Interest Group and Holistic Production Control Strategy Subgroup: Christian Wölbeling, Werum (Leader); Lorenz Binggeli, B. Braun, Christoph Herwig, TU, Vienna; Michael Fossler, IT consultant; Birgit Kraus, Sanofi; Hans-Martin Schwarm, consultant

Biotech Special Interest Group and Process Science Subgroup: Christoph Herwig (Leader, TU Wien, CD Laboratory on Methods for Improved Bioprocesses); Patrick Sagmeister, Exputec; Christian Wölbeling, Werum; Joachim del Boca, Vetter.

References

1. Hohfeler, Clemens. Data Integrity in Manufacturing Execution ... A Process Oriented Approach." Presented at ISPE 2015 Annual Meeting, 18–21 September 2016, Atlanta, Georgia, US.
2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. "Pharmaceutical Quality System: Q10." 4 June 2008. www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Step4/Q10_Guideline.pdf
3. US Food and Drug Administration. Guidance for Industry. "Process Validation: General Principles and Practices." January 2011. www.fda.gov/downloads/drugs/guidances/ucm070336.pdf
4. ———. Guidance for Industry. "Q8, Q9, and Q10 Questions and Answers (R4)." November 2011. Revision 1. www.fda.gov/downloads/Drugs/.../Guidances/UCM210822.pdf
5. ———. Guidance for Industry. "PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance." September 2004. www.fda.gov/downloads/Drugs/.../Guidances/UCM070305.pdf
6. Woodcock, J. "The Concept of Pharmaceutical Quality." *American Pharmaceutical Review* 47(6): 1–3, 2004.

About the authors

Prof. Dr. Christoph Herwig, bioprocess engineer, graduated from the process engineering department, RWTH Aachen university of technology in 1994. He worked in industry in the design and commissioning of large chemical facilities prior to enter his interdisciplinary PhD studies at the École Polytechnique Fédérale de Lausanne, Switzerland, in the field of bioprocess identification. Since 2008, he is full professor of biochemical engineering at the Vienna University of Technology, Austria, researching methods for integrated, science-based and efficient bioprocess development along PAT and QbD principles. He has been an ISPE member since 2002.

Christian Wölbeling is Senior Director, Global Accounts, at Werum IT Solutions based in Lueneburg, Germany, part of the Körber Medipak Systems Group. He has worked in Life Sciences Manufacturing IT for the past 25 years, with experience in all GMP-related processes. An ISPE member since 2001, he has served as a steering committee member of the PAT and Lifecycle Control Strategy CoP, DACH Affiliate Board member, KNC Co-Chair, GAMP SIG MES Co-Chair, and leader of the MES-related chapter in the for the Data Integrity Good Practice Guide. He holds a master's degree in mechanical engineering.

Thomas Zimmer, PhD: held numerous positions at Boehringer Ingelheim between 1981 and 2013: pharmaceutical development, pharmaceutical production, international production, quality management, quality standards, corporate lead auditor GMP, implementation production alliance Europe, product transfers, transition management from national to international supply, plant manager/directeur industriel of pharmaceutical production in France, senior vice president of global quality, qualified person, and senior vice president of environment, health, and safety and sustainability. Since November 2013 he has served as the Vice President of ISPE's European Operations. He has been an ISPE member since 2005.

Pharmaceutical Water and Pure Steam Systems

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



Online Total Organic Carbon Analysis

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



CORROSION INVESTIGATION OF PHARMACEUTICAL CLEAN STEAM SYSTEMS

Drew C. Coleman and Daryl L. Roll

This article presents current research on the problem of rouge in clean steam generators and their distribution systems, as well as possible deleterious effects on capital equipment and final drug products.

WATER QUALITY PLAYS A MAJOR PART IN ROUGE PRODUCT CHEMISTRY

Pharmaceutical clean (pure) steam systems consist of a generator, distribution tubing or piping, thermodynamic or balanced pressure thermostatic traps, control valves, pressure-reducing regulators, pressure gauges, pressure-relief valves, and volumetric totalizers. Most of these components are made of 316L stainless steel and contain fluoropolymer gaskets (most commonly polytetrafluoroethylene, also known as PTFE or Teflon), as well as semimetallic or other elastomeric materials. These components tend to corrode or degrade in service, potentially compromising the quality of the final clean steam (CS) utility product.

This project investigated stainless steel coupon samples from four CS system case studies, testing condensate for metals and particles, and conducting a risk assessment of potential corrosion effects on process and critical utility systems. Examining the corrosion byproducts involved preparing sample coupons of corroded tubing and components from distribution systems.⁹

These case studies investigated a variety of surface conditions, and included analysis of typical rouge products and corrosion effects. The referenced sample surfaces were evaluated for rouge deposits by visual inspection, scanning electron microscopy (SEM), auger electron spectroscopy (AES), and electron spectroscopy for chemical analysis (ESCA)/x-ray photoelectron spectroscopy (XPS). These techniques reveal the physical and atomic properties of the corrosion and deposits, and identify potential contributions to the critical utility fluid properties or final product.¹

OVERVIEW

Stainless steel corrosion products are encountered in a variety of forms, such as a ferric oxide rouge layer (red or brown) on the metal surface found under- or overlying the thicker ferrous oxide layer (dark gray or black).² The rouge layer is crystalline in structure and potentially dynamic, or capable of migrating downstream. The ferrous oxide (black rouge) layer tends to thicken over time as the deposit becomes more pronounced; its migratory presence is evidenced by particles or deposits found on sterilizer chamber surfaces and on equipment or vessels after steam sterilization. Laboratory analyses of condensate samples illustrate

the particulate nature of the rouge as well as the level of soluble metals in the CS fluid.⁴

While there are multiple causes of these phenomena, the CS generator is often a significant contributor. It is not uncommon to notice ferric oxides of rouge (red/brown) on the surface, with ferrous oxides (gray/black) at the steam discharge, with both types slowly migrating throughout the CS distribution system.⁶

The CS distribution system is a branching configuration that has multiple use points, terminating at distant areas or ends of a main header and various branching subheaders. The system may include a series of regulators to reduce pressure/temperature at certain use points; these may be sites for corrosion. Corrosion can also occur in hygienically designed traps placed at various points within the system to remove condensate and air from the mobile clean steam, in downstream piping/tubing to drains, past the traps, or in condensate collectors. Reverse migration is evident in most cases, with rouge deposits forming above the traps and growing upstream into adjacent use point piping or into subheaders and beyond; the rouge that forms in traps or other components is found upstream from this source and continues to migrate both upstream and downstream.

Rouge in steam systems can be found in all forms including:

- Class 1: migrating rouge that forms in one place and migrates to another surface
- Class 2: rouge that forms on the surface where the corrosion occurs
- Class 3: rouge formed in higher-temperature conditions (over 95°C)¹⁰

At use points, ball valves or valve housings exhibit significant rouge accumulation. Certain stainless steel components also demonstrate moderate to high levels of a disparate metallurgical structure, including delta ferrite. Ferrite crystal structure is suspected of lowering corrosion resistance, even though its content may only be 1%–5%. In addition, ferrite does not possess the corrosion resistance of austenitic crystal structure, therefore, it will corrode preferentially. Ferrite can be detected accurately with a ferrite meter or semi-accurately (and with significant limitations) using a magnet.

SUMMARY

From system inception, when a new CS generator and distribution tubing is first commissioned and energized, several potential factors for corrosion are present:

- In addition to clean steam, the CS generator begins to generate corrosion particles (class 1 rouge) that have the potential to migrate.
- Separately, pressure regulators begin to generate (class 3) rouge downstream, and possibly upstream as a function of time.
- High levels of delta ferrite, metallic inclusions, or other material defect content in components begin to generate corrosion products (class 2 rouge).
- Condensate traps can add further migration-capable corrosion (class 1 rouge).
- Distribution tubing will show corrosion effects and accumulated rouge (class 2 and 3 rouge).
- Ball valves can generate corrosion from trap lines as well as at use points.

Further, as a function of time, these corrosion factors may produce corrosion products as they meet, combine, and overlap with a blend of ferrous and ferric rouge. Generally, black rouge is first seen in the generator; rouge then emerges at the generator discharge piping and eventually throughout the CS distribution system.

SEM OBSERVATIONS

We conducted SEM analyses to illustrate the microstructure of the corrosion byproducts that covered the entire surface with crystalline and other particles. The background or underlying surface upon which the particles are distributed ranged from various gradations of ferrous (Figures 1–3) to the

most ubiquitous sample, a silica/ferrous, glassy, tenacious, uniform deposit (Figure 4). A steam trap bellows (Figures 5–6), was also investigated.

AES results

AES testing is an analytical method used to determine the surface chemistry of stainless steel and predict its corrosion resistance. It also shows the degradation of the passive film and the reduction of chromium concentration in the passive film as the surface degrades due to corrosion.

AES survey scans (depth profiles of elemental concentrations at the surface) were used to characterize the elemental composition of each sample surface. The analysis sites and SEM magnifications were carefully selected to provide information from typical regions. Each survey provided information from the top few molecular layers (estimated at 10 ångstroms [Å] per layer) down to the alloy metal depth (200–1,000 Å). Various amounts of iron (Fe), Cr (chromium), oxygen (O), nickel (Ni) and carbon (C) were found in all areas of rouge. AES figures and results are described in the Case Studies section.

Typical AES results of initial conditions show heavy oxidation on the received sample with very high Fe and O concentrations (iron oxide) and low Cr at the surface. This rouge buildup leads to particulate release and potential contamination of product and product-contact surfaces. After the rouge is removed, the “passivated” samples show complete restoration of the passive film, with Cr reaching a higher concentration than Fe, and a Cr:Fe ratio from 1.0 to 2.0 at the surface, with a distinct lack of iron oxides.

XPS results

Some rouged surfaces were analyzed using XPS/ESCA to compare the elemental concentrations and oxidation states of the spectra for Fe, Cr, sulfur (S), phosphorous (P), sodium (Na), calcium (Ca), and nitrogen (N), as well

Figure 1: SEM of surface: Case 1 (10,000X)

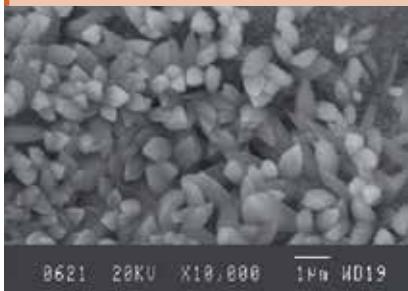


Figure 2: SEM of surface: Case 2 (4,000X)

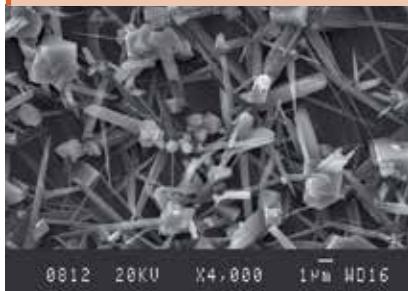


Figure 3: SEM of surface: Case 3 (2,000X)

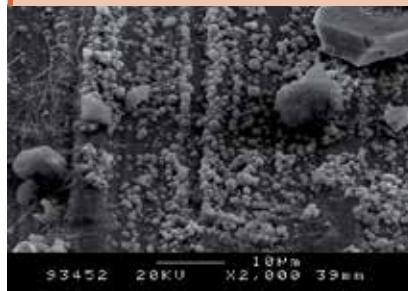


Figure 4: SEM of surface: Case 4 (500X)

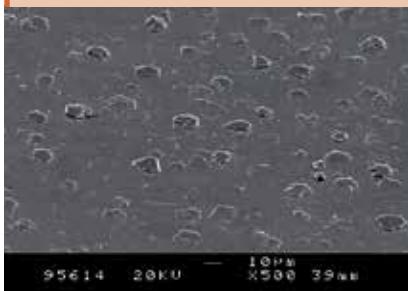


Figure 5: SEM of steam trap surface: (4,000X)

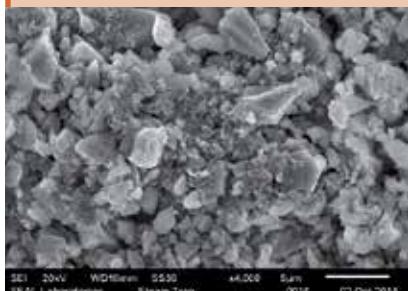


Figure 6: Photo of steam trap/bellows



as O and C (Table A). Cr content varies from near-passive-layer values to lower values typically found in the base alloy. The Fe and Cr levels found on the surface are indicative of different thicknesses and classes of rouge deposits. XPS testing reveals increases in C, Na, or Ca in the rouged surfaces over the clean and passivated surface.

Table A: Elemental concentrations

Element	Case 1: Rouged	Case 3: Rouged	Case 3: Passivated
Carbon	46.0	64.2	37.1
Chromium	7.7	1.1	6.9
Iron	5.3	1.0	2.8
Nitrogen	< 1.0	4.4	3.2
Oxygen	40.5	25.2	47.9
Phosphorous	1.1	< 1.0	< 1.0
Sodium	5.9	2.1	2.0

XPS testing also shows the ferrous (black) rouge contains a high C content as well as Fe(x)O(y) (iron oxides) within the rouge. XPS data was not significantly helpful in understanding the surface changes during the corrosion process, since it evaluates the rouge and the base metal concurrently. Further XPS testing using more samples are required to be able to evaluate the results. Previous authors also had difficulty evaluating XPS data.¹⁰

Field observations during actual removal revealed the C content was high and generally removed via filtration during the processing. SEM micrographs taken before and after derouging treatments illustrate the surface damage created by these deposits, including pitting and porosity, which are a direct effect of corrosion.

XPS results after passivation show a much higher Cr:Fe content ratio at the surface as the passive film is reformed, reducing the corrosion rate and damaging effects on the surface.

Chemical processing

Sample coupons showed substantial increases in the Cr:Fe ratios between “as-received” surfaces and passivated surfaces. As-received sample Cr:Fe ratios tested between 0.6 and 1.0, while the passivated after-treatment ratios ranged between 1.0 and 2.5. Typical values for electropolished and passivated stainless steel range between 1.5 and 2.5. The depth of the maximum Cr:Fe ratios (determined by AES) ranged between 3 and 16 Å on the after-treatment samples. These compare favorably to previous research data reported by both Coleman² and Roll.⁹

All samples had typical levels of Ni, Fe, Cr, O, and C on the surface. Low levels of P, S, Cl, Ca, N, and Na were also detected on most samples. These are common residues of cleaning chemistries, purified water, or the electropolishing process. In subsequent analyses, a slight Si contamination was detected at differing levels on the surface and on the austenitic crystals themselves. Their source is the silica content of the water/steam, mechanical polishing compounds, or visual sight glasses slowly dissolving or etching within the CS generating unit.

CORROSION PRODUCTS

Corrosion products encountered in CS systems, as noted, are highly variable. This is due not only to the variety of conditions within these systems, but also the placement of assorted components such as traps, valves, and other appurtenances, which can give rise to corrosive conditions and corrosion products. In addition, replacement components that have not been well passivated are introduced into the system all too often. Corrosion products are also heavily influenced by the design of the CS generator and water quality.

Some generator unit types are reboilers, while others are tube flash evaporators. CS generators usually utilize terminal mesh screens to remove moisture from clean steam, while others employ a baffle or cyclone separator. Some develop an almost uniform ferrous patina within the distribution tubing, accompanied by overlying ferric rouge.

Units with baffles generated not only a dark ferrous film with ferric oxide rouge beneath, but also formed a secondary upper surface phenomenon of a soot-like rouge, which may be more easily wiped from surfaces. In general, this ferrous, soot-like deposit is considerably more pronounced than the ferric rouging and much more mobile.

The rouge that forms in the condensate trail at the bottom of distribution tubing has ferric oxide rouge on top of the ferrous rouge, due to the higher oxidation state of iron in the condensate fluid. The ferric oxide rouge migrates through the condensate traps, is evident in drain lines, and the upper layers are easily wiped from the surface.

Water quality plays a major part in rouge product chemistry. Higher hy-



Figure 7: As-received surface (2,000X)

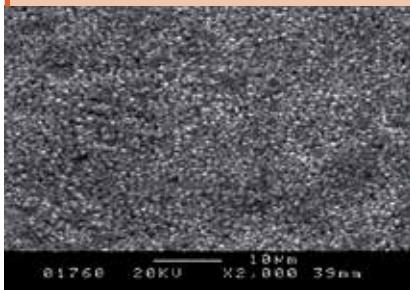


Figure 8: As-received surface (10,000X)

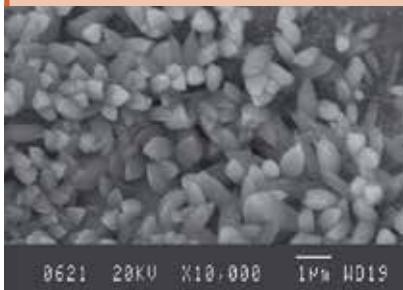
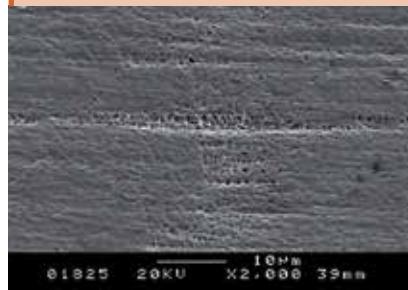


Figure 9: Derouged and passivated surface (2,000X)



drocarbon levels generate additional black carbon in the rouge, and higher silica levels lead to higher silica content, forming a shiny or smoother rouge layer. As mentioned above, water level sight glasses have also been shown to erode, releasing their silica and debris into the system.

CS SYSTEMS CASE STUDIES

Rouge is a concern in steam systems because it forms relatively thick layers that generate particles. These particles can be found on steamed surfaces or in steam sterilization equipment. The potential effect on pharmaceutical products is presented in the following sections.

Case 1

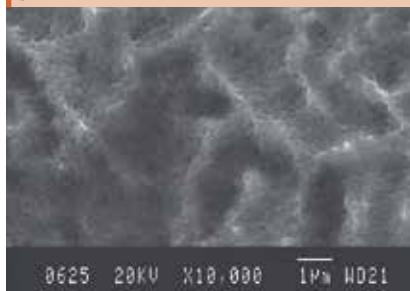
The as-received sample SEMs shown in Figures 7 and 8 illustrate the microcrystalline nature of the class 2 rouge in Case 1. The iron oxide crystals form a relatively tight matrix on the surface, appearing like a fine-grain residue. The derouged and passivated surface shows the damage caused by corrosion, producing the rough and slightly porous surface texture shown in Figures 9 and 10.

The AES scans in Figure 11 show the original surface condition in the as-received sample with heavy iron oxide on the surface. The derouged and passivated surface (Figure 12) shows that the passive film has attained a slightly higher Cr (red line) content above the Fe (black line) at > 1.0 Cr:Fe ratio. The thin (< 80 Å) chromium oxide passive film is much more protective than the hundreds of angstroms thick iron oxide crystalline film of the rouge layer and base metal, with over 65% Fe content. The chemistry of the derouged and passivated surface is now similar to a passivated mill-finished material.

The rouge in Case 1 is a class 2 rouge that formed in place; as the rouge accumulates, this type produces particulates that grow in size and migrate

with the steam. The corrosion exhibited in this case does not severely pit or significantly degrade the surface. Derouging on a regular basis will limit both corrosive effects on the surface and remove potential for excessive migration of particles that often reach visible

Figure 10: Derouged and passivated surface



size range in fluids or products.

In Figure 11, AES results show a thick layer high in Fe and O (500 Å iron oxides; blue and lime green lines, respectively) near the surface that transitions to alloy levels of Fe, Cr, Ni, and O. The Fe concentration (blue line) is significantly higher than any of the other metals, rising from 35% at the surface to over 65% in the alloy. The O level (lime green line) transitions from nearly 50% at the surface to near zero in the alloy at more than 700 Å in depth of the oxide film. The Ni (dark green line) and Cr (red line) levels start very low at the surface (< 4%) and transition to normal levels (11% and 17%, respectively) at alloy depth.

The AES chart in Figure 12 shows that the rouge layer (iron oxides) has been removed and the passive film has reformed. In the first 15 Å, the Cr level (red line) is above the Fe level (black line), indicative of the passive film. The Ni level starts at 9% on the surface and rises to above the Cr level (± 16%) between 60 and 70 Å, then transitions to the alloy levels at 200 Å. The carbon level (blue line) starts at 12% and drops to zero at 30 Å. The Fe level starts low (< 15%) and rises to equal the Cr level at 15 Å and continues to the alloy level of over 65% at 150 Å. The Cr level rises from the surface to a level of 25% at 30 Å, returning to 17% in the alloy. The high O level near the surface (lime green line) drops to zero after a depth of 120 Å. This analysis shows a well-developed passive film on the surface.

The SEM photos in Figures 13 and 14 illustrate the rough, rouged, and porous crystalline nature of the class 1 and 2 ferrous oxide layer on the surface. The derouged surface shows the effects of the corrosion in its roughened, partially pitted surface (Figures 18–19).

Case 2

As noted, the derouged and passivated surface in Figures 13 and 14 lost its heavy oxidation. Figures 15 and 16 show a restored passive film on the metal surface. In Figure 17, the Fe concentration (black line) drops dramatically throughout the near-surface area (< 100 Å), while the Cr content (red line) increases in the first 20 Å to develop a passive film, with a Cr:Fe ratio of approximately 1.5 in the first 25 Å of the surface (approximately three molecular layers). The O level (lime green line) remains high in the first 30 Å of the passive film. The C level (blue line) remains high at the surface, but drops as the surface transitions into the alloy.

Case 3

Figures 18 and 19 illustrate the size of oxide crystals that can grow from steam corrosion. These class 2 corrosion products begin as very small crystal growths on the surface, then grow into particles from 5 to 50 microm-

Figure 11: Case 1 AES scan, as received

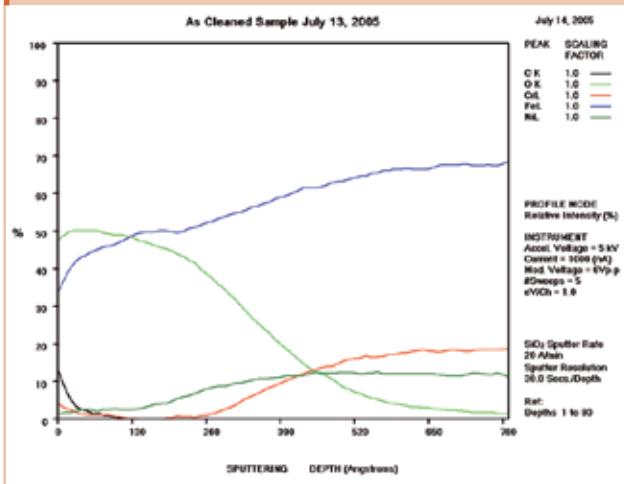
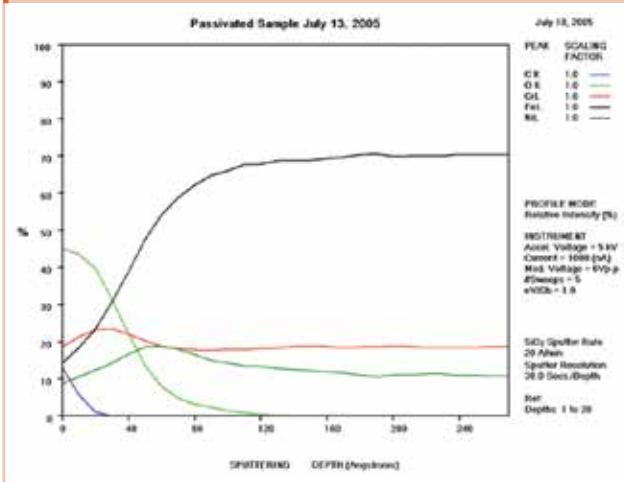


Figure 12: Case 1 AES scan, derouged and passivated



eters (μm) in size and even larger. These crystals may be released into the steam and migrate into the process stream or onto product contact surfaces.

Figures 20 and 21 show conditions of the CS tubing in the distribution system.

Figures 22 and 23 show that the clean derouged surface is void of the iron oxide material, with minor pitting and roughness generated from the corrosion of the surface. The SEMs show the surface rouge as inspected. The ferrous oxide rouge on the surface has a thin nonuniform overlaying film of ferric oxide rouge.

The AES scan of Figure 24 shows excessive carbon and iron oxide on the rouged surface with no passive film. Figure 25 shows the surface after derouging and passivation, with recreation of the passive film and loss of the iron oxide film. In the first 50 Å of the as-received sample, the C, O, and Fe levels are very high, showing the iron oxide film with elemental carbon on the surface, typical of CS rouge of class 2 corrosion with a high carbon level.

Case 4

Figures 26–29 show how a shiny black surface appears microscopically. The

surface is much smoother than typical rouge crystals due to the amorphous silica that appears like a glassy coating. Once removed, however, the surface reveals its low-level pitting and austenitic metallic crystal edge deformation.

Figure 30 reveals establishment of the passive film after iron oxide deposits were removed. The Cr:Fe ratio at the surface is slightly greater than 1:1 in the first 20+ Å, as the Fe (blue line) and Cr (red line) merge toward the surface. The O level (lime green line) starts high at the surface (at 40%) and drops to zero at 120 Å, while the Ni level (dark green line) begins at 7%, rises quickly to nearly 15%, then then levels off at about 10% into the alloy composition below 150 Å.

Measuring soluble metals and particulates

CS systems can be monitored for metals in the condensate and steam flow, measuring the number and size of particles from 5 to > 100 μm . The results presented in Table B show ranges of metal content and particulate in the CS critical utility of three case studies. Particle sizes above 50 μm are visible contaminants,³ and significant numbers of particles greater than 50–100 μm present a high risk for contamination on surfaces that are steamed by this critical utility.

Removing corrosion byproducts

Ferrous oxide rouge deposits may be removed using organic acids with chelant combinations (and other variable complexes) in the proper concentrations, contact times, and temperatures. Other advocated mineral acid

**Do you need point-of-use
Clean Steam in your Lab or Facility?**

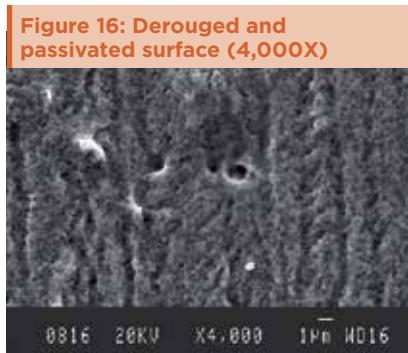
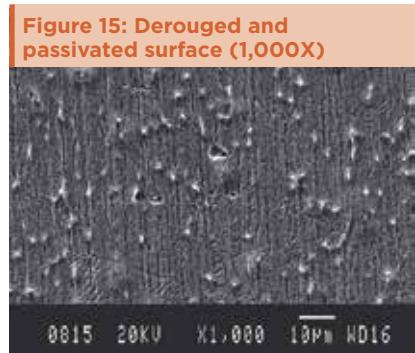
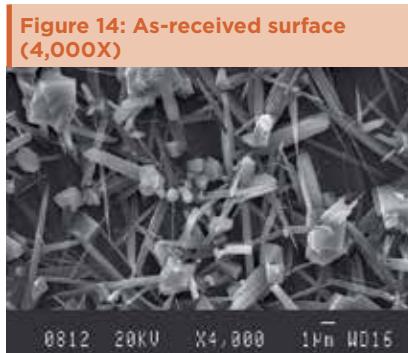
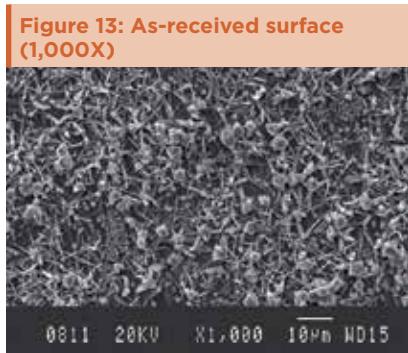
Electro-Steam offers four models – **V-Block, LG-Series, LB-Series and LB-Indirect Series** designed to produce high quality clean steam for bio-pharma processes.

- ◆ 316L S.S. material on all wetted surfaces for DI, RO or WFI water
- ◆ Available from 10kW and up, in any Voltage domestic or foreign
- ◆ Adjustable pressure controls (0-100 psi), ASME safety valves, and automatic Low-Water and High Pressure cutoffs on all models
- ◆ Full compliance to ASME, Boiler code, UL and C-UL



Electro-Steam
ESTABLISHED 1952

Toll-Free: 1-866-617-0764
sales@electrosteam.com • www.electrosteam.com

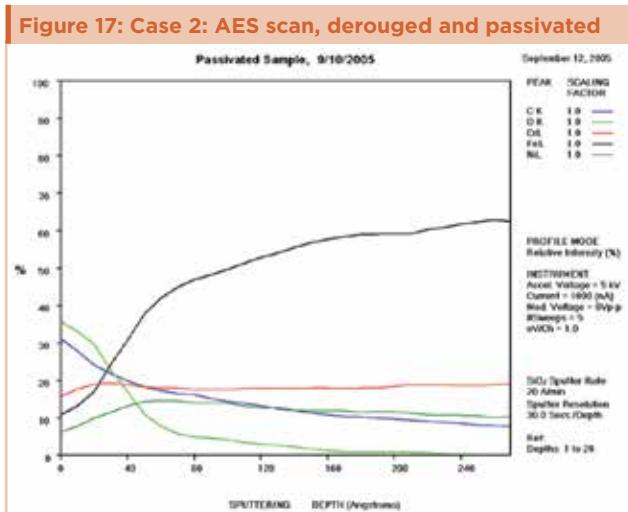


treatment approaches include, but are not limited to:

- Commercial acid detergents
- Mineral acids with halogenated additives, such as ammonium bifluoride
- Phosphoric acid blends
- Various chemical pickling remedies

The objective of the derouging process is to remove the iron oxide deposits while protecting the stainless steel substrate surface from any additional pitting corrosion.

To ensure that polished surface finishes are not damaged by the derouging solutions, it's also important to avoid aggressive techniques that can remove base metal. Following the rouge and oxide deposit removal, a



passivation treatment can restore the passive film by removing elemental iron and iron oxides from the first few molecular layers in the surface while maintaining the protective chromium oxide layer. This can minimize continued corrosive mechanisms upon return to service.

CONCLUSION

The corrosion byproducts encountered in clean and pure steam systems—carbon, silica, and iron oxide compounds—are present to some degree in every system. Many CS systems lack proper routine inspection and maintenance that could control corrosion and particulate migration from oxide deposit exfoliation.² Corrosion problems are exacerbated by poor gasket specifications, components with dissimilar metals, and decreased stainless steel surface quality, as well as the uncontrolled nature of mechanical/electrochemical polishing materials and methods combined with poor material handling and lack of routine derouging and passivation techniques.⁷

It has also long been suspected that stainless steel materials are not necessarily delivered at a desirable quality level. Manufacturing processes, combined with subsequent material handling unit operations and fabrication techniques, establish the surface chemistry (chromium oxide content of the passive film), corrosion resistance, and surface finish quality, which all affect the final product.

Claims that these grayish/black deposits are stable, inevitable, and should be left alone have very little credibility. Corrosion produces rouge that is evidenced as discolored stains on product contact surfaces, and generates mobile particles that accumulate on steam sterilized surfaces. CS rouge contaminants have been found in final filtration processes, becoming a potentially uncontrolled material in the final process fluids and gasses. While we acknowledge that the examples presented here are specific cases, they are not unique. They are similar to cases found within other systems, especially those where corrosion has been left to continue without proper corrective treatment.⁴

Finally, corrosion within CS systems will generate migratory rouge that can be identified and measured in the steam, the condensate, and on the system interior surfaces. Proper design and maintenance is critical in the operation of CS generation and distribution systems for high-purity applications.

Future research measuring the time, conditions, and properties of rouge development could be compared to particulate generation to establish risk of product contamination. Systematic, routine measurements over a two-year period could track corrosion products to illustrate changes in particulate release and transport within the CS system studied, as well as the surface conditions within the generation and distribution equipment. ◊

Figure 18: As-received surface (500X)

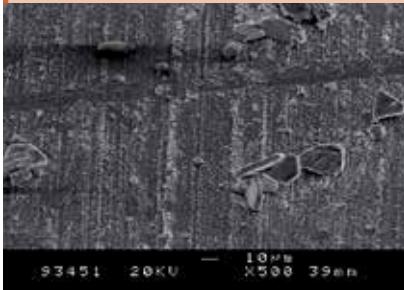


Figure 19: As-received surface (2,000X)

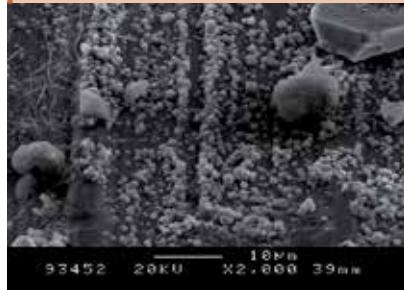


Figure 20: Distribution tubing



Figure 21: Pretreatment view



Figure 22: Derouged and passivated surface (500X)

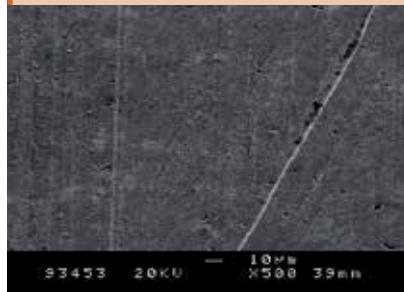


Figure 23: Derouged and passivated surface (2,000X)

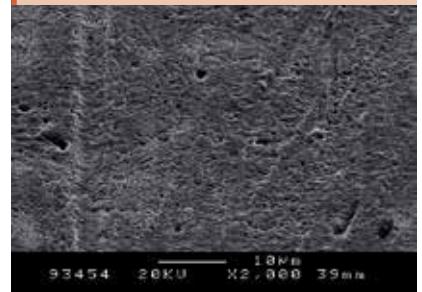


Table B: CS Systems, particulate counts

Size, μm	> 5 μm	> 15 μm	> 25 μm	> 50 μm	> 100 μm
Sample	Particle count per 100 milliliters condensate				
CSG 1	166	200	133	30	1
CSG 2	310	84	56	22	2
CSG 3	5330	6400	4660	166	18
CSD 1	200	45	21	34	1
CSD 2	404	81	26	4	0
CSD 3	2020	403	132	22	8

CSG: Clean steam generator CSD: Clean steam distribution

References

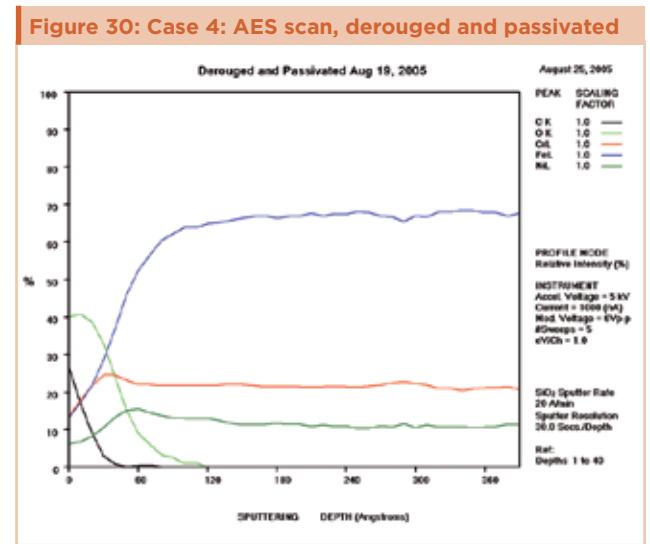
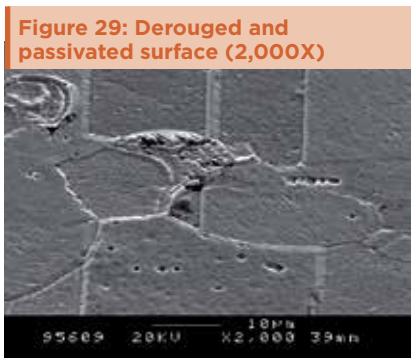
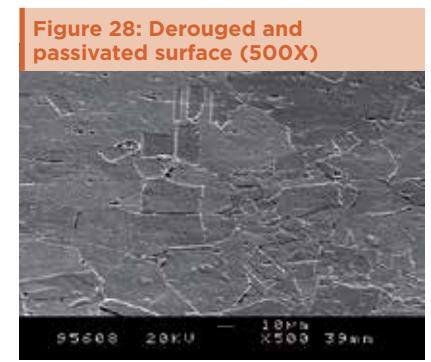
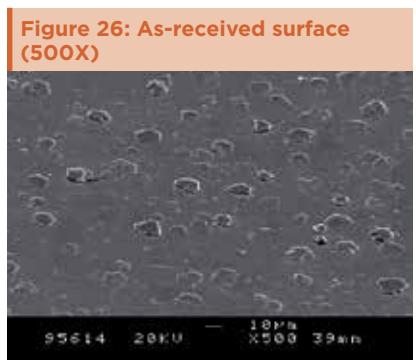
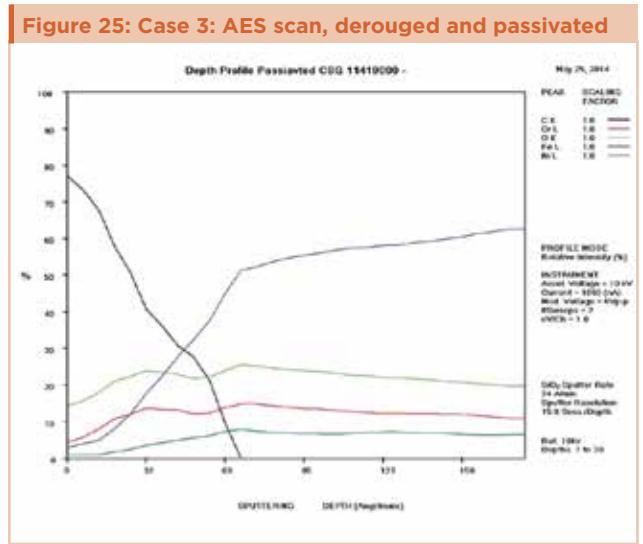
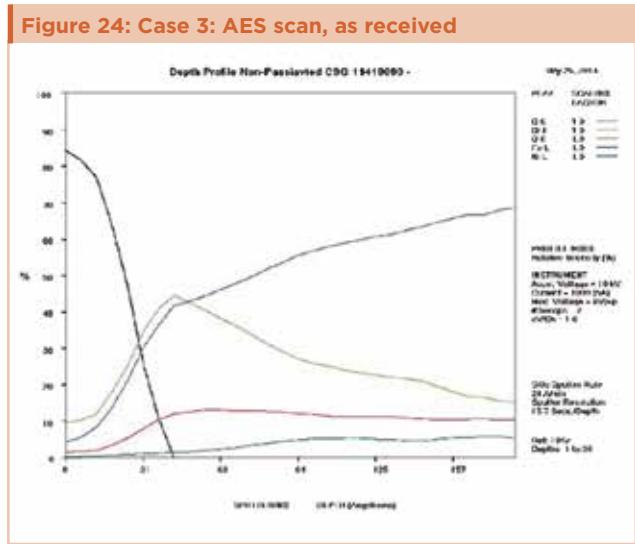
- American Society of Mechanical Engineers. ASME BPE Bioprocessing Equipment Standard. 2014.
- Coleman, D.C., and R. W. Evans. "Fundamentals of Passivation and Passivity in the Pharmaceutical Industry", *Pharmaceutical Engineering* 10, no. 2(March-April 1990): 43-49.
- Essmann, M., and R. Gomez. "Quality Requirements for Pure Steam." In *Pharmaceutical Water*. GMP Publishing, 2012. https://www.gmp-publishing.com/media/files/table_of_contents/Pharmaceutical_Water_TOC_web.pdf
- Evans, R.W., and D. C. Coleman. "Corrosion Products in Pharmaceutical/Biotech Sanitary Water Systems." Parts 1 and 2. *Ultrapure Water* 16, nos. 8 and 10, October 1999.
- Frantsen, J., et al. "Effects of Gas Atmosphere and Surface Quality on Rouging of Three Stainless Steels in WFI." Proceedings of NACE Corrosion 2003, paper no.0374, San Diego, California, March 2003.
- International Society for Pharmaceutical Engineering. Critical Utilities D/A/CH COP. "Rouge in Pharmaceutical Water and Steam Systems, *Pharmaceutical Engineering* 29, no. 4 (July-August 2009). http://ispe.org/galleries/journal_ja09/09ja-cu_dach_cop.pdf
- . *Water and Steam Systems: Pharmaceutical Engineering Guides for New and Renovated Facilities*. Baseline Pharmaceutical Engineering Guide, Volume 4, first edition. 2001.
- Latham, T. "Clean Steam in the Pharmaceutical Industry." PDH Online Course K109. <http://www.pdhonline.com/courses/k109/k109.htm>
- Roll, D., and R. Webb. "Developing an Effective Passivation Process to Maintain Laser Mark Integrity for Medical Device Components." *Medical Product Outsourcing*, 9 December 2010. http://www.mpo-mag.com/contents/view_technical-features/2010-12-09/developing-an-effective-passivation-process-to-mai
- Tverberg, John C., and James A. Ledden. "Rouging of Stainless Steel in WFI and High Purity Water Systems." Presented at Institute for International Research, "Preparing for Changing Paradigms in High Purity Water," San Francisco, California, October 1999. <http://www.csdesigns.com/uploads/white-papers/rouging.pdf>

Acknowledgments

The authors would like to give credit (posthumously) to Robert W. Evans for his efforts in joining Drew Coleman during initial research and drafting phase of this article. He envisioned the need to bring to the industry the effects of corrosion and subsequent rouge products in CS systems with their potential for detrimental process or product contamination. In addition, we would like to thank Dr. Brent Ekstrand for his editing efforts in finalizing this technical article to more clearly bring our message to the industry.

About the authors

Drew Coleman holds an Unlimited Steam Engineer's License and is also a Licensed Chief Operating Engineer. He has worked for Genentech, Amgen, ICOS Corporation, and ID Biomedical, where he directed the design of BL-3 facilities and processes to produce novel recombinant vaccines. He founded Biodynamics International in 1991 to consult in the areas of facility and process design, validation, and operations. Coleman completed the Executive



Leadership Program at Harvard University, JFK School of Government, and is a graduate of the Kodokan Judo Institute in Tokyo. He is active as a consultant to pharmaceutical and biotechnology companies and evaluates process engineering, utilities, water for injection, and pure steam systems. He has been an ISPE member since 1985, and was named ISPE Committee Person of the Year in 1992.

Daryl Roll, PE, is Astro Pak Corporation's Technology Officer, leading the development and management of corporate technology objectives and support requirements. Additionally, Daryl serves as the primary senior technical advisor to clients and employees for corrosion, surface chemistry and stainless steel passivation. He is a member of the ASME BPE Subcommittees for surface finish, material joining and metallic materials (member) requirements, and a leading contributor for the passivation, rouge, and surface chemistry task groups. His papers on passivation and rouge control have been published in *Pharmaceutical Engineering*, *IEEE Micro*, and *Chemical Engineering Journal*. Daryl holds a degree in Chemistry and Earth Science from the California State University of Fullerton and a Professional Engineer's license from the State of California.



FOYA | 2017

Facility of the Year Awards

— Innovation. By Design. —

www.FacilityOfTheYear.org

CELEBRATE FOYA WINNERS AT THE ISPE ANNUAL MEETING & EXPO

The FOYA Program recognizes state-of-the-art pharmaceutical manufacturing projects utilizing new and innovative technologies to improve product quality, reduce cost, and demonstrate advances in project delivery.

Be among the first to congratulate the 2017 Facility of the Year Award Overall Winner!

The overall winner will be announced during the Membership Breakfast and Awards on Tuesday, 31 October.

Winning Project Presentations will be featured on Monday, 30 October at 11.00 - 12.30 and 13.45 - 15.15.

DON'T FORGET: THE 2018 APPLICATION DEADLINE IS MONDAY, 20 NOVEMBER 2017.



Register Now for the
2017 ANNUAL MEETING & EXPO

www.ISPE.org/2017-Annual-Meeting

EXTRACTABLES AND LEACHABLES: NOT THE SAME

Nassrine Lablack, Mathieu Tricot, and Malik Belattar

With the integration of single-use systems (SUS)* into downstream processing and thus closer to the final drug product, considerations of extractables and leachables (E&L) have become a critical issue within the industry. Lack of standardization, however, leads to incomplete E&L studies that do not cover the conditions encountered throughout the process train. This makes it difficult for end users to select suitable single-use components.

The pharmaceutical industry's challenges are:

- Prevent misinterpretation of regulatory requirements for E&L as they are used on finished product containers by applying them to process contact materials as well
- Bridge the gaps between end user expectations and supplier capabilities by defining the limit of responsibilities and the scope of operations for both.

The objective of this article is to clarify and highlight the importance of distinguishing between extractables and leachables when evaluating SUS. Our goal is to propose consensus E&L guidelines for all industry stakeholders, using risk management and quality by design (QBD) approaches, and supporting single-use development and market promotion.

This paper presents risk-based approaches for evaluating E&L from SUS. In fact, regulations on single-use-technologies (SUT) do not exist yet, although the basis for such regulation exists. In the United States, for instance, 21 CFR 211.65 states, "Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements."¹

TWO WORDS, TWO PERSPECTIVES

SUT has been part of the biopharmaceutical industry for about a decade. Because terminology is a key element in preparing and understanding any new area, it is of crucial importance to define common terms and use them properly.

Many people use "extractables and leachables" as a single term, but these concepts reflect two very different chemical species, although both migrate from the component.

Extractables are chemical compounds that migrate from SUS into model solvent solutions under controlled and exaggerated conditions depending on temperature, pH, polarity, and time. SUS are normally not exposed to such conditions in biopharmaceutical processes.

Leachables are chemical compounds that migrate from SUS into process solutions under normal biopharmaceutical process conditions; they may end up in the final drug product formulation. For the most part, leachables are a subset of extractables, although interaction with product components may produce leachables not seen as extractables.

Extractable and leachable studies pursue different objectives: Extractable studies are designed to obtain a fingerprint of chemical components that can be extracted under exaggerated conditions. Toxicological review of these fingerprints and risk assessments for potentially problematic components helps select appropriate SUS. Extractable studies can also be used as a baseline to ensure SUS consistency over time.

Leachable studies determine the chemical compounds that migrate from SUS into process solutions and characterize possible adsorption and/or absorption of process fluid (under normal process conditions). This data enables a toxicologist to determine if components that can compromise patient safety are present in the drug product. In addition, leachables data can indicate the presence of chemical components that could potentially interact with the drug product itself, and can help assess the potential for alterations of the drug potency and/or stability. Since leaching continues over time, posing a risk to patient safety and drug product efficacy, leachables may also appear in stability studies.

These definitions (especially for extractables) are not totally balanced. Different applications and situations in biomanufacturing process must be categorized to highlight the weight and criticality of both E&L profiles in product contact material.

COLLABORATION

Regulatory authorities expect that the final dosage form will have a well-characterized degradant profile, including leachables from process contact materials, even if they do not pose any major health risk for the patient. As part of this profile, E&Ls must be targeted, assessed, and mitigated. This is challenging due to the number of parameters that can affect E&L evaluation and the need for trace-level analysis.

Collaboration and clear definition of roles between SUS manufacturers, suppliers, and end users (drug product manufacturers) are crucial to ensuring patient safety and product efficacy. This is true even for the transportation and storage of single-use components and assemblies prior to use in the drug product manufacturing process.

* Presterilized products, equipment, and packaging designed to be used once or a few times, depending on specific circumstances, and discarded.

The easiest way to determine responsibilities is to establish clear communication and transparent exchange of documentation (certification, report, conclusion, minutes of decision meeting, and any legal agreements). Tools such as a RACI (responsible, accountable, consulted, informed) responsibility assignment table could be used to determine stakeholder responsibilities.

RISK-BASED APPROACH

A risk assessment for both extractables and leachables that balances business risk and patient safety should be established for different phases of SUS manufacturing and drug development. Business risk must be considered, but never at the expense of patient safety. Suppliers have considerable commitment to the cost of extractable analysis with regard to end user expectations (user requirement specifications) and the feasibility of conducting a more complex extractables study.

Both end users and suppliers have a stake in the business impact analysis. Ultimately, the main consideration must be on product quality and safety, which should be assessed with appropriate risk assessment and mitigation strategies (such as quality risk management). The amount of leachables per unit of final drug product dosage form (along with posology) is the final regulatory expectation. End users must comply with this patient-risk approach as required by regulatory bodies.

QBD APPROACH

An E&L program should be based on QBD principles and a thorough understanding of the biomanufacturing process. Using this approach, suppliers should conduct E&L studies on in-process SUS from sourcing of raw materials to disposal—including key milestones such as sterilization—in compliance with baseline safety assessment and chemical studies. End users should first evaluate the criticality of the SUS component regarding process flow, based on documentation provided by the supplier.

Chemical fingerprint analyses will ensure that no toxic substances are found (or are well below the limit) and that the product is unlikely to interact with the final drug product. Controlled extraction studies are needed to make an informed selection of materials, meet regulatory expectations, evaluate safety of materials, and control leachables absorbed in the final dosage form.

MANY PEOPLE USE “EXTRACTABLES AND LEACHABLES” AS A SINGLE TERM, BUT THESE CONCEPTS REFLECT TWO VERY DIFFERENT CHEMICAL SPECIES, ALTHOUGH BOTH MIGRATE FROM THE COMPONENT

EXTRACTABLE EVALUATION METHODOLOGY

Before conducting an extractables study on an in-process SUS, end users should assess single-use material attributes—dosage form, formulation composition, intended use, and stability—within a risk-assessment approach, considering the intended use and process conditions of the SUS component. The experiment design should consider several factors (Figure 1) that could affect the quality of extraction and resulting analysis:

- Model solvents selection
- Surface area to volume ratio
- Mass of each extractable or leachable per volume of model solvent
- Time points of extraction
- Type of material tested
- Related structural and physical properties: SUT resin, film, component, assembly, and system

Components should be tested using multiple extraction techniques and solvents of various polarities according to a wide range of targeted species and dosage forms. Because “most” does not mean “better,” one should not expect a maximal number of chemical compounds during contact material extraction (time of contact, concentration of solvent, extraction kinetic) but

Figure 1: Ishikawa diagram of an accurate, efficient, and suitable extraction

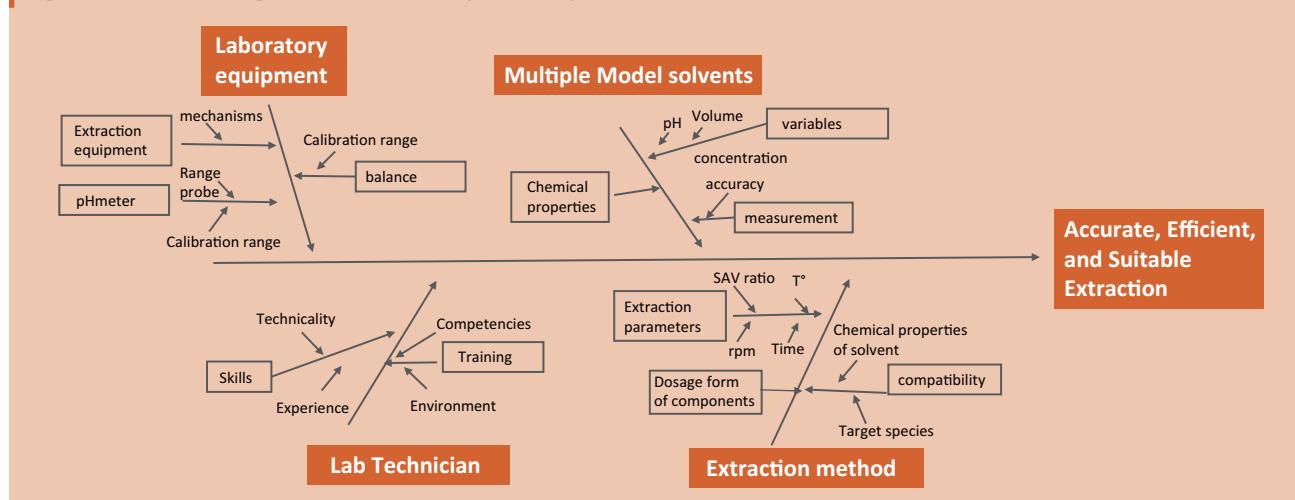
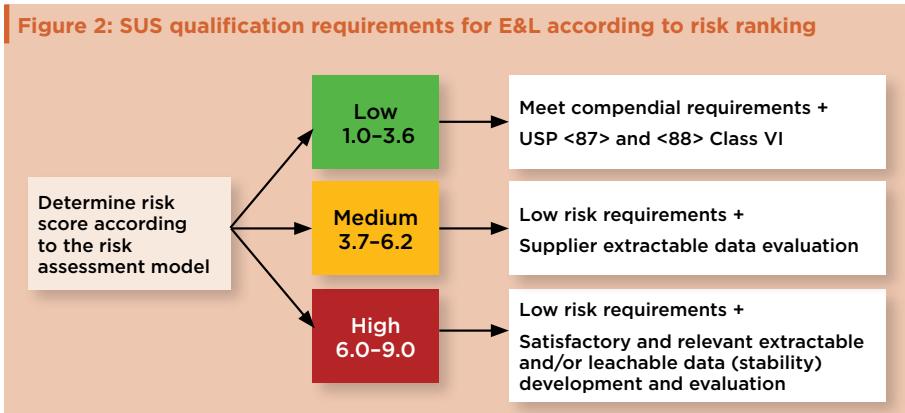


Figure 2: SUS qualification requirements for E&L according to risk ranking



rather select appropriate extraction conditions and analytical approaches predictive for leachables produced in a specific application. The extract is then evaluated with analytical techniques based on sensitivity, limit of detection, and the target species properties (considering first volatiles, semivolatiles, or nonvolatiles).

Following a toxicological analysis, the extractable can be identified and evaluated for its potential toxicity and safety threshold. If potential toxicity is discovered, end users should report the results to suppliers and stop using the SUS component tested until a risk mitigation strategy has been enacted. Suppliers should follow common extraction methodology based on standards recognized by all industries, and communication to end users must be based on consensual reporting methods.

LEACHABLE EVALUATION METHODOLOGY

Evaluation of SUS leachables should be based on a risk- and science-based approach to ensure the safety and purity of the final drug product. Process knowledge, experience gained during development, and a comprehensive process understanding should be used to assess risk associated with implementing SUS. Risk management principles can identify, evaluate, communicate, and mitigate leachables that can affect product quality and patient safety. A leachable profile should be used to determine the residual chemical identity of the SUS in normal process conditions and the toxicological impact on drug product and on patient safety. A leachable material is objectionable if it adversely affects critical quality attributes such as purity, safety, efficacy, identity, strength of the final and/or intermediate product, or its successful production.

Risk may be based on severity of the harm caused by leachates from SUS, probability that leaching will occur, and probability of detecting the leached substances through in-process manufacturing controls. Once the overall risk rating of the single-use component of interest is finalized and ranked (low, medium, or high), qualification requirements should be established to qualify the single-use component for its intended use (Figure 2).

We recommend a case-by-case approach to define which extractables should be analyzed in a leachables study. For medium and higher rated risks, product-specific assessments should be based on extractable data and conducted under a toxicologist’s supervision. Given high-quality data that is applicable to the end user bioprocess, extractables data can guide and define the depth of a leachables study. In addition, end users should consider that leachables may also be derived from the interaction between

an extractable and a drug formulation compound.

CONCLUSION

A key advantage of implementing this approach for process contact materials is that it identifies where a leachable study is needed, and focuses the effort according to leaching propensity. QbD risk assessment and synergetic collaboration between suppliers and end users are leading principles that should facilitate SUS implementation by providing better understanding of industry expectations for suppliers. This

drives uniformity of study design, allowing integration of data from multiple suppliers, and facilitating evaluations and comparisons between components. ◊

Acknowledgements

Malik Belattar thanks coauthors Nassrine Lablack, Quality and Regulatory Compliance Engineer at the SUTAP organization, and Mathieu Tricot, Quality and Regulatory Engineer at Pharmabiot’Expert, for their technical assistance and contribution for drafting the article. He is also grateful to Christopher J. Smalley, Director at Merck & Co., and Sabrina Restrepo, Associate Director, Component Engineering at Merck, for their valuable insights and technical review of this paper.

References

1. US Food and Drug Administration. Code of Federal Regulations, Title 21, Chapter I, Subchapter C, Part 211, Subpart D, Sec. 211.65, “Equipment Construction.” <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=211.65>

About the authors

Nassrine Lablack is a BioProcess Engineer and expert in biotech quality and regulatory from the Single-Use Technology Assessment Program (SUTAP), a nonprofit initiative for the standardization of single-use technology. As team coordinator, she works on the composition of ASTM standards on quality requirements for single-use systems. She graduated from Sup’Biotech, a biotechnology engineering school with a specialization in health care and the pharmaceutical industry.

Mathieu Tricot is Project Engineer in biotech quality and regulatory at Pharma Biot’Expert, a pharma/biotech company dedicated to the management of biotech manufacturing projects, with an expertise in single-use systems. A member of the ASTM Committee E55.04 on General Biopharmaceutical Standards, he graduated from Sup’Biotech, a biotechnology engineering school with a specialization in health care and the pharmaceutical industry.

Malik Belattar is the founder and CEO of Pharma Biot’Expert, a pharma/biotech expertise company dedicated to the management of biotech manufacturing projects with a focus on single-use systems. He is also cofounder and deputy director of the Single-Use Technology Assessment Program (SUTAP), a nonprofit initiative for the standardization of single-use technology. He holds two master’s degrees: one in technology of management of pharmaceutical production with a specialization in sterile product from University of Paris-Sud, and one in development of health products with a specialization in biotech from University of Paris-Denis Diderot. An ISPE member since 2012, he has served as Chair of the Disposables CoP since 2015, and is currently involved in the preparation of the ISPE Single-Use Technologies Good Practice Guide.

AN INTRODUCTION TO PREDICTIVE MAINTENANCE

James Butler and Christopher Smalley

Much has been published on advantages of predictive maintenance, yet many do not realize that it is a tool to help achieve their facility's goals and objectives. If you need to convince management of the need for PredM, this article contains information that you can use as an "elevator speech."

Predictive maintenance (PredM) is a general method that uses ongoing analysis of operational data to determine when equipment maintenance will be required. When applied appropriately, it can reduce maintenance expenses while improving reliability. This article outlines several PredM applications and discusses its applicability to aging facilities.

WHAT IS PREDM?

Maintenance of GMP facilities is necessary to ensure that they operate in a qualified and validated state and are fit for their intended use. Traditional preventive maintenance has direct costs, may require downtime of equipment or entire production lines, and may increase the risk of contamination. Insufficient maintenance, on the other hand, can cause inefficient operation, premature equipment failure, and other more serious consequences.

Preventive maintenance scheduling is often driven by elapsed time of use (e.g., equipment run hours) or calendar time, with maintenance intervals based on a statistical analysis of past performance and failures. Preventive maintenance can be effective, but it is not sufficient to prevent unplanned downtime through unpredicted failure; it can also result in unnecessary maintenance.

PredM, in contrast, uses ongoing measurements and metrics to calculate equipment health and the corresponding risk of failure. Its primary goal is to predict the need for maintenance, allowing it to be scheduled at convenient times. Other potential benefits include:

- Reduced maintenance cost
 - Maintenance is performed when needed, reducing or eliminating the need for regularly scheduled maintenance
 - Root cause analysis of problems using performance data enables more efficient repairs and improves the first-time successful repair rate
- Lower frequency of failures
- Less unplanned downtime
- Reduced quality risk
- Opportunity to improve planning, personnel scheduling, and parts availability as unnecessary activities are eliminated.

PREDM USES ONGOING MEASUREMENTS AND METRICS TO CALCULATE EQUIPMENT HEALTH AND THE CORRESPONDING RISK OF FAILURE

Unlike traditional scheduled preventive maintenance, which is an intermittent activity, PredM is an ongoing process that involves:

- Data collection and analysis
- Root cause analysis of any identified problems
- Scheduling of maintenance activities as required

Scheduled preventive maintenance continues to remain a viable option, however, because facilities regularly experience shutdowns for product changeovers or vacation breaks. PredM can complement preventive maintenance in these and other circumstances, providing important benefits such as minimizing unplanned downtime, while preventive maintenance can plan for major equipment rebuilds or replacement during shutdown periods.

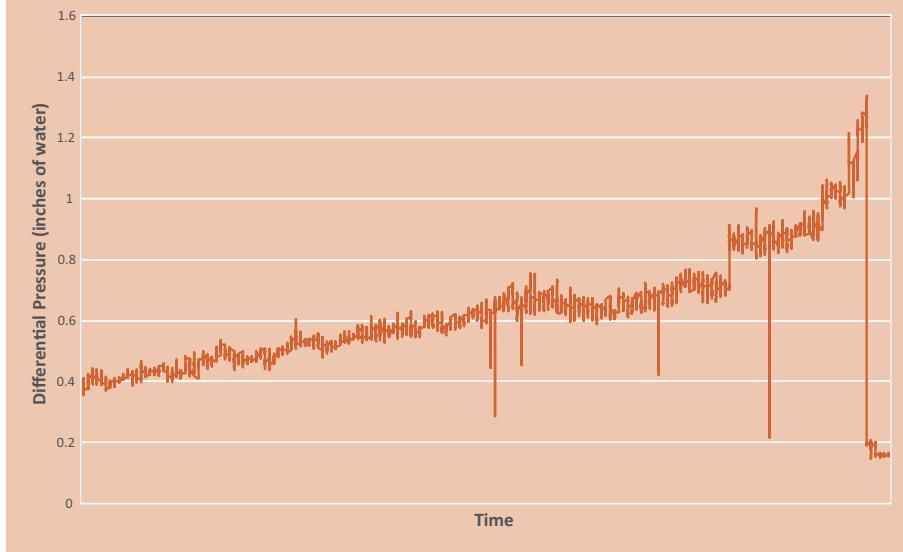
CALIBRATION PROGRAM

PredM relies on data, which must be appropriate for its intended purpose. One way to obtain reliable data on facility and equipment performance is to establish a robust calibration program that identifies the instruments and controls that require calibration—including the frequency, range, accuracy, and precision of those instruments. In GMP facilities, instruments and controls that produce data needed for GMP purposes also become part of the calibration program. Remaining instruments are usually not calibrated, except for the calibration provided by the vendor when first installed.

A robust PredM calibration program should identify and appropriately calibrate those instruments and controls that monitor facility and equipment performance. We emphasize "appropriately" because calibration requirements for frequency, accuracy, and precision will likely be less stringent than those for GMP instruments (often referred to as "GMP critical"). This may mean that more instruments are included in the calibration program than would be the case with preventive maintenance. It may also result in increased costs, but if the information contributes to the PredM program, it will be a value-added proposition.

AUTOMATION CAN RESULT IN MORE CONSISTENT APPLICATION OF ANALYSIS METHODS AND MORE TIMELY RESULTS

Figure 1: Air filter differential pressure



DATA MANAGEMENT

Companies in our industry accumulate a tremendous amount of data, so one step may be to manage that data more appropriately. For instance, operations accumulates data on steam sterilizer operation; could some of that data be identified for maintenance as well? Where there is no data source, installing new tools such as vibration or temperature sensors could help anticipate pump failure by adding specific readings to checklists and having maintenance technicians replace items when a certain value or pressure drop is registered.

If data collection and basic data analysis are largely automated, subject matter experts (SMEs) can focus on high-value-added tasks where the consequences will have a large impact—such as HVAC that supports a sterile production facility. In this era of “big data” analytics, specialized software is increasingly used to detect emerging problems and is becoming part of root cause analysis. While it’s important to note that automated tools used to trend and analyze data for GMP decision-making must be validated, automation can result in more consistent application of analysis methods and more timely results.

PREDM EXAMPLES

The following examples show how PredM could be implemented in pharmaceutical facilities. It is easy to imagine other situations in which the general principles of PredM could be applied.

WFI systems

Water for injection (WFI) system data is customarily acquired and trended by the quality unit. Such monitoring takes data and trends it to determine if the system is operating acceptably and whether the performance is consistent. As mentioned earlier, it is important to integrate information: Does the quality unit include total organic carbon data in its trending reports? Could it provide information on seasonal changes influenced by changes in the water source (surface or well water)? The results of such analyses would be used to make decisions about if/when/how to perform

maintenance on the WFI system, and whether engineering changes are needed to ensure acceptable performance.

Air filters

By trending the measured differential pressure across an air filter, it is possible to predict when filter replacement will be necessary (Figure 1). This will often result in lower costs compared to a conservative time-based filter-replacement schedule. If a particular filter is becoming loaded at a rate that significantly exceeds expectations, HVAC system component inspection or other maintenance activities can be scheduled. Other filters in pharmaceutical production equipment would also benefit from such analysis.

Redundant sensors

A bioreactor might have multiple redundant dissolved oxygen sensors in the same way that a steam sterilizer will have a monitoring and controlling sensor. A difference in readings between the two sensors that exceeds a given threshold for a specified period triggers an alarm. Trending the difference may reveal whether one sensor is drifting at an unacceptable rate; this would allow both sensors to be recalibrated before the next alarm occurs. Note that sensor recalibration due to trend analysis would generally be done in addition to recalibration at regular intervals.

Preventing excessive wear

Excessive wear caused by poorly tuned control loops or improper applications may cause valve and damper actuators to fail prematurely, even if the control loop or application was appropriate at installation and qualification. Utility pressure or temperature changes, for example, could result in excessive actuator movement; over the life of the actuator this can lead to wear. Calculation of accumulated actuator movement is straightforward using the time series of the actuator position, or using the time series of the position command signal if position feedback data are not available. If certain actuators are experiencing excessive movement, root cause analysis should be performed so that appropriate maintenance can be scheduled.

PREDM IN AGING FACILITIES

Facility operations staff should embrace PredM concepts by understanding facility and equipment performance, as well as risks to that performance. For aging facilities, PredM can play an important role in risk management and also contribute to the obvious potential for cost savings. Many attributes of an aging facility can be avoided through the correct implementation of PredM.

Most risks associated with aging facilities should be generally understood by facility personnel based on their operating experience. Ideally these risks have been documented (and periodically reviewed) as a part of a formal risk assessment process such as failure mode and effects analysis. Aging facilities often experience risks that recently commissioned facilities do not, such as the diminishing availability of spare parts for older equipment. Suppliers are valuable sources of information about aging equipment, and they may be able to provide specific recommendations about preventive maintenance and PredM procedures that will extend equipment life.

In some situations, more data will provide better predictive capability. Data in paper-based records, for example, can be entered into computer databases. Additional sensors may also be needed: While a mechanic might know that a gearbox should be inspected if it gets hot to the touch, for example, a sensor could monitor the gearbox temperature and generate an alarm when it exceeds a certain threshold. The mechanic's knowledge is an example of tacit knowledge; adding an appropriate sensor and alarm can make that knowledge explicit. Of course, the cost and potential regulatory impact of such changes must be weighed against the expected benefits.

Given a good understanding of risks that may affect a facility's ability to perform its missions and the costs of existing preventive maintenance programs, PredM can reduce risks and maintenance costs. ♦

About the authors

Jim Butler is Chief Technical Officer of Cimetrics Inc., where he is responsible for the company's R&D activities and technology consulting. Jim's principal area of technical expertise is communication protocols for distributed control systems. He has participated in the development of three ASHRAE standards, and was the founding manager of the BACnet Testing Laboratories. Jim received BS and MS degrees in aeronautics and astronautics from the Massachusetts Institute of Technology, and a certificate from MIT's Advanced Study Program.

Chris Smalley has recently retired from Merck, where he had responsibility for innovative implementation and validation, including single-use systems, globally. He had previously been director of quality operations for Wyeth Pharmaceuticals. Research experience includes responsibility for quality in the US operations of the Sanofi Research Division, and as a plant manager for Johnson & Johnson. Chris holds an MBA from Temple University Fox School of Business, and an MS in pharmaceutical chemistry from Temple University School of Pharmacy, Philadelphia, Pennsylvania, US. An ISPE member since 2012, he is a member of the Disposables CoP.



zenon

YOUR INDUSTRIAL SOFTWARE FOR GMP AUTOMATION RIGHT OUT OF THE BOX



- ▶ *ISA 88 – Batch Control and Electronic Batch Records*
- ▶ *Historian & Reporting solutions*
- ▶ *Line Management*
- ▶ *FDA Part 11 Compliance*
- ▶ *GAMP 5 – software category 4*

www.copadata.com/pharmaceutical



COPADATA

do it your way

Microsoft Partner

Gold Application Development
Gold Intelligent Systems
Silver Cloud Platform



EMBRACE SPECIAL CAUSE VARIATION DURING CPV

Tara Scherder

Understanding the fundamental assumption of independence (and the violation thereof) enables an appropriate response to control chart trend rule violations, and challenges us to think differently about special cause variation in control charts.

To align with the 2011 US Food and Drug Administration (FDA) guidance on process validation, actions must be taken during the continued process verification (CPV) stage so that “[o]ngoing assurance is gained during routine production that the process remains in a state of control.”¹ Process monitoring during this stage provides valuable information that can be used to address process problems and identify opportunities for improvement. Successful implementation of CPV requires not only that decisions and actions be aligned with these goals; the use of statistical tools such as control charts must also be understood within the context of pharmaceutical/biologics manufacture and a risk-based approach to lifecycle process validation.

DISCUSSION

It is common practice to use Shewart control charts to monitor process behavior during the CPV stage. Quite often manufacturers apply a selection of the Western Electric or Nelson rules* to their control charts.²⁻³ These rules were designed to signal significant process change and to justify action, often in real time, to address the change in process behavior.

Often not incorporated into the design and interpretation of these control charts, however, is the influence of the most important assumption underlying conventional interpretation: independent observations.⁴ When observations are independent, variation is a result of random sources; the output of batch #1 is no more similar to batch #2 than it is to batch #25. Because this assumption is rarely met for pharmaceutical quality attributes, adaptation of typical control chart interpretation is critical; otherwise, CPV programs can be designed that not only misguide and waste resources, but actually hinder CPV goals.

Why is understanding this assumption so critical to a successful CPV program? Reach for almost any Lean Six Sigma reference to process control and you will find variability described as either “common cause,” due to typical, random sources of variability, or “special cause,” which reflects unexpected variability that is likely the result of a process change. Further description of the two types typically assigns an assessment of process control. Specifically, a process displaying only common cause variation is often said to be “in control” or “stable and predictable.” Special cause variation, in contrast, is generally described as unexpected

THE IMMEDIATE TRANSLATION OF A STATISTICAL SIGNAL TO POTENTIAL LOSS OF PROCESS CONTROL IS VALID ONLY IF THE FUNDAMENTAL ASSUMPTION OF INDEPENDENCE IS MET

or unnatural variation, and indicates that the process may be “unstable and unpredictable” or “out of control.”⁵⁻⁷

When a process is in a state of control and sources of variability have random influence across time, points on the control chart should have a random pattern.^{4,8} Evidence of special cause variation can be an unexpected event, such as a single point outside of a control limit or a pattern not expected by random chance. In commonly used statistical software packages, such events can be associated with the Nelson rules, and identified on a control chart as a red symbol and a number identifying the specific pattern, commonly referred to as a statistical signal. This special cause designation is often associated with a call for action or investigation into the process to bring it back to a state of control. Thus, “red” is viewed as a problem. Some references are more extreme, stating that special causes must be eliminated before the control chart can be used as a monitoring tool.⁸

It is critical to understand, however, that the immediate translation of a statistical signal to potential loss of process control is valid only if the fundamental assumption of independence is met. And in the usual manufacture of pharmaceutical and biological products, non-independence is the norm, since typical sources of variability (raw materials, equipment, lab factors, etc.) are not used randomly. They meet the “typical” and “expected,” but not “random” criteria of the common cause variability definition.

In this scenario, patterns of variability that result from the nonrandom use of these typical sources may be identified as special cause variation. Practically speaking, this is a different situation than special cause variation that results from a true process upset, such as error in addition

* To distinguish between natural and unnatural variation, Western Electric expanded on the three standard error decision rules of Walter Shewhart. Based on these decision rules, Lloyd Nelson later formulated a set of tests for assignable causes.

Figure 1: Assay results include multiple manufacturing and laboratory campaigns

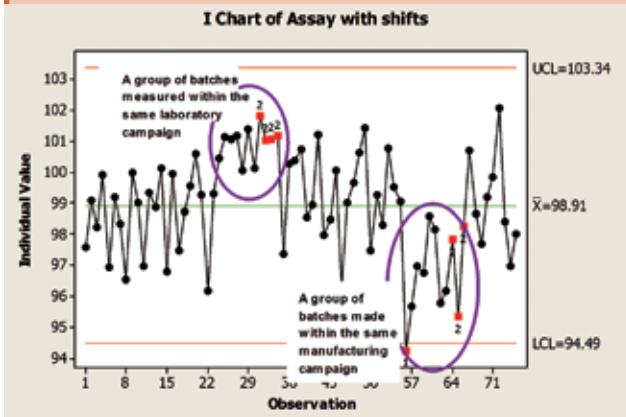
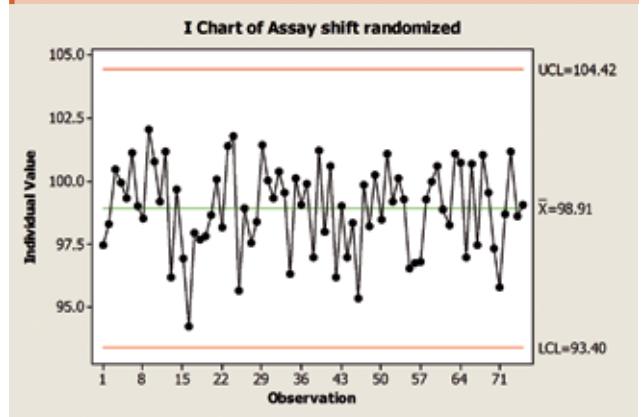


Figure 2: Assay results randomized across time



of raw materials. In the realm of non-independence, overreaction can occur when all special cause notations are automatically perceived as reflections of a process that is out of control.

If non-independence precludes the conventional interpretation of trend rules and special cause variation,⁴⁻⁵ does that mean basic control charts can't be used? Certainly not. These tools, in their simplest forms, are very powerful, even in the presence of non-independence. The nonrandom use of variability sources (such as different raw material lots) is not the problem. The problem results when control chart interpretation is not appropriately modified from the classical statistical process control (SPC) paradigm in which independence is assumed.

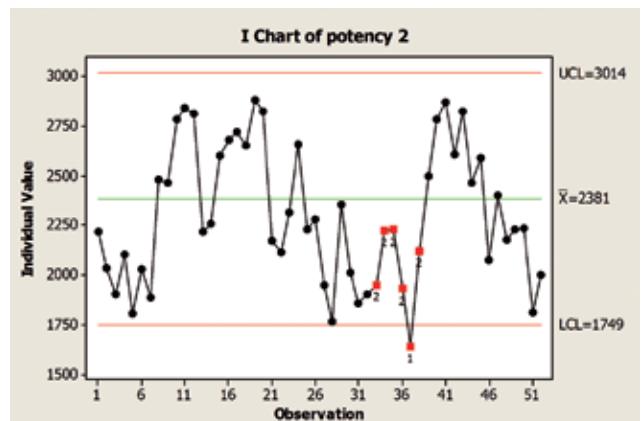
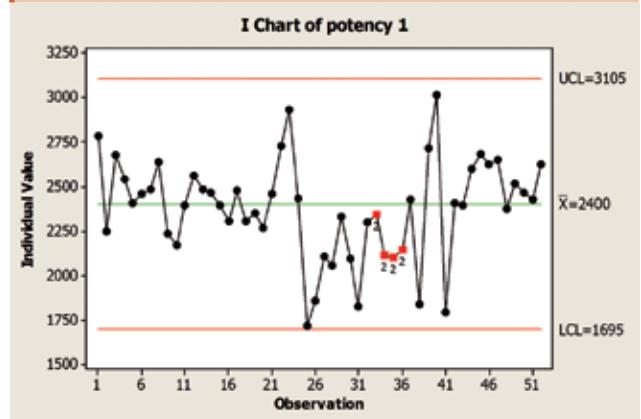
When common cause sources of variability are not used randomly across time, “unlikely” patterns are really not so unlikely. For instance, the pattern of nine points on the same side of the control chart centerline can be expected. These patterns do not necessarily indicate that the process is out of control; it is often a reflection of the process as designed. The absence of statistical signals cannot be required to claim a state of control. Because of non-independence, the “state of control” may include results identified as special cause variation, as shown in Figure 1.

The figure shows two shifts in the data, one representing a group of batches measured in the same laboratory campaign, and another produced during the same manufacturing campaign. The observed behavior is not inherently unexpected; the process is not necessarily “out of control,” in the sense that the shifts in mean forecast instability and risk. The shifts may in fact be expected, since batches within the same laboratory and manufacturing campaign share common sources of variability that are quite likely different from the other campaigns represented. Even the point below the lower control limit is a potential artifact of non-independence. (See the discussion preceding the conclusion.)

Figure 2 is a chart of the same data in random order. Randomizing results reflects what could be expected if the common cause variables that influence individual campaigns were experienced randomly across time. Not surprisingly, no special cause variation is identified. Note, too, that the true process performance in Figure 2 is no better than that of Figure 1. Process performance and control cannot be measured by the amount of “red.” The charts could be interpreted incorrectly if the underlying data structure—and its effects on chart interpretation—were not understood.

Given this context, the appropriate response to this variation is not as straightforward as a simple textbook case, where a red symbol on a control chart becomes a call for action. Nor are the patterns and resulting signals in Figure 1 false alarms in the statistical sense; they do indicate performance that is statistically unexpected relative to overall performance. Thus, they can provide valuable information regarding the sources of variability, di-

Figure 3. Two cases of a shift in the mean potency result



rectly enabling the CPV goals of ongoing quality assurance and continual improvement.

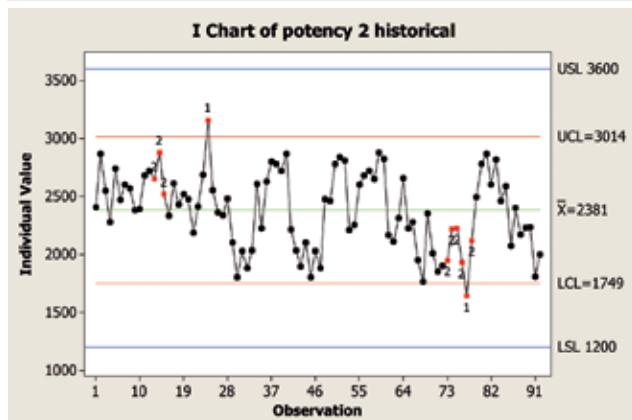
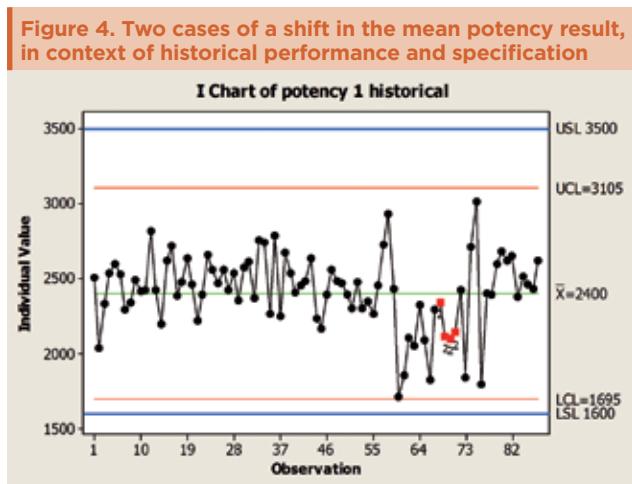
When textbook statistical interpretation of signals is not valid, a risk-based approach can define the urgency and appropriate reaction to special cause variability. Consider the following pair of charts:

In each case, a shift in the mean is identified with a red number 2 following 9 points in a row on the same side of the mean. The magnitude of the shift relative to overall performance is about the same. But should reaction to these patterns also be the same?

In a presentation at the 2015 ISPE Statistician Forum on process validation, a member of the FDA Center for Drug Evaluation and Research, Office of Pharmaceutical Quality, noted that “...all signals are not created equally” and “... magnitude of the response depends on the severity of the signal ...”⁹ In this hypothetical situation, how might that advice be interpreted? Both figures reflect the same attribute (potency), and it is likely that potency would be rated as a high severity attribute. Does that mean that every signal must be investigated, and to the same level? What additional information might be useful to define the severity of the signal and an appropriate response in each scenario?

Consider the charts in Figure 4, which include more historical data prior to the shift, and specification limits (blue lines). This additional information is used to assess: 1) if the pattern is truly unexpected, and 2) risk.

With this additional information, an informed risk-based response is possible. In Potency 1 chart, the shifted results are quite close to specification.



USING CONTROL CHARTS IN CPV REQUIRES A MINDSET CHANGE FROM TYPICAL APPLICATION AND INTERPRETATION WITHIN THE SPC PARADIGM

In addition, because this type of behavior has not been observed in the past, this shift is unexpected. And although the process has returned to normal behavior, we cannot know whether the factor that caused the shift will occur again; if it does, the risk of results outside specification is clearly apparent. In this situation, therefore, immediate attention is warranted.

This contrasts with the situation shown in the Potency 2 chart. Not only is the process trending well within specifications, shifts similar to the most recent one have been observed historically. Note that like the shift in assay in Figure 1, patterns identified in the Potency 2 data could indeed provide valuable information about sources of variability, and opportunity for continual improvement, thereby enabling a primary goal of CPV. The urgency for investigation, however, would not rise to the level warranted for the Potency 1 situation.

While process knowledge may certainly be gained through the evaluation of signals, the requirement that they be investigated regardless of the risk to patient and business can result in substantial, misdirected resources. Ultimately, this lack of prioritization serves neither the patient nor the business. Akin to the previous example, some manufacturers have designed decision trees or matrices to incorporate a risk-based approach to statistical signals in control charts and ensure an appropriate level of attention is given to observed signals.

Examples of decision rules include:

- Process capability (e.g., using process performance index)
- Distance of signal from specification
- Distance of signal from mean
- Number of batches affected
- Historical patterns of variability

Signal response is commensurate with the risk and opportunity identified considering those multiple elements, and can vary from a simple acknowledgment at the lowest level to a formal investigation documented within the quality system. The BioPhorum Operations Group CPV and Informatics Team formulated one such risk-based approach to signals, published in the January-February 2017 issue of this magazine.¹⁰

Fearing unnecessary attention to signals and knowing that they are expected, some manufacturers choose to remove these signals from their charts. If the context were real-time SPC requiring rapid process-adjustment decisions, the number of signals may indeed pose a problem. But this does not pose the same risk in CPV, where immediate adjustments or decisions are not typically sought. And if the business process defines a risk-based approach to signals, overanalysis and/or overreaction should not occur.

Questionable effectiveness is another reason some manufacturers

WHEN SPECIAL CAUSE VARIATION TRIGGERS AN APPROPRIATE RISK-BASED RESPONSE, THE RESULTING VISIBLE PATTERNS CAN HELP ACHIEVE CPV GOALS

choose to omit signals. For instance, specific statistical requirements can result in the situation of a shift that is detectable by a keen eye, but does not trigger a signal. The logic for omission continues: If signals are not triggered for all shifts and they can be misinterpreted as a lack of control, why use them at all? Indeed, careful review of charts for excursions and patterns by a process subject matter expert can be more effective than simple reliance on statistical signals. This careful review does not always exist, however, and even when it does the pattern of color from signals can aid interpretation. This is particularly true in early stages of process understanding, due either to the age of the product or the age of the CPV program.

There may indeed be cases where it's reasonable to omit specific signals, as they provide little benefit or may even be detrimental. This decision should be considered carefully, however, by assessing what knowledge about variability might be forfeited, and recognizing that the biggest value of the charts can be the pattern they reveal.¹¹ If signals are viewed negatively due to inadequate training of users and reviewers, cumbersome reporting, or overreaction, more benefit may be realized by addressing these deficiencies than by widespread omission.

An additional note regarding both examples: These charts have "Shewhart" control limits derived from the average moving range, thus they reflect short-term standard deviation. In the context of nonrandom variability sources, this estimate tends to be less than the longer-term estimate computed by the typical standard deviation formulation of a sample. For this reason, Shewhart limits may be too narrow to bracket expected total variability, and more values may be expected to be outside the limits compared to the number expected if sources of variability are truly random. Hence, some manufacturers choose to derive limits based on the longer-term estimate of standard deviation. Others maintain the short-term estimate, and recognize this feature in their risk-based response to statistical signals.

CONCLUSION

Using control charts in CPV requires a mindset change from typical application and interpretation within the SPC paradigm. Indeed, while both paradigms utilize control charts, their intended use and assumed data structure are not the same. Thus, it should be expected that interpretation also differs. Because the fundamental assumption of independence integral to conventional SPC is not met in typical pharmaceutical or biopharmaceutical manufacture, response to variation identified as special cause is unfortunately not a simple application of statistical rules and common definitions. Ignoring the influence of this assumption and imposing actions as if it had been in fact met is not only statistically inappropriate, it can result in wasted resources, improper focus, lost

opportunities, and frustrated employees. None of these outcomes serve either the business or the patient. And while omitting the identification of "expected" special cause variation to avoid too many signals might be important in the context of real time SPC, it can inhibit the CPV goal of continued understanding of process variability.

Control chart interpretation within the context of CPV requires a combination of process knowledge, adequate statistical understanding, and a business process that incorporates them into a risk-based decision framework. When special cause variation triggers an appropriate risk-based response, the resulting visible patterns can be embraced to help achieve the goals of CPV.

Instead of dreading statistical signals in control charts, a new appreciation can be acquired where "red is the new black." ♦

References

1. US Food and Drug Administration. Guidance for Industry. "Process Validation: General Principles and Practices." Revision 1. January 2011. <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM070336.pdf>
2. Western Electric Co., Inc. *Statistical Quality Control Handbook*. Easton, Pennsylvania: Mack Printing Company, 1956.
3. Nelson, Lloyd S. "Technical Aids." *Journal of Quality Technology* 16, no. 4 (October 1984).
4. Montgomery, Douglas C. *Introduction to Statistical Quality Control*, 7th ed. John Wiley & Sons, Inc., 2013.
5. George, Michael L., et al. *The Lean Six Sigma Pocket Toolbook*, McGraw-Hill, 2005.
6. Wedgewood, Ian D. *Lean Sigma: A Practitioner's Guide*, Prentice Hall, 2007.
7. Brue, Greg. *Six Sigma for Managers*, McGraw-Hill, 2002.
8. Six Sigma Academy. *The Black Belt Memory Jogger*, 1st edition, GOAL/QPC, 2002.
9. Viehmann, Alex. "Process Monitoring Expectations and Establishing Acceptance Criteria." Presented at the ISPE Statistician Forum, Silver Spring, MD, 14-15 April 2015.
10. Mark DiMartino, et al. "CPV Signal Responses in the Biopharmaceutical Industry." *Pharmaceutical Engineering* 37, no. 1 (January-February 2017): 57-64
11. Chowdhury, Subir. *Design for Six Sigma*. Dearborn Trade Publishing, 2002.

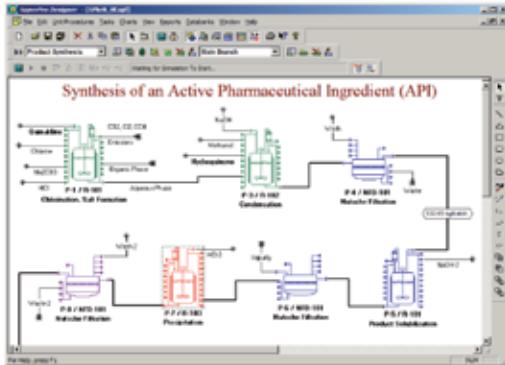
About the author

Tara Scherder, partner at SynoloStats, has over 25 years of experience in the chemical and pharmaceutical industries as a statistician, process engineer, and master black belt. She has functioned as both an in-house and external statistical consultant to drug substance and drug product teams across the product lifecycle for large-molecule, small-molecule and medical device platforms. Her current focus is the implementation of statistical methods and associated business processes for lifecycle process validation. She is passionate about teaching others the business value and practical application of statistical methods. Tara's formal education includes a BS in chemical engineering from the University of Pittsburgh and an MS in statistics from Carnegie Mellon University. An ISPE member since 2013, she is very active in ISPE conferences, publications, and training related to process validation.

Intelligen Suite®

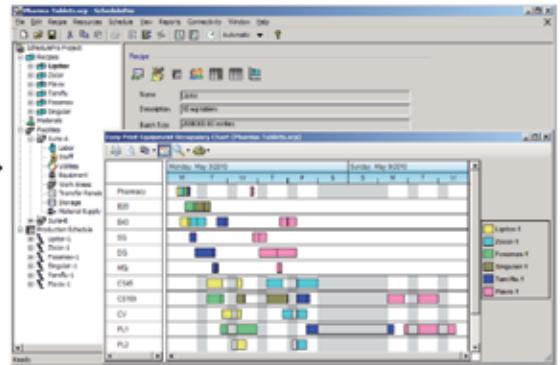
The Market-Leading Engineering Suite for Modeling, Evaluation, Scheduling, and Debottlenecking of Multi-Product Facilities

SuperPro®

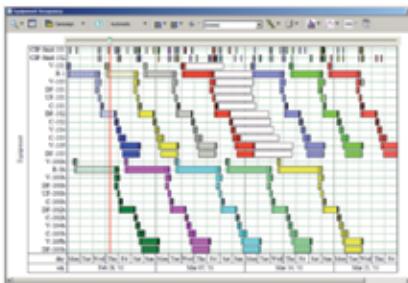


Use SuperPro Designer to model, evaluate, and optimize batch and continuous processes

SchedulePro®



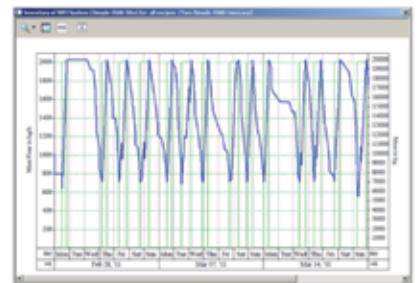
Migrate to SchedulePro to model, schedule, and debottleneck multi-product facilities



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

INDEX

Aqua-Chem	53
Bürkert Werke GmbH	34
Commissioning Agents, Inc.	39
CRB	1
Electro-Steam Generator Corp	55
Elettracqua Srl	Inside Back Cover
Fluor Corporation	5
Fristam Pumps US	7
GEMÜ Gebrüder Müller Apparatebau GmbH & Co. KG	47
GEMÜ Valves, Inc.	23
Gericke AG	21
Getinge Life Science	3
Ing. Punzenberger COPA-DATA GmbH	65
Intelligen Inc.	70
Letzner Pharmawasseraufbereitung GmbH	50
LEWA-Nikkiso America, Inc.	15
OPTIMA Packaging Group GmbH	Inside Front Cover
Pharma Access	43
Steriline Srl	11
Stilmas SpA	Back Cover
Valsteam ADCA Engineering, SA	26
Watson-Marlow Fluid Technology Group	25

CLASSIFIEDS

Architects, Engineers, Constructors

CRB
7410 NW Tiffany Springs Pkwy. Suite 100
Kansas City, MO 64153 US
+1 816-880-9800

Aseptic Processing Solutions

Steriline Srl
Via Tentorio 30
22100 Como, Italy
+39 031 592064

Construction

Fluor
100 Fluor Daniel Drive
Greenville, SC 29607 US
+1 864-281-4400

Contamination Prevention

Getinge Life Science
1150 Emma Oaks Trail, Suite 140
Lake Mary, FL 32746 US
+1 407-327-8488

Electric Dry Steam Generators

Electro-Steam Generator Corp.
50 Indel Avenue
PO Box 438
Rancocas, NJ 08073 US
+1 609-288-9071

Facility Engineering and Maintenance

Valsteam ADCA Engineering, SA
Rua da Guia, 3105-467
Guia PBL, Portugal
+351 236 959 060

Filling and Packaging Equipment

OPTIMA Packaging Group GmbH
Steinbeisweg 20
74523 Schwäbisch Hall, Germany
+49 791 9495-0

Information Technology

Ing. Punzenberger COPA-DATA GmbH
Karolingerstrasse 7b
Salzburg, Austria 5020
+43 662 43 10 02-0

Instrumentation

Bürkert Werke GmbH
Christian-Bürkert-Strasse 13-17
D-74653 Ingelfingen, Germany
+49 (0)7940 10 0

Machinery Design and Construction

Gericke AG
Althardstrasse 120
CH-8105 Regensdorf, Switzerland
+41 44 871 36 36

Pharmaceutical Turnkey Solutions Consultant

Pharma Access
411/413 Dilkap Chambers, off Veera Desai Rd.
In the lane of Fun republic, Andheri (W)
Mumbai, Maharashtra, India - 400 058
+91 22 4031 3888

Pumps

Fristam Pumps
2410 Parview Road
Middleton, WI 53562 US
+1 800-841-5001

Watson-Marlow Fluid Technology Group
37 Upton Technology Park
Wilmington, MA 01887 US
+1 800-282-8823

Pumps and Systems

LEWA-Nikkiso America, Inc.
132 Hopping Brook Road
Holliston, MA 01746 US
+1 508-893-3218

Software Simulation and Processing Systems

Intelligen, Inc.
2326 Morse Avenue
Scotch Plains, NJ 07076 US
+1 908-654-0088

Validation Services

Commissioning Agents, Inc.
652 N. Girls School Road
Indianapolis, IN 46214 US
+1 317-271-6082

Valves/Fittings/Hoses/Tubing

GEMÜ Gebrüder Müller Apparatebau GmbH & Co. KG
Fritz-Müller-Straße 6-8
74653 Ingelfingen-Criesbach, Germany
+49-79 40-123 0

GEMÜ Valves, Inc.
3800 Camp Creek Parkway Bldg. 2600, Ste. 120
Atlanta, GA 30331 US
+1 678-553-3400

Water/Steam Systems

Aqua-Chem
3001 E. Governor John Sevier Highway
Knoxville, TN 37914 US
+1 865-544-2065

Letzner Pharmawasseraufbereitung GmbH
Robert Koch Str. 1
42499 Hückeswagen, Germany
+49 2192/92170

Stilmas SpA
Viale delle Industrie, 14
Settala (MI) 20090 Italy
+39 02 9508061

Water Treatment and Purification

Elettracqua Srl
Via Adamoli 513
16165 Genoa, Italy
+39 010 8300014

Please see the ads for each of our advertisers in this issue

DIABETES AND THE INTERNET OF THINGS

Megan was diagnosed with Type¹ diabetes in 2007 when she was five months pregnant with her first child. She began the routine, familiar to many of the 415 million diabetics worldwide, of measuring her blood glucose levels with finger pricks, followed by insulin injections. She kept a pen-and-paper log of her glucose levels and diet to help manage her disease.

“I knew keeping track of my levels led to good control of my health,” the 36-year old mother of two said. “But I always found it cumbersome. I wanted to see graphs and trends to help me make decisions.”

The situation improved in the summer of 2009 when she started to use a body-mounted insulin pump. Her programmable Animas Ping delivered an insulin injection every three minutes through a port embedded in her abdomen. In 2016 Megan received a Dexcom G4 continuous glucose monitor (CGM), a small wearable device that sends data wirelessly to her Animas Vibe pump, which keeps a record of her levels. Megan then uploads this information to Diasend, a cloud-based database. Megan, her doctor, and health care team all have access to the information, which allows them to work together to manage her disease. In future, the data will be incorporated in an electronic health record.

All of this is made possible by the Internet of Things (IoT), the network of computerized sensors embedded in medical (and other) devices that can collect, send, and receive data via the Internet. The amount of data, the speed at which it is transmitted, and its aggregation, storage, and analysis is revolutionizing the management of chronic diseases like diabetes. The IoT could lead to lower health care costs, fewer doctor visits, and the ability to amass clinical data from large populations to provide insight into treatment options.

Chronic disease patients can now be fitted with wearable devices similar to fitness products Fitbit and Jawbone, which track step counts, pulse, and sleep patterns. Intel and the

THE IOT IS REVOLUTIONIZING MANAGEMENT OF CHRONIC DISEASES LIKE DIABETES

Michael J. Fox Foundation, for example, have collaborated on a smartwatch with an app for Parkinson’s disease patients that measures tremors and communicates with users, reminding them to take medications and giving them info on disease management.¹ In the ICU, glucometers, scales, and monitors that report heart rate and blood pressure have been joined by a new device that can measure core temperature and urine output in catheterized patients.²

Computers will soon be able to collect Megan’s real time data, collate historical information, then mine it for patterns to allow her to make informed choices about her life habits. Some health care start-ups, hospitals, and pharmaceutical companies have already started to do this by working with IBM Watson Health, a cognitive computing platform:

- Novo Nordisk, in partnership with digital and analytics company Glooko, are working with Watson to improve management and treatment options for diabetics.³
- Medtronic makes CGMs, insulin pumps, and an app for diabetics that collect data on a user’s exercise and carbohydrate consumption. Watson analyzes the data collected by the devices and uses it to predict potential hypoglycemic events that might occur as many as three hours later. If Watson believes the meal the user is about to eat may be harmful based on his or her historical data, it can send an alert.
- The American Diabetes Association is using Watson’s computing power to sift through more than 66 years of clinical and research data.⁴ By comparing an individual’s data to that of large populations, the team hopes to identify risk factors and create personalized treatment plans.

One challenge to IoT in the medical landscape is the lack of interoperability, which prevents medical devices, equipment, and databases from communicating with each other. Standardized interfaces will be necessary for this information to be useful in aggregate and to avoid it being marooned on “data islands.”⁵ There are also privacy concerns and cybersecurity threats. Most ransomware attacks are already aimed at health care organizations;⁶ IoT medical devices could also be vulnerable.

For Megan, the hope is that these kinks can be worked out.

“Having a CGM, I can see the data all the time, anytime,” Megan said. “It’s made a huge difference in how I relate to my disease.” ◆

—Scott Fotheringham, PhD

References

1. LiveWell. “Using Wearable Technology to Advance Parkinson’s Research.” 12 December 2016. <http://www.livewellrec.org/tech-watch/2016/12/8/using-wearable-technology-to-advance-parkinsons-research>
2. Future Path Medical. <http://www.future-path.net>
3. Novo Nordisk. “Novo Nordisk and Glooko Partner to Develop Digital Health Solutions for People with Diabetes.” Press release. 25 October 2016. <http://www.novonordisk.com/media/news-details.2069517.html>
4. IBM. “American Diabetes Association and IBM Watson Health Join Forces to Reimagine How Diabetes Is Prevented and Managed.” Press release. 12 June 2016. <http://www-03.ibm.com/press/us/en/pressrelease/49903.wss>
5. Dimitrov, D. V. “Medical Internet of Things and Big Data in Healthcare.” *Healthcare Informatics Research* 22, no. 3 (July 2016): 156–163. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4981575/pdf/hir-22-156.pdf>
6. Siwicki, B. “Ransomware: 88 Percent of US Attacks Hit Healthcare Entities.” *Healthcare IT News*. 7 September 2016. <http://www.healthcareitnews.com/news/ransomware-88-percent-us-attacks-hit-healthcare-entities>



ELETRACQUA

pure water technologies

SINCE 1965

PHARMACEUTICAL WATER SYSTEMS

OSMOSIS + EDI UNIT HOT WATER SANITIZABLE



DOUBLE PASS REVERSE OSMOSIS + EDI UNIT + 85 °C SWRO
HIGH TEMPERATURE SANITIZATION + CONCENTRATE RECOVERY (ED/ED)

MULTIPLE EFFECTS DISTILLATION UNIT



PURE STEAM GENERATOR

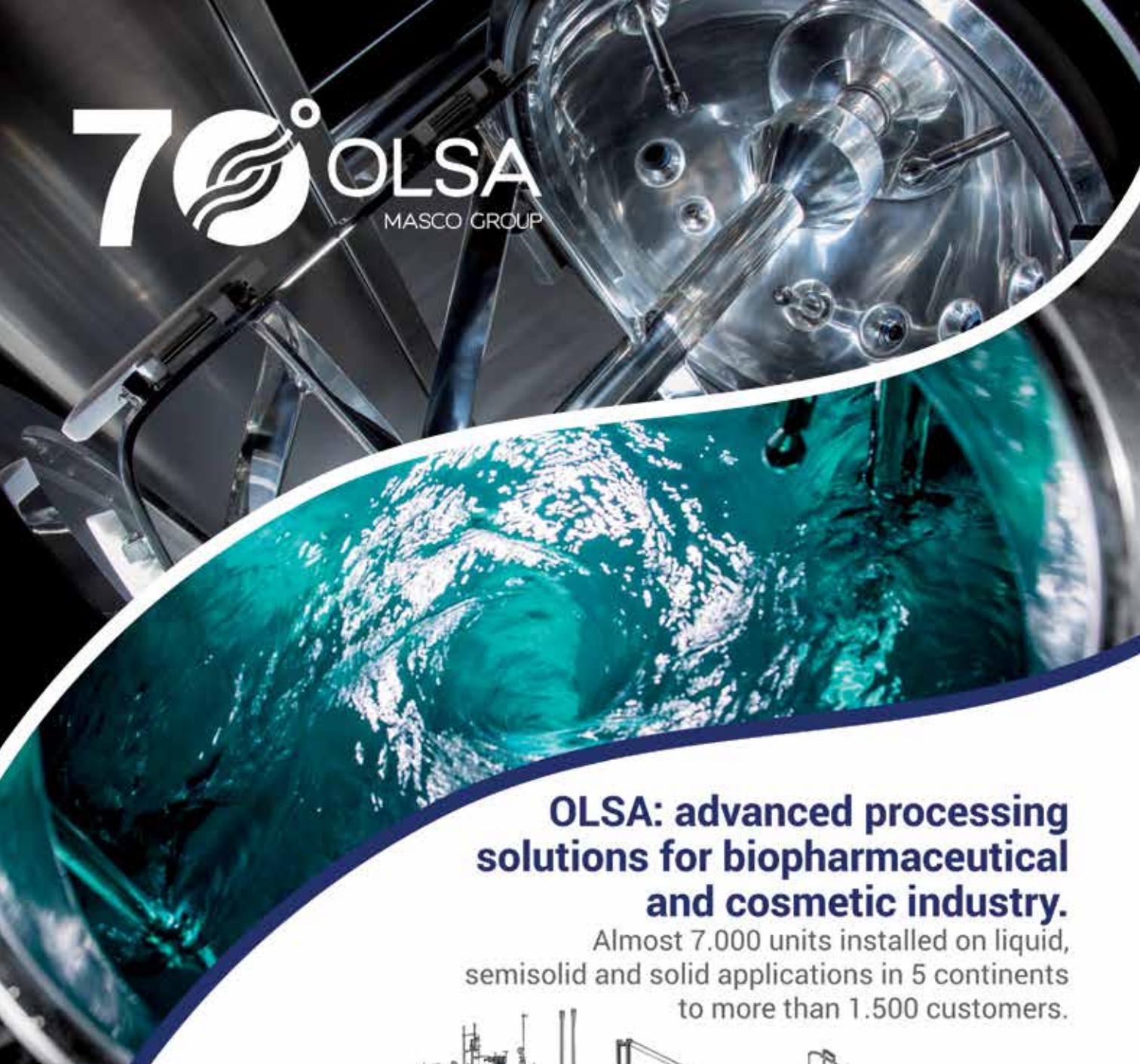
DESIGN AND CONSTRUCTION OF PURIFIED WATER PACKAGES + DOUBLE PASS REVERSE OSMOSIS + R.O. + ELECTRODEIONIZATION HOT WATER SANITIZABLE + ULTRAFILTRATION + MULTIPLE - EFFECT DISTILLATION UNITS + PURE STEAM GENERATORS + STORAGE AND DISTRIBUTION LOOP + COMPLETE TURN KEY PROJECTS + VALIDATIONS IQ, OQ

www.elettracqua.com





70^o
OLSA
MASCO GROUP



OLSA: advanced processing solutions for biopharmaceutical and cosmetic industry.

Almost 7.000 units installed on liquid, semisolid and solid applications in 5 continents to more than 1.500 customers.



WWW.OLSA.COM