PHARMACEUTICAL ENGINEERING®

The Official Magazine of ISPE

January-February 2020 | Volume 40, Number 1

Industry Leaders

Applying Holistic Control Strategy in Pharma 4.0™

A Systems-Based Approach to Digital Design and Operation

Evaluation of Visual Inspection in Parenteral Products

ISPE®

ispe.org/pharmaceutical-engineering

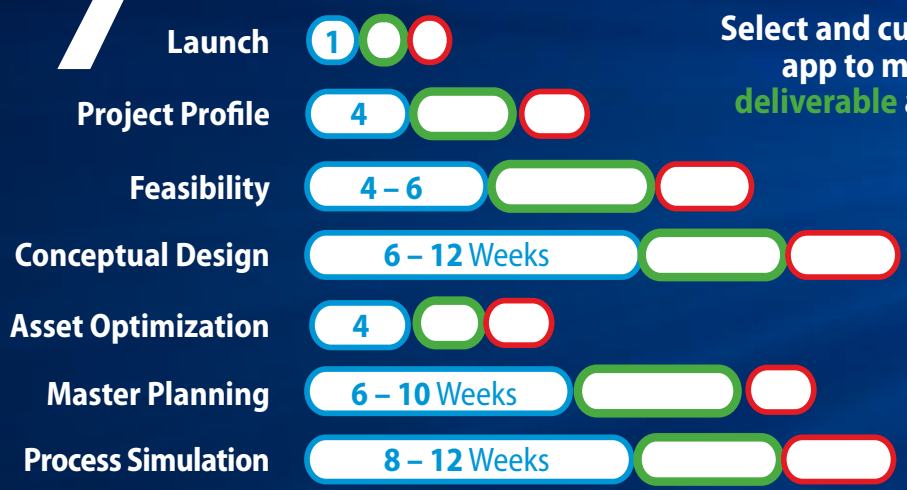
FLUOR INNOVATES.

Engineering Solutions and Building Capacity in Life Sciences Worldwide

Announcing EPIC³ an innovative work process containing implementation applications and tools aimed at driving accurate early definition packages within our client's budget and schedule objectives.

EPIC³ Solutions

7 Fully Customizable Applications



Select and customize your app to meet duration, deliverable and certainty expectations

30 Years in Life Sciences

Over **30** Core Tools

1,000+ projects

Delivering Certainty to…

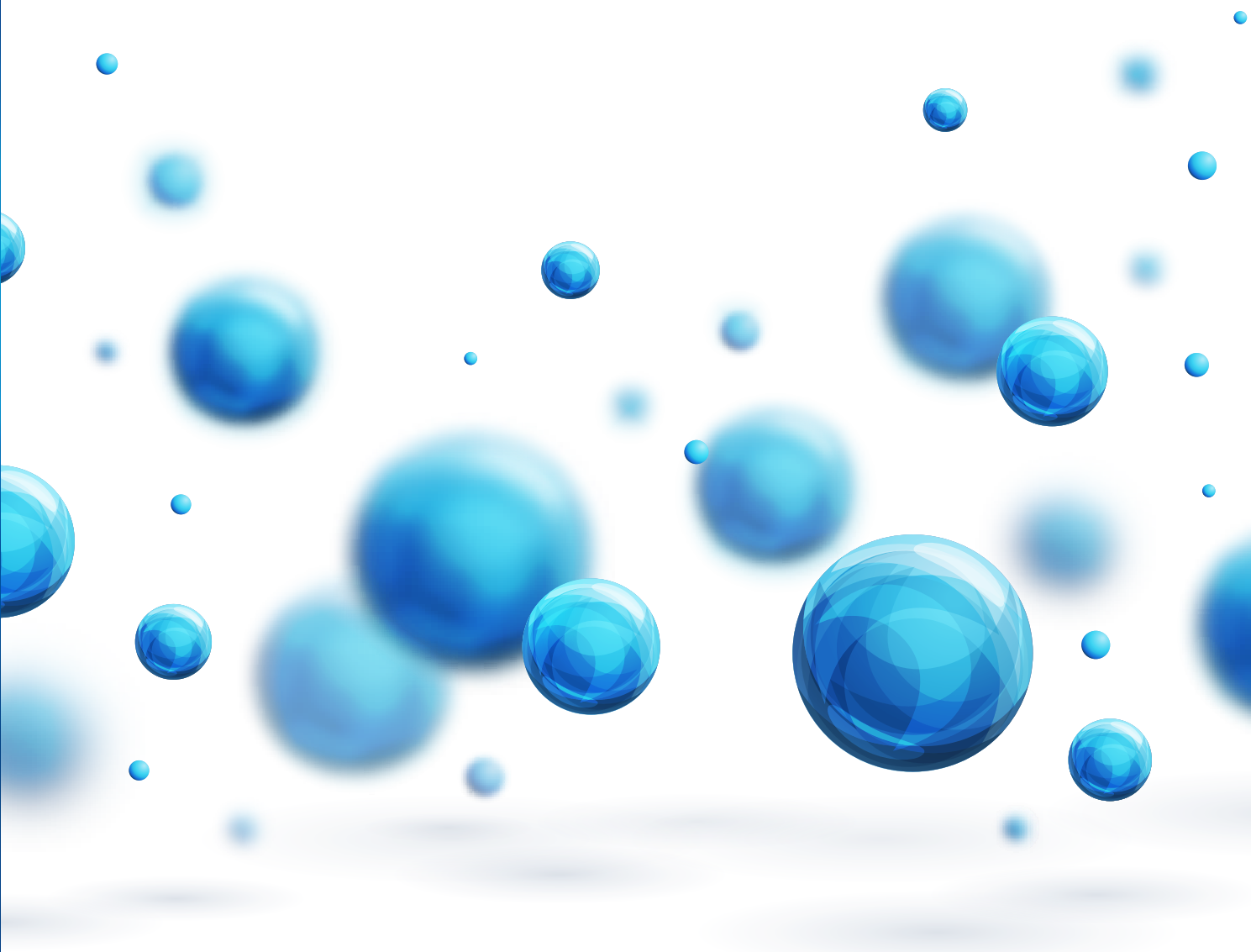
C³ **Function Cost Schedule**

Since 1912, Fluor has been designing and executing innovative solutions that bring our clients greater capital efficiency with improved cost and schedule certainty.

www.fluor.com

FLUOR®

STEADFAST IN THE LIFE SCIENCES



ENGINEERING | ARCHITECTURE | CONSTRUCTION | CONSULTING
crbusa.com

PHARMACEUTICAL ENGINEERING®

JANUARY / FEBRUARY 2020

12

INTRODUCING INDUSTRY LEADERS

Pharmaceutical Engineering is launching a new series of profiles of industry leaders. This ongoing series will look at the lives and careers of individuals who are changing the face of the pharmaceutical industry.

ON THE COVER A symbolic representation of industry leaders: they stand out from all others in the sea of pharmaceutical engineers.

COVER STORIES

Endgame for Data Integrity Warning Letters!

When GMP compliance meets transparency and flexibility:

- *Connect your existing machines and manufacturing lines*
- *User Access Control, audit trail, time synchronization*
- *Automatically record GMP-critical process parameters*
- *Detect deviations in real time*
- *Generate reports that support batch review by exception*

Gold Microsoft Partner

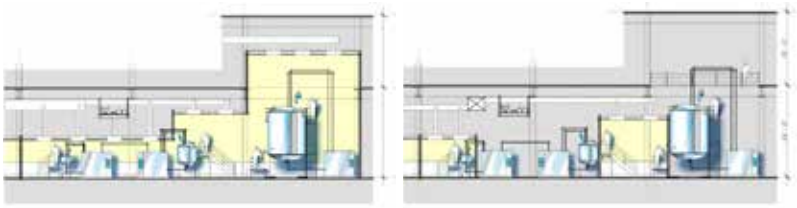
GAMP 5

FDA 21 CFR Part 11 Compliant

zenon by COPA-DATA

www.copadata.com/pharmaceutical

JANUARY / FEBRUARY 2020



ISPE

PHARMACEUTICAL ENGINEERING

Volume 40, Number 1
Published since 1980

Senior Director, Editorial: Susan Sandler, ssandler@ispe.org

ISPE Headquarters
6110 Executive Blvd., Suite 600
Rockville, MD 20852 US
Tel: +1 301-364-9201
Fax: +1 240-204-6024

ISPE Operations
600 N. Westshore Blvd., Suite 900
Tampa, FL 33609 US
Tel: +1 813-960-2105
Fax: +1 813-264-2816

ISSN 0273-8139

Pharmaceutical Engineering is published six times a year by ISPE.

Advertising and Sales
Deborah Bahr, VP Business Development and Sales
+1 301-364-9213 ext. 433 dbahr@ispe.org

Alisa Pachella, Sales Account Manager
+1 813-739-2274 apachella@ispe.org

Doug Whittemore, Sales Account Manager
+1 813-739-2300 dwhittemore@ispe.org

Stock Photography and Illustration
iStock

Art Direction and Graphic Design
THOR Design, Inc., www.thor.design

Printing
Royle Printing

Letters to the Editor
Pharmaceutical Engineering welcomes readers' comments. Letters must include the writer's full name, address, and organization. If published, letters may be edited for length and clarity. Send correspondence to ssandler@ispe.org.

Article reprints can be ordered through Sheridan Content Solutions at sheridancontentsolutions@sheridan.com.

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

Pharmaceutical steam trap from Spirax Sarco

FDA compliant, fully certified

The Spirax Sarco BT6-B is a high specification sanitary balanced pressure thermostatic steam trap that minimises contamination when steam is in direct contact with pharmaceutical product. Its unique design with certifications and approvals, ensures the BT6-B is economical and exceeds the capabilities of other models currently available on the market.

The only one in the market fully certified

- 'Gold Standard' EN10204 3.1 Certification, across all wetted parts.
- FDA and USP compliant.
- Full material traceability 3.1, including all wetted parts.
- Surface finish certificate available.
- Assembled and packed in ISO Class 7 clean room.

Contact your local Spirax Sarco representative to learn more about the BT6-B.

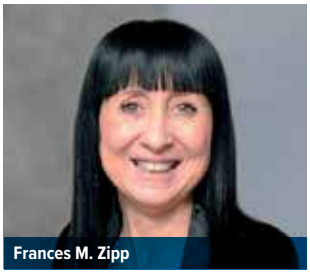
First for Steam Solutions

EXPERTISE | SOLUTIONS | SUSTAINABILITY

spirax sarco

By Frances M. Zipp

Making the Connection


Frances M. Zipp

As I sit at my computer to write my first column as ISPE International Board Chair, my thoughts are centered on how I can personally help drive our unifying vision, "Connecting Pharmaceutical Knowledge," and how we as members of ISPE have an outstanding opportunity in the year ahead to provide outreach and resources to expand our networks of people, technology, and information to accomplish the goals of that vision.

I look forward to achieving that vision with all of you. At its heart, ISPE is an organization of people who are here to improve and advance our industry. Without you, ISPE would not be the industry leader that it is today. To keep you well informed, I want to share a brief overview of several key areas of strategic focus for the year ahead that we may achieve together.

A FOCUS ON LEADERSHIP

In our targeted efforts to focus on the latest, most innovative channels, ISPE will improve our operating model by designing and implementing key digital transformation initiatives in content development, knowledge management, access, and distribution.

We will also build and scale initiatives relevant to current and emerging therapeutic modalities to reinforce ISPE's thought leadership for members of our organization and industry professionals around the globe.

HIGH-VALUE ENGAGEMENT

In the coming years, ISPE will focus on engaging our members and pharmaceutical professionals at all career stages, providing exceptional networking and knowledge platforms that offer solutions to complex industry challenges in a socially responsible manner.

Among these efforts, ISPE will improve and expand the relevance, impact, and efficiency of ISPE's operating and volunteer models. Based on market research, we'll strengthen engagement with stakeholders in prioritized target geographic markets through initiatives including Women in Pharma® and Workforce of the Future.

GETTING TOGETHER

The year ahead will provide many opportunities to gather, network, and share during ISPE's many conferences and trainings. With our focus on modernization, globalization, and transformation in pharmaceutical science as well as manufacturing across the globe, our events offer an outstanding opportunity to pharmaceutical professionals to engage in industry-critical conversations.

I look forward to talking with you this year, whether you are a new member or a member of many years. If we don't get the chance to connect in person, please reach out to me. Every ISPE member is important, and each voice deserves to be heard.

Let's join together to advance ISPE's mission through sharing ideas and knowledge, spirited debate and discussion, and mentoring those new to the life sciences and ISPE. Through these efforts, we continue to build momentum that will empower and energize our members, which will ultimately benefit the healthcare of people around the globe.

Let's all get motivated! Let's all pledge to contribute! And let's all get started today!

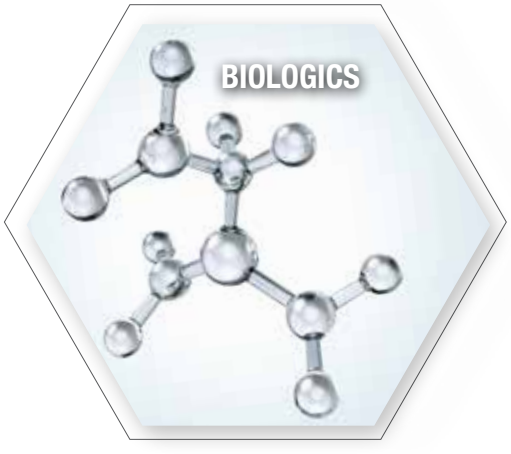
Frances M. Zipp is the 2020 ISPE International Board of Directors Chair and President and CEO of Lachman Consultant Services, Inc.

ISPE®

PHARMACEUTICAL ENGINEERING®

PICARRO

World's Leading Solution for Monitoring Residual VHP

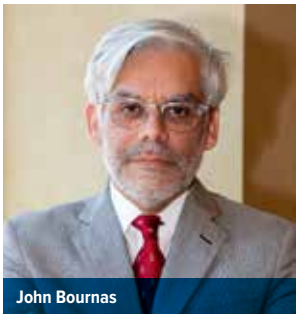


The Picarro PI2114 gas concentration analyzer measures hydrogen peroxide (H_2O_2) levels as low as 3 ppb to help avoid oxidation and safeguard drug stability. Major pharmaceutical, CMO, and isolator companies use Picarro hydrogen peroxide analyzers in high-potency API and biologics manufacturing and in aseptic fill and finish.

- Measure residual H_2O_2 levels as low as 3 ppb
- Optimize your decontamination process
- Reduce manufacturing costs

Confidence comes with continuous measurement from Picarro.

Learn more at www.Picarro.com/Pharma


John Bournas

INTRODUCING ISPE'S NEW STRATEGIC PLAN

The pharmaceutical industry is ever-changing, as we saw demonstrated during the 2019 ISPE Annual Meeting & Expo, and at other ISPE conferences around the world. In fact, change is accelerating—and to support the trends and developments in the industry, ISPE has developed a new three-year Strategic Plan.

The new plan commences this year and continues through 2022. It builds upon the successes of the previous Strategic Plan (2016–2019), which laid the groundwork for our next steps.

BUILDING THE PLAN

Our new plan reflects what you, ISPE's members, want and need to support the essential and valuable work you do every day.

To learn about these wants and needs, ISPE obtained input from over 1,600 individuals who participated in surveys, focus groups, and interviews. Participants in this information-gathering initiative included individual members and nonmembers, Chapters, Affiliates, knowledge networks, the ISPE International Board of Directors, and former Board members.

The plan was developed in support of ISPE's Mission Statement: *ISPE is the global industry leader in connecting pharmaceutical knowledge to deliver manufacturing and supply chain innovation, operational excellence and regulatory insights to enhance industry efforts to develop, manufacture, and reliably deliver quality medicines to patients.*

It also supports ISPE's Vision Statement: *Provide solutions to complex pharmaceutical industry challenges through manufacturing innovation, member and workforce development, technical, regulatory, and compliance collaboration.*

STRATEGIC THEMES

The new Strategic Plan has eight themes. This is an overview of the themes and the related initiatives we will be working on.

Build and scale content and initiatives relevant to current and emerging therapeutic modalities. ISPE will continue to be a thought leader driving innovative solutions for pharmaceutical manufacturing, supply chain operations, regulatory compliance, and quality assurance. We aim to be the go-to organization in technical problem-solving for continuous and agile manufacturing of current and emerging therapeutic modalities, including biotech (large molecules), small molecules, and cell and gene therapies. ISPE will continue to drive digital transformation of manufacturing/data analytics through initiatives such as Pharma 4.0™.

Balance portfolio of programs, products, and services to optimize ISPE's mission-related initiatives. ISPE will establish a more disciplined approach to align ISPE content, products, and services with the Strategic Plan. We will identify and prioritize ISPE's mission-critical activities, balancing between industry, membership, and regulatory priorities—always mindful of the patient. ISPE will enhance programs with significant industry impact, such as GAMP®, drug shortages prevention, and quality metrics.

Lead the acceleration of the pharmaceutical industry's efforts to develop the workforce of the future. ISPE will develop and implement a Workforce of the Future program, with the goal of the following desired outcomes: workforce flexibility that is agnostic to therapeutic modalities; transition of mature workforce to leverage their experience across the pharmaceutical industry; and equipping pharmaceutical industry professionals with the knowledge necessary to make optimal use of electronic systems to accelerate product development, licensure, and launch.

Drive member value with targeted content, communications, and member experiences based on professional areas of interest and demographics. ISPE will evaluate and prioritize targeted content to specific membership needs based on geography and/or professional status in the pharmaceutical industry. It will strengthen engagement in targeted geographic markets. ISPE will continue to sponsor the Global Pharmaceutical Manufacturing Leadership Forum (GPMLF) to define pharmaceutical industry initiatives that drive solutions to complex industry challenges. ISPE will establish Young Professional programs to improve the knowledge base.

Design and implement global digital transformation initiative for content development, knowledge management, access, and distribution. ISPE will continue to modernize its digital platforms to enhance the member experience worldwide, and will increase engagement of subject matter experts and regulators on the timely delivery of content through guidance documents, conferences, and professional development.

Foster partnerships and collaborations that advance ISPE's mission. ISPE will maintain and foster regulatory interactions to advance common interests among the pharmaceutical industry and regulatory agencies. It will selectively identify and partner with other industry organizations on topics where expertise can be leveraged to a common interest consistent with ISPE's mission.

Improve relevance, impact, and efficiency of ISPE's volunteer operations. ISPE will enhance its volunteer model to drive agility and efficiency. It will develop a comprehensive engagement process for the Communities of Practice (CoPs) to drive efficiency and align with regulatory and pharmaceutical industry initiatives. ISPE will also engage Affiliates and Chapters to enhance ISPE's operating model at the local level.

Promote and Support the ISPE Foundation. ISPE will develop and execute a plan to promote the ISPE Foundation, the philanthropic arm of ISPE. It will identify opportunities to support the initiatives of the ISPE Foundation using ISPE's knowledge-sharing platforms. Foundation initiatives include the Student and Young Professional Travel Grant Program, Women in Pharma®, and the Emerging Markets Knowledge Exchange. ISPE will assess opportunities to support ISPE members and pharmaceutical professionals in addressing new and evolving industry challenges and trends.

The International Board of Directors, ISPE leadership, and ISPE staff are looking forward to working on these strategic initiatives with you, our members. We are excited about what the future holds for these next steps at ISPE and in sharing in your contributions, with the end goal of the patient in mind.

John Bournas is President and CEO of ISPE.

For More Information

Details about the new ISPE Strategic Plan, including a video overview, are on the ISPE website:

https://ispe.org/about/strategic-plan-2020-2022


LeAnna Pearson Marcum

CELEBRATING THE FIRST GLOBAL ISPE HACKATHON

On 26–27 October 2019, the first Global Student & Young Professional Hackathon was held at the 2019 ISPE Annual Meeting & Expo. Thirty-six ISPE Young Professional (YPs) and Student members came from around the world to participate in the two-day event that demonstrated innovative thinking, collaboration, and project management.

This event was designed by an amazing group of task team volunteers: Heather Bennett, Project Manager/Process Engineer, ACCO Engineered Systems; John Clarke, Biopharmaceutical Operations Lead, Pfizer Dublin, Ireland; Wendy Haines, Associate Director of Technical and Scientific Services, PharmEng Technology; and Alex Schramm, Automation Engineer, Banks Integration Group.

ABOUT THE GLOBAL HACKATHON

YPs and students were split into six multidisciplinary teams. All teams were given one of two Facility of the Future presentations paired with a unique challenge to solve. All teams were also given access to resources including *Pharmaceutical Engineering* and the ISPE Communities of Practice. At the end of the two days, each team pitched to a group of judges and industry leaders.

These were the topics tackled by each team: Team 1: future expansion; Team 2: resiliency against environmental event; Team 3: supply chain; Team 4: future flexibility; Team 5: environmental impact; and Team 6: serialization and resource usage.

Team coaches were Dante Amatangelo, Validation Specialist/Consultant, VaLogic LLC; Nissan Cohen, Company Owner, Biopharmaceutical Water Doc; Stephen M. Hall, PE, Chief Process Engineer, Genesis Engineers; Monique Sprueill, PMP, Senior Manager Strategy, Insights and Innovation, Johnson & Johnson; and Zen-Zen Yen, Venture Manager, Bayer AG. The ISPE Staff Membership Liaison was Debbie Kaufmann, Manager, Professional Communities.

Judges were Michael Arnold, Senior Director, Strategic Relationships, Investigational Products Business Process Owner, Pfizer, Inc. Global Clinical Supply Chain, Connecticut, and Past Chair, ISPE; Heather Bennett, Project Manager/Process Engineer, ACCO Engineered Systems; Paul-Gerd Heiden, Head of Corporate Quality, Bayer AG, Germany; Tim Howard, Vice President, CPIP, PE, HR-D, Vice President of Strategic Development, CAI, North Carolina, Vice President for CAI-Asia Operations, and Past Chair, ISPE; Eamon Judge, EMEA Major Project Planning Leader, Global Engineering, Eli Lilly & Co., Ireland; Kelly Keen, Vice President, Project Management, and Head of PMO, Celonic Ag, Switzerland; Tony Moreira, Vice Provost for Academic Affairs, University of Maryland Baltimore County; Randy Perez, retired from Novartis Pharmaceuticals, and Past Chair, ISPE; and Christian Wölbeling, Senior Director Global Accounts, Werum IT Solutions, Germany.

All teams gave stellar presentations and demonstrated leadership, delegation, collaboration, and innovation with their presentations and problem-solving skills.

All teams gave stellar presentations and demonstrated leadership, delegation, collaboration, and innovation with their presentations and problem-solving skills. Because all teams did an outstanding job presenting creative, useful, and realistic solutions to difficult real-world challenges, the judges had a hard time deciding on the overall winner. Ultimately, Team 4, Project Mini Zoom, was selected for that honor. This team included Sarah-Catherine Dannellȳ, GEMU Valves, Inc.; Kathrine M. Pargā, Keck Graduate Institute; Phuong (Sophie) Le, University of Minnesota; Matthew Ong, National University of Singapore; Elice Kitchen-McKinley, North Carolina State University; and Yemisi Mohammed, North Carolina Central University.

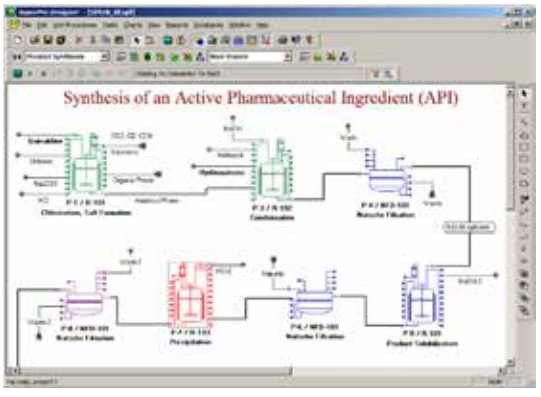
Congratulations to the Project Mini Zoom team and all participants!

LeAnna Pearson Marcum is a Senior Project Manager at PharmEng Technology and the 2019–2020 ISPE International Young Professionals Chair. She has been an ISPE member since 2009.

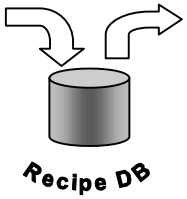
Intelligen Suite®

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

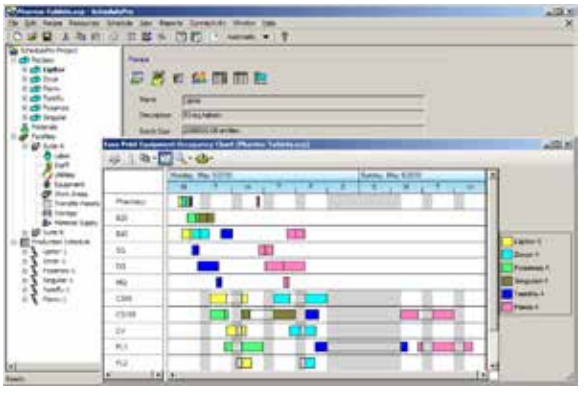
SuperPro®



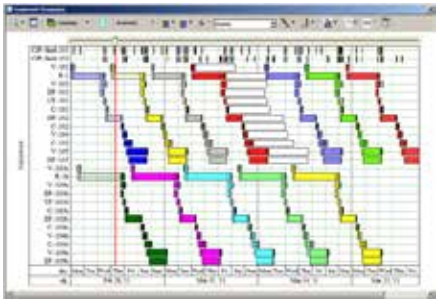
Use SuperPro Designer to model, evaluate, and optimize batch and continuous processes



SchedulePro®

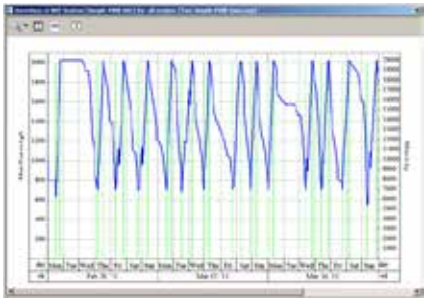


Migrate to SchedulePro to model, schedule, and debottleneck multi-product facilities



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

INTRODUCING INDUSTRY LEADERS

By Susan Sandler

With the start of the new year, *Pharmaceutical Engineering* is launching a new series of profiles of industry leaders. This ongoing series will look at the lives and careers of individuals who are changing the face of the pharmaceutical industry.

WHAT IS AN INDUSTRY LEADER?

An article published by McKinsey & Company a little over a year ago reported on survey research investigating what life science executives think is needed for successful leadership heading into the future [1]. The findings offer a good starting point for understanding what makes an exceptional leader serving the changing pharmaceutical industry. "Successful life-science organizations will look very different in the future than they do today," the authors noted. "They likely will be smaller; more specialized, automated, digital, and agile in their operations; more sophisticated in their commercial approaches; and more integrated with providers, partners, and consumers."

The McKinsey research identified five "distinctive muscles" that leaders will need:

- **An adaptive mindset:** Being able to deal with ambiguity and adaptive challenges where there are no already known solutions—such as developing new therapies—will be important. Exceptional problem-solving skills and risk tolerance are needed for future-oriented leadership.
- **3D savviness:** Data, design, and digital (the three Ds) and keeping up with change require leaders to build knowledge about advanced technologies such as artificial intelligence, the cloud and DevOps, and digital product management.
- **Partnership skills:** Leaders are expected to join forces with various partners, including patients, vendors, and health systems, and they need to look outside the pharma industry for inspiration and strong business development.
- **Agile ways of working:** Agility is key to survival in a changing world.
- **A balanced field of vision:** The ability to balance growth and efficiency was the final leadership trait identified by the research.

ISPE AND LEADERSHIP

The industry leaders profiled in this issue and those who will be profiled in upcoming issues of *Pharmaceutical Engineering* all display these leadership traits—even though their journeys to develop as leaders have varied greatly. Investment and participation in ISPE is a common theme in every profile: the industry leaders consistently acknowledge and appreciate the value of ISPE membership, noting that the learning, bonds formed with others, and friendships have helped them become the leaders they are today and for the future.

The industry leaders profiled in this issue, Ranjana Pathak and Christian Wölbeling, come from different regions and cultures, and have taken differing paths to leadership success. They share a commitment to the industry and to ISPE, and both are dedicated to continuing to make contributions for the good of the industry that serves patient health.

The science and technology that are the regular focus of *Pharmaceutical Engineering* content constitute part of the story of achievement and moving the industry ahead—the people in this industry and their commitment to excellence are the other side of the story. We hope you enjoy getting to know these leaders and their accomplishments in this issue and upcoming issues of PE.

Reference

1. Darino, L., A. Ogeah, and R. Srinivasan. "Developing Tomorrow's Leaders in Life Sciences." McKinsey & Company website. Published October 2018. https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/developing-tomorrows-leaders-in-life-sciences

About the author

Susan Sandler is the Senior Director, Editorial, for ISPE.

AN ADVOCATE FOR QUALITY

By Paul J. Cumbo, MS, MLitt

Ranjana B. Pathak, BSc (Hons), MBA, DHA, has spent nearly 40 years in the pharmaceutical industry. Currently the President and Global Head of Quality, Medical Affairs, and Pharmacovigilance at Cipla Ltd. in Mumbai, India, Pathak's long tenure has afforded her an informed perspective on the past, present, and future of the industry. An active member of the ISPE India Affiliate, she has served as a speaker or panel member at numerous meetings. Hers is a story of versatility, resilience, and perseverance—three tenets also essential to companies seeking to play a vital role in the continuing evolution of pharmaceutical manufacturing. Focusing on people, products, processes, and plans, Pathak shared her perspectives during a recent conversation with *Pharmaceutical Engineering*.

Ranjana B. Pathak

Pathak's career journey has been one of constant evolution and considerable movement around the globe. The worldwide scope of her career may have been inspired in part by her father's career as an airline pilot, which enabled her to travel frequently during her childhood in India. "My dad encouraged me to study computer programming, but I wanted to leave India. I felt I was somehow a generation ahead. Around age 20, I didn't have any specific ambition other than to have a different life. I wanted to live where I could get music and chocolates easily!" It was this enthusiastic desire for novelty and change that brought Pathak to the United States in 1980 on Thanksgiving Day.

Pathak enrolled at a small data programming school in New Jersey, where she studied the computer language COBOL for six months. Following Indian cultural tradition, she entered into an arranged marriage soon after.

Early in her career, she was "bored to tears," she noted. "My computer programming background wasn't working out. I had studied COBOL and RPG II, but companies wanted Fortran. So I needed a new plan. I wanted to be back in control of my life." Following a friend's suggestion, she shifted her focus to chemistry and began working for a small pharmaceutical firm in Long Island, New York, where she was the only woman.

Following the birth of her first child in 1984, Pathak felt increased financial pressure. Realizing the limitations of the local pharma industry and the high cost of living in Long Island, she resolved to learn more to provide herself with more options. "I studied the *U.S. Pharmacopeia*. It's a fascinating book. I would study the chapters at home, and I realized how much I didn't know." Pathak described the challenges of raising her children while building her knowledge of the pharmaceutical world, balancing the roles of mother and professional.

"I was cognizant that I had only an undergraduate degree in chemistry. It was an honors degree from a good college in India, but I really wanted a US degree. I was driving in Long Island when I

saw a sign on the back of a bus. It said, 'Why follow when you can lead?' It was an advertisement for an executive MBA program. I thought, 'I'm already in my late 30s. But hey—why not?' I applied, and it turned out my employer would pay for it. I was working full time as a lab director and attending an all-day MBA program from 7:00 a.m. to 5:00 p.m. on Saturdays."

Later, Pathak spent four years earning a doctorate in health administration in her late 40s—again while working full time in a demanding position. When she graduated, her two adult children, both of whom are board-certified physicians, were in attendance. In her mid-50s, she made yet another intercontinental move, returning to India to care for her father while embarking on the next leadership role in her pharma career.

AGILITY AS AN ART FORM

"I wanted to be a Bollywood actor when I was young," Pathak said, referring to the Hindi-language film industry based in Mumbai. She noted that her early training in Bharat Natyum, a form of dance that emerged out of millennia-old temple traditions, gave her confidence, poise, and patience—qualities that have helped her navigate her complex and varied career. "You can't dance if you don't have confidence and courage," Pathak commented. "You're taught how to face an audience."

Dance also taught Pathak intuition and perception, which she uses to understand the human elements of achieving quality in manufacturing. "I firmly believe that people are at the heart of any operation," she said. As a dancer, "you learn to be attentive and convey ideas with more than words. In dance, there are usually two parts: There is movement itself, but there is also a story. It works across cultures. It allows us to connect without words. You don't have to translate smiles or tears." Similarly, in industry, "Culture is the foundation for quality. It includes the mindset of the leader and the worker. The culture has to be such that everyone understands the meaning and principles of quality. Quality is hard to quantify, but it can be felt and experienced. It is often unwritten and unspoken. People are intelligent. They can hear, but they also can *sense* what leaders are and aren't saying."

PEOPLE AND PLANNING

In the pharma industry, Pathak believes that "the quality of a product is intertwined and interlaced among various disciplines—R&D (including clinical groups), regulatory affairs, technology transfer, routine manufacturing, quality assurance, quality control, and, finally, life-cycle management." Facilitating this interplay requires intentionality and planning, beginning with the acquisition and development of talent.

Pathak emphasized the importance of ensuring that the people hired in the industry have the mindset and training to execute their jobs. "Learning and training should be at the core. In today's 'war for talent,' it is difficult to hire and retain talented people. Hence, the onboarding process must be robust. This is where companies have to invest in employees," she noted. "It's not a one-time investment; rather, it has to be a continuum because these are the people that will make or break the company. The onboarding program should aim to equip people with an understanding of the 'why' behind doing things right, and the implications of not doing so. Too often, our bias is to emphasize only 'what' we do. But to ensure quality, people have to understand the 'why.'"

CLEAR PROCESSES AND PRODUCT OWNERSHIP

Having the right people is essential, but without clarity of processes and procedures, true quality is out of reach. Pathak offered some advice in this regard. "Procedures must be specific and clear. They must be written in language that people understand. It's best if these directives are written in collaboration with those expected to execute the tasks. Procedures also should be as simple as is feasible, with clear work instructions, job aids, visuals where possible, and flowcharts that illustrate process."

Quality also requires a sense of product ownership across all aspects of manufacturing and among the various departments. "The people touching the product are most important. Companies must invest in this cadre. While these jobs are routine, they are not mindless. Individual leaders cannot take their eyes off the process. There should be mechanisms in place to continuously judge the 'fitness for use' and course-correct based on results," Pathak emphasized. When stakes are high and numerous variables have to work in tandem, pharmaceutical companies require "trained staff, open communication, and a quality mindset among everyone." In other words, "People at every level of seniority, at every stage of the process, must share the same high sense of pride and ownership of the product. Leaders have to nurture this."

THE VALUE OF DIVERSE PERSPECTIVES

As a leading woman in the pharmaceutical industry, Pathak has both subjective and objective insights concerning gender dynamics in organizations. "It is not my bias that leads me to say that women bring a different point of view. Diversity is critical for problem-solving. By nature, there are innate and inherent differences between men and women, and these differences can enable better outcomes," she said. "Constructive dissent can lead to better conclusions. Often there is 'group-think,' and domineering men will take over the conversation and decision-making. This hurts companies because the perspective is not balanced. It is important that companies foster an environment where views coming from a minority voice (often that of women in the leadership ranks) are not looked down upon."

Pathak offered specific insights about the benefits of women's perspectives. "As a woman and a mother, I know that I am very tolerant and understanding of problems that occur. Women seem to have a 'sixth sense' that helps us understand the human elements at work in situations." She commented on how society at large, including government and educational systems, can work to eliminate barriers that prevent women from contributing to leadership in various industries. "Mentoring programs are key, and building them right means engaging female mentors as well as male mentors who are both sensitive to gender differences and

"People are the foundation. People innovated the products and processes. People made the plans. People have surmounted the challenges of the past, and our call to action is to work collectively on the quality journey. We need to keep quality at the forefront of both thought and action."

genuine believers in the benefits of female leadership. Once this is started, it can spread like wildfire. It's also vitally important to promote women based on their skills, so as not to cause reverse discrimination."

Ultimately, Pathak believes gender dynamics within organizations have to evolve to ensure genuine appreciation of what both women and men can offer. "Companies have to be able to harness the inner strength a woman brings. Passion and commitment are women's strong suits. Structured programs and academies can help them rise to the top."

THE FUTURE OF THE QUALITY JOURNEY

Asked what excites her most about the future of the pharma industry in the context of quality, Pathak focused on closing the gaps between regulatory bodies and industry players. "Those gaps are starting to shift in the right direction by becoming narrower. Part of the issue is that too often, the dialogue between regulators and industry is perceived as too daunting. I am all for punitive measures when there is clear evidence of wrongdoing, but I would like the quality journey to be such that the default line of thinking is not punitive. Rather, it's focused on mutual improvement of products and services."

Pathak explained that she is especially excited by recent innovations. "Novel technologies have emerged, whereby the previously unthinkable is happening—such as using our own bodies to heal, as is the case with chimeric antigen receptor T cells (CARTs). Innovation like this excites me and needs to be encouraged by academia and government; companies cannot bring these technologies to their full potential alone."

She went on to offer her thoughts about pharma's impact on society. "Making medicine should be one of the most gratifying industries. I feel grateful for being able to play a small role in it. Pharmaceuticals have done a lot of good—increased longevity, reduced infant mortality, eradicated diseases such as a smallpox, and improved quality of life for those suffering from chronic diseases such as diabetes."

Despite these advances and benefits, Pathak emphasized the importance of relentless efforts focusing on quality pharmaceutical manufacturing to face challenges old and new. "We are also seeing a resurgence of disease and the emergence of 'superbugs.' We need new therapies; otherwise, we could find ourselves back in the early 19th century, when a common cold could be fatal."

Pathak commented on the importance of ISPE and the resources it brings to bear in the industry. "ISPE is an industry knowledge hub—a place where expert knowledge is shared. I always look forward to reading the papers and reports based on the strong body of research conducted over the years." She urged Young Professionals to get involved in their local Chapter or Affiliate. "My strong recommendation for those serious about their profession in pharma is to join ISPE and participate actively in the meetings. This is particularly true for Young Professionals. It is a great place to learn, connect, and look for support for old and new topics."

As we wrapped up our conversation, Pathak returned to the themes of people, products, processes, and plans, encouraging others to make a commitment to these four prongs of pharmaceutical progress. "People are the foundation. People innovated the products and processes. People made the plans. People have surmounted the challenges of the past, and our call to action is to work collectively on the quality journey. We need to keep quality at the forefront of both thought and action—without that, nothing will survive for long. I encourage every one of us in the industry, regardless of our roles, to see our essential part in the quest for quality. We have to make that quest part of our professional DNA."

About the Author

Paul J. Cumbo, MS, MLitt, a veteran high school teacher and administrator, is a freelance writer, editor, and communications consultant serving a variety of industries. He has collaborated with some of the world's most well-known manufacturers, consulting firms, and global nonprofits, including the World Economic Forum, on projects ranging from internal documents to major white papers and other publications. His work for *Pharmaceutical Engineering* began with the July–August 2018 cover story on the Fourth Industrial Revolution featuring Enno de Boer of McKinsey & Company. Paul is a Principal and Co-Founder of the Camino Institute, which offers service-oriented travel and retreat experiences for families and organizations.

BRINGING PHARMA 4.0™ INTO THE WORLD

By Mike McGrath

ISPE® | PHARMA 4.0™

Every important cause needs its champion. Champions have a vision of how things should be, and a passion to reach their goals. They are committed and determined to achieve positive results, are willing to do the heavy lifting, and will take consistent and massive action until results are achieved.

Christian Wölbeling

The pharma industry certainly has its Pharma 4.0™ champion in Christian Wölbeling, a 56-year-old IT expert. Starting with ideas jotted down on a restaurant napkin, he has tirelessly and expertly led ISPE's global efforts to define the industry's slow but sure progression toward a holistic strategy to achieve the Pharma 4.0™ goal.

Born and raised in Hamburg, Germany, Wölbeling took a decidedly unconventional route to his pharmaceutical career. After finishing high school, he enrolled in a technical university where he focused on electronics but soon decided that the course of study was not the right path for him. Feeling that he wanted to "do something practical," Wölbeling decided to pursue vocational training as a ship's mechanic and spent two and a half years aboard a vessel. "It was quite inspiring because I learned a lot about technology, and, being confined to a small space for a very long time, I learned about dealing with all kinds of people. On board as crew, we are all one team when it comes to typhoons and hurricanes," he said.

Following his short career as a seafarer, Wölbeling studied mechanical engineering at the Hamburg University of Applied Sciences, where he completed his master's degree in 1990. He then started work as a Project Engineer at Blohm & Voss AG, a Hamburg-based shipbuilding and engineering company. After engineering highly efficient power stations that generate both heat and electricity for a year, he realized that he wanted to make a career change when he discovered software was entering the business fields.

One Saturday morning, he opened the newspaper—there were no job websites or LinkedIn in 1992—and came across an advertisement for Werum Software & Systems GmbH, as it was called at that time, based in Lüneburg, Germany. Wölbeling joined the Sales and Marketing team and has since seen Werum grow from an organization of only 65 employees to an international supplier of manufacturing execution systems (MES) software and IT

solutions for the pharma and biopharmaceutical industries. When *Pharmaceutical Engineering* spoke with Wölbeling, he had been at Werum for almost 28 years. He is currently Senior Director of Global Accounts.

PHARMA BEGINNINGS

"In the early days, we had some automation software, mainly supervisory control and data acquisition (SCADA) systems, process control, and monitoring and real-time software applications and databases," recalled Wölbeling. "At a certain point, we received a request for proposal from a pharmaceutical company in eastern Germany (this was shortly after Germany reunified). They were looking for an automation system along with recipe management and material control modules, and we sold them what was at that time known as our PAS-PLS (Process Automation System–Prozess Leit System) and completed the software package by adding weigh and dispense, recipe, warehouse, and quality management modules; that system was the predecessor to our PAS-X product, which today makes us the MES market leader for pharma and biotech."

That breakthrough sale was the first of three within Germany and was followed by the company's first international contract win with Krka, a large international generics manufacturer based in Slovenia. "This was my first experience in an international environment," said Wölbeling. "I learned a lot about dealing with multinationals with regard to software as well as contract negotiations." Krka still uses Werum software, he noted.

"Around 2000, we decided we needed to get more global. I had the opportunity to travel to the United States to help set up our first subsidiary there and to get the first orders in. This was my first time selling software in America, and we were fortunate to receive an order from Novartis, which needed an MES program for a new site in New York state. It became a lighthouse project for us, and it opened the door to all of the big American pharmaceutical companies."

BECOMING AN ISPE TRAILBLAZER

Wölbeling first became involved as a member of the ISPE Germany/Austria/Switzerland (D/A/CH) Affiliate in 1998, and a defining moment in his ISPE life came in 2004, when he attended his first ISPE Annual Meeting & Expo in the United States. It was there that he met well-known ISPE member David Selby, who knew that Wölbeling was working in IT and had previously founded an ISPE special interest group (SIG) for process analytical technologies (PAT) within the D/A/CH Affiliate. At that time, there was a new FDA guideline for PAT, and Selby asked Wölbeling to join the steering committee for the ISPE PAT Community of Practice (CoP), as a representative of the local ISPE PAT activities.

"Of course, I said yes. It was an honor for me; I was still a young guy," recalled Wölbeling. "From that moment on, I have been involved in PAT CoP steering committee meetings; later, I also became Co-Chair. Back then, we also had FDA representatives within the CoPs, and I got to know former FDA Officer Ali Afnan. It was a really good platform for me to develop my network around automation and process optimization."

> "I have educated myself through ISPE, and I have built a huge network, which has been tremendous for me."

Wölbeling noted that the 2004 FDA guideline on PAT was an early step toward Pharma 4.0™. "When you read through those guidelines, there is already some basic information about the FDA's expectations regarding data management and data integrity, which is still one of the hottest topics in pharma today."

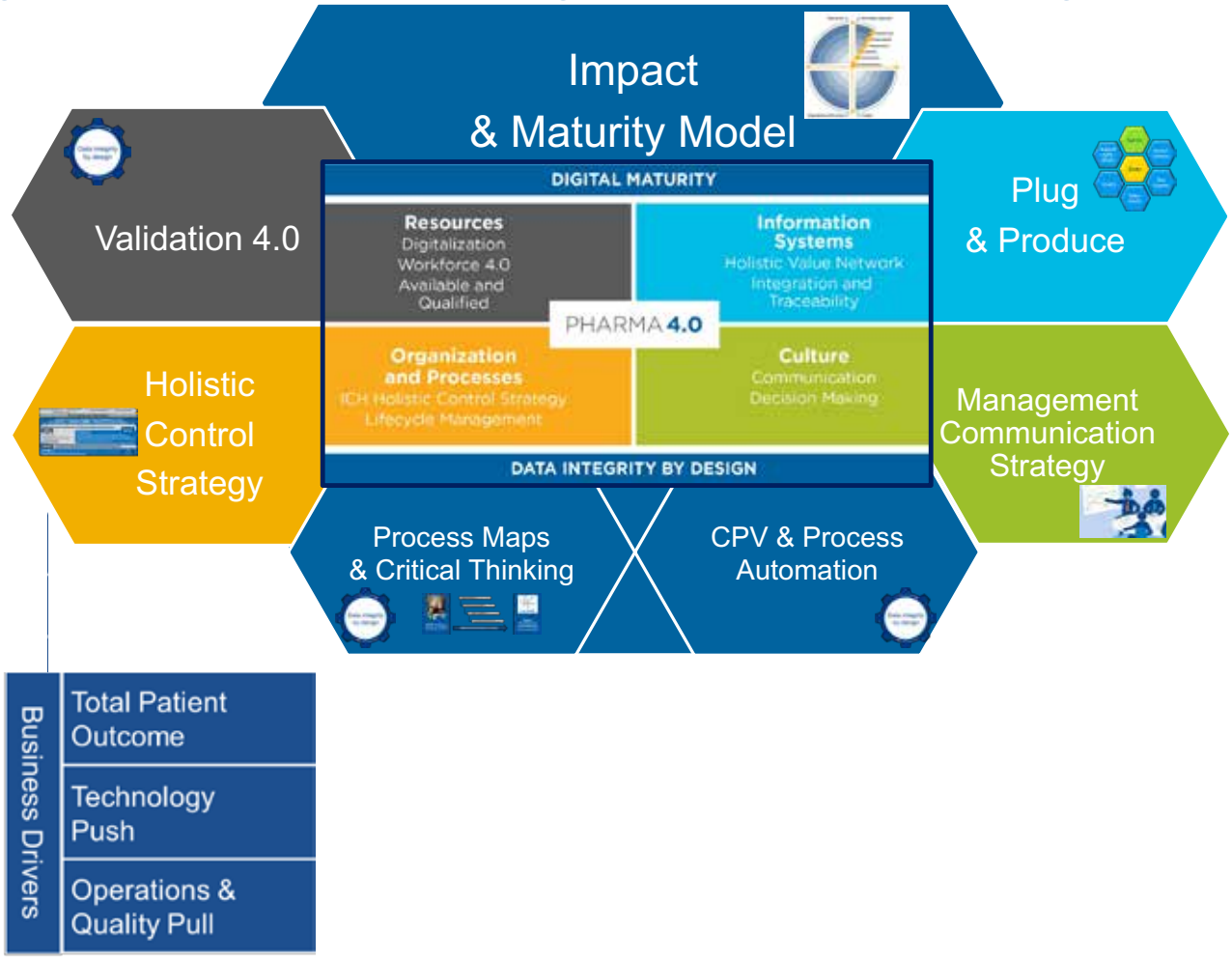
Leadership and continuous involvement in committees, both in Europe and globally, have been through lines of Wölbeling's ISPE membership. He started as a board member of the local D/A/CH affiliate, and over the years became global steering committee member and chair for several years of the PAT & Lifecycle Control Strategy CoP, Chair of the ISPE Knowledge Network Council, Co-Chair of the GAMP® MES SIG, GAMP® Europe steering committee member at large, and the Founder and Chair of the Pharma 4.0™ SIG. In addition, he is currently part of ISPE's European Leadership Team and the Young Professionals Advisor for the D/A/CH affiliate.

With credentials like these, it's clear that Wölbeling considers ISPE to be an important aspect of his professional life. "I have educated myself through ISPE, and I have built a huge network, which has been tremendous for me," he said. "I have known some people I met through ISPE for a very long time, and they have given me a lot of advice. There is always someone I can call to get the information I need. Even if they don't know, they'll know someone else who might. ISPE connections have been a big help for me, even in my daily life as I also have many personal friends in ISPE."

IT STARTED ON A NAPKIN

Great ideas often come to life in unusual ways, and the birth of Pharma 4.0™ was no exception. Sitting in a small restaurant in Basel, Switzerland, in 2015, Wölbeling and fellow ISPE D/A/CH Board Member Marcel Staudt were discussing fundamental problems of automation, integration, and validation in commercial manufacturing when they started to brainstorm. "It was such a creative moment, and we wrote our ideas on a napkin," Wölbeling recalled.

Figure 1: The ISPE Pharma 4.0™ operating model and its working groups.



The pair discussed the issues inherent in the pharmaceutical industry that set it apart from other industries with a strong manufacturing component, such as the automotive, aviation, and semiconductor sectors. Across industries and around the world, terms like "smart factory," "factory of the future," "the industrial internet of things," and "Industry 4.0" are buzzwords representing a shift in manufacturing concepts driven by digitalization.

Other industries have conquered the challenges of manufacturing high-quality products with a high degree of process automation and real-time quality control by broadly implementing PAT over many years. "So what is so different in pharma? Are the pharmaceutical regulations really hindering us from process automation and flexible manufacturing?" Wölbeling and Staudt identified one core element of the regulations as key to flexible automated manufacturing: the ICH-defined control strategy (i.e., ICH Q8–Q12).

"From the beginning, Staudt said that the control strategy is what we have to care about, because it defines the product and is executed later in recipes in the manufacturing space," said Wölbeling. Bridging the automation concepts found in Industry 4.0 with the pharma-specific ICH guidelines would become the root principles behind Pharma 4.0™ to manufacture high-quality products in a flexible and agile way.

As they wrote down their ideas, Wölbeling coined the phrase Pharma 4.0.

Since that initial dinner, Wölbeling has dedicated countless hours to promoting Pharma 4.0™, giving more than 50 presentations around the globe over the last two years alone, and helping found and run the ISPE Pharma 4.0™ SIG.

The SIG currently has about 80 active members in working groups, mainly in Europe. "We are getting more involvement and interest from around the globe, and we are currently discussing in

> "We need to get rid of paper, and we must understand and control the processes based on accurate real-time data. Then we need to break down the silos between product development, manufacturing, engineering, and IT."

ISPE how to organize this best in the interest of the global membership, as a next step," Wölbeling said.

"When new members join our group, we generally do an onboarding call to explain the root principles," he explained. "Then they can decide if they want to be part of one of our working groups, which is very valuable because it gives them the opportunity to work on a concrete task on a specific topic."

The SIG has currently six working groups, each corresponding to an element or enabler of the overall Pharma 4.0™ operating model (Figure 1): Holistic Control Strategy from R&D to Commercial Manufacturing; Impact & Maturity Model; Process (Data) Maps & Critical Thinking; Plug & Produce; Management Communication Strategy; and Continued Process Verification (CPV) & Process Automation.

A LENGTHY TRANSITION

Wölbeling recognizes that the road to industry-wide Pharma 4.0™ adoption will likely be a long one. "I would say it will take 10 to 15 years," he said. "I find it fascinating that while the pharma industry is doing very well financially, it is still far behind in automation. The R&D side is more advanced, but when it comes down to what we are producing for our patients, we are far behind. We

"If we break the silos between quality, operations, and engineering, and allow them to work together, we can make this data-driven holistic control strategy happen; also, we have to digitalize the Pharma Quality System as of ICH Q10. This is what the Pharma 4.0™ operating model is all about."

need to get rid of the paper, and we must understand and control the processes in a flexible and electronic way based on accurate real-time data. A prerequisite for the digitalization for me is to break down the silos between product development, manufacturing, engineering, and IT."

He also noted that the pharma industry treats quality differently than other industries do. "Quality is always the driver in other industries for efficiency and for delivering a good product. When I look at the car I am driving today, it is completely different from what I drove 10 years ago because the manufacturer has created a new specification for the car for me to buy. When you look at pharma, the product specifications are still the same, and change management for the manufacturing control strategy to improve quality is a lengthy and expensive process. Quality looks at the processes but not creating new processes that produce higher quality and apply new technologies such as PAT or digitalized processes to the manufacturing control strategy. I think this is a key problem. In consequence, Pharma 4.0™ projects have to be quality- and operations-driven reorganizational projects and not IT projects!"

So, what inspires Wölbeling's passion for getting industry to adopt Pharma 4.0™? "We have a simple message: There is a way we can do this better," he said. "Process understanding in the industry is still low, quality by design not very well adopted, and we still have a conservative view on quality. However, if we break the silos between quality, operations, and engineering, and allow them to work together, we can make this data-driven holistic control strategy happen; also, we have to digitalize the Pharma Quality System as of ICH Q10. This is what the Pharma 4.0™ operating model is all about. It is bringing the regulatory piece together with the operations and best-practice engineering pieces."

GLOBETROTTING AND OTHER ADVENTURES

Wölbeling's career at Werum and his involvement with ISPE have taken him around the globe. He calls himself a "world traveler" and says he and his wife have visited Japan, China, Chile, Canada, and all parts of the United States together. It was not always easy to combine his strong work commitment with his family priorities. Wölbeling has two sons, now in their thirties, and he did not always have enough time for his family. "I am learning to keep a better balance," he said.

In his spare time, he enjoys running and completed the Munich Marathon four years ago. "I'm not sure I would want to do it again, but it was a very nice experience," he said. In the winter, he enjoys skiing together with his sons, a sport he has been practicing since he was three years old.

Wölbeling and his wife live in Scharnebeck, a town just northeast of Lüneburg, where he works. They also own a home in Travemünde, which is near the Baltic Sea in the north of Germany. He loves sailing, and at least once a year, he and some friends rent a boat to sail around the Mediterranean or Baltic Sea.

LOOKING TO THE FUTURE

Wölbeling sees more promotion of Pharma 4.0™ on the horizon. "So far, we have brought this term to a global level and, together with ISPE, I hope that we can continue to spread it as a good idea," he said.

An important step in this direction for the Pharma 4.0™ SIG occurred at the 2019 ISPE Annual Meeting & Expo in Las Vegas, when MHRA representative David Churchward presented on the four MHRA focus topics for the future, including "Digital Health and Pharma 4.0."

Wölbeling also wants to continue motivating students and Young Professionals to become involved within ISPE. He pointed to the success of Hackathons, which he participated in from the beginning as networking events in Europe, and noted that the first US Hackathon took place at the 2019 Annual Meeting. "These are great opportunities for Young Professionals to get in contact with key people in the industry to work on their careers and to improve their skills. I hope to motivate students and Young Professionals to become engaged by volunteering their spare time to an organization like ISPE, because they will see that, in return, they will receive dividends."

About the author

Mike McGrath is a freelance writer and corporate communications consultant. For the past 15 years, he has helped organizations in the aerospace, transportation, telecommunications, and pharmaceutical industries develop their digital and print communications strategies. He has been a regular contributor to *Pharmaceutical Engineering* since 2015.

ELETTRACQUA

pure water technologies

SINCE 1966

PHARMACEUTICAL WATER SYSTEMS

MULTIPLE EFFECTS DISTILLATION UNIT 12M³H

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 TURNKEY PROJECTS ♦ VALIDATIONS IQ, OQ

www.elettracqua.com

IN SEARCH OF FLEXIBILITY:

The Biotech Industry's Continuing Quest for Optimized Manufacturing Facility Design

By Jeffery N. Odum, CPIP

Since the early 1990s, when the "upstart" biotech industry realized that its future success would be heavily influenced by the ability to manufacture multiple products within the same facility [1], the quest for flexible manufacturing assets has driven much of the advancement in facility design and execution. This article takes a historical look at the evolution of facility design, focusing specifically on how "flexibility" has advanced to the industry's current process and possible future states.

A BRIEF HISTORY OF BIOTECH FACILITY DESIGN

The first edition of the ISPE *Biomanufacturing Facility Baseline Guide* [2], published in 2004,included a graphic (Figure 1) that painted a well-defined picture of how facility design evolution had been influenced by a combination of regulatory guidance shifts, equipment technology advancement, and manufacturing operational approach changes. The main driver of this evolution was a developing, clearer understanding of the impact of closed-system design, as was defined in the Baseline Guide.

Figure 1 illustrates the significant impact that the shift from open-system operations to a more closed-system approach (where validated closed-system design in manufacturing equipment allowed for a loosening of area classification requirements) had on facility design and the ability to provide more flexibility in manufacturing options, especially for large-scale monoclonal antibody (mAb)–focused products.

As shown in cases 1–4 in Figure 1 from the ISPE *Biotech Manufacturing Facilities Baseline Guide* and in the case 2 example in Figure 2, moving from the "traditional" extensive open-system classified space to a more closed-system design implementation yielded operational and maintenance cost savings as well as schedule flexibility and improvement [2].

The Arrival of Single-Use Systems

In the mid-2000s, the impact of single-use technology and its advancement in equipment design launched a shift in how the biotech industry viewed facility design, which influenced the operational approach for many companies. As acceptance from global regulatory agencies for single-use system (SUS) implementation grew, companies shifted the design approach to incorporate both the closed system and SUS attributes into solutions that focused on footprint reduction, greater layout flexibility, and reduced operational costs (Figure 3) [3].

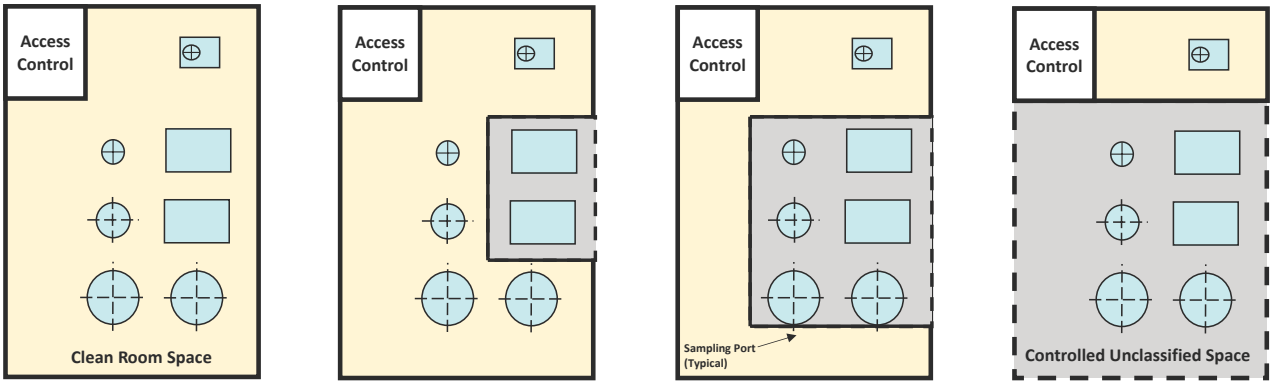
Closed Systems and Controlled Nonclassified Space

Addressing the industry need to better define operational characterization around closed systems, the BioPhorum Operations Group (BPOG) focused on addressing flexibility in biomanufacturing operations; the impact of closed systems served as a driver to implement an operational philosophy around controlled nonclassified space. Their 2011 publication was the first challenge to current industry thinking around the need for classified space to support biologic drug substance manufacturing, and it opened the door for new views on flexibility [4].

With BPOG's challenge to the facility design and operational paradigm came the next step in the design approach shift: the introduction of the open "ballroom." The early concept of a ballroom approach was driven around the principle that validated that closed, single-use, or hybrid systems could be operated within a single manufacturing space (Figure 4) and not increase product contamination risk [5]. Because physical segregation was the most expensive solution to protect the product, this approach received tremendous interest from both industry and regulators.

The publication of the BPOG ballroom approach [6] gave credibility to the idea of flexible manufacturing for biologic drug substance in a batch-driven approach. The first major manufacturing facility to implement the ballroom approach into biologics manufacturing elements and receive licensure from the FDA was the Amgen Singapore Biologics Manufacturing Facility. This facility (Figure 5) received significant attention in the industry due to its

Figure 1: Closed systems in controlled unclassified space. Reprinted from reference 2.



Case 1
- All processing equipment in a 'Clean Room.'
- Sampling of vessels performed in 'Classified' environment.
- All equipment subject to cleaning, maintenance, and changeover is within a "Gowned" environment.

Case 2
- Most processing equipment in a 'Clean Room.'
- Sampling of vessels performed in 'Classified' environment.
- Most equipment subject to cleaning, maintenance, and changeover is within a "Gowned" environment.
- Some "Closed" equipment in "Controlled Unclassified" Space.
- Clean room envelope is reduced, architectural finishes and life cycle cost of environmental maintenance reduced.

Case 3
- Some processing equipment in a 'Clean Room.'
- Sampling of vessels performed in 'Classified' environment.
- Most equipment subject to cleaning, maintenance, and changeover is outside the "Gowned" environment.
- Most "Closed" equipment in "Controlled Unclassified" Space.
- Clean room envelope is reduced, architectural finishes and life cycle cost of environmental maintenance reduced.

Case 4
- Minimum processing equipment in a 'Clean Room.'
- Closed sampling of vessels performed in 'Controlled Unclassified' environment.
- Most equipment subject to cleaning, maintenance, and changeover is outside the "Gowned" environment.
- All "Closed" equipment in "Controlled Unclassified" Space.
- Clean room envelope is greatly reduced, architectural finishes and life cycle cost of environmental maintenance greatly reduced.

Figure 2: Case 2 example (left) and case 3 example (right). Reprinted from reference 2.

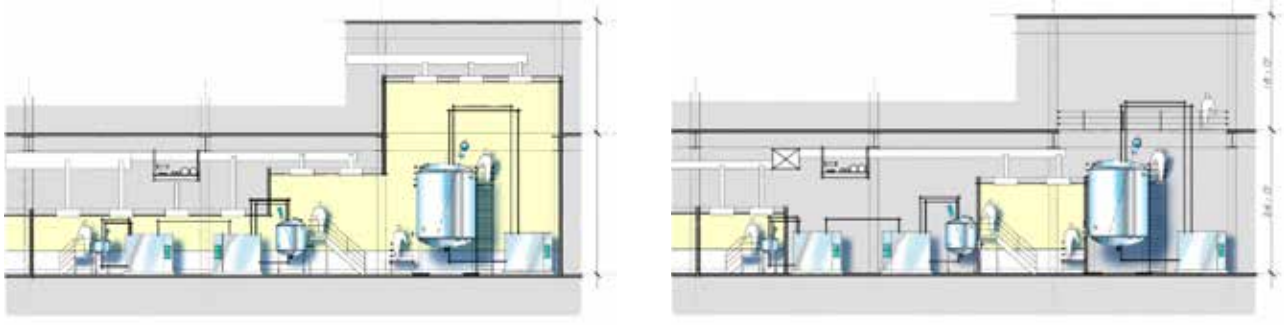


Figure 3: Reduced footprint: Stirred tank replaced by SUS. Reprinted from reference 3.

Figure 4: Ballroom schematic. Reprinted with permission from reference 5.

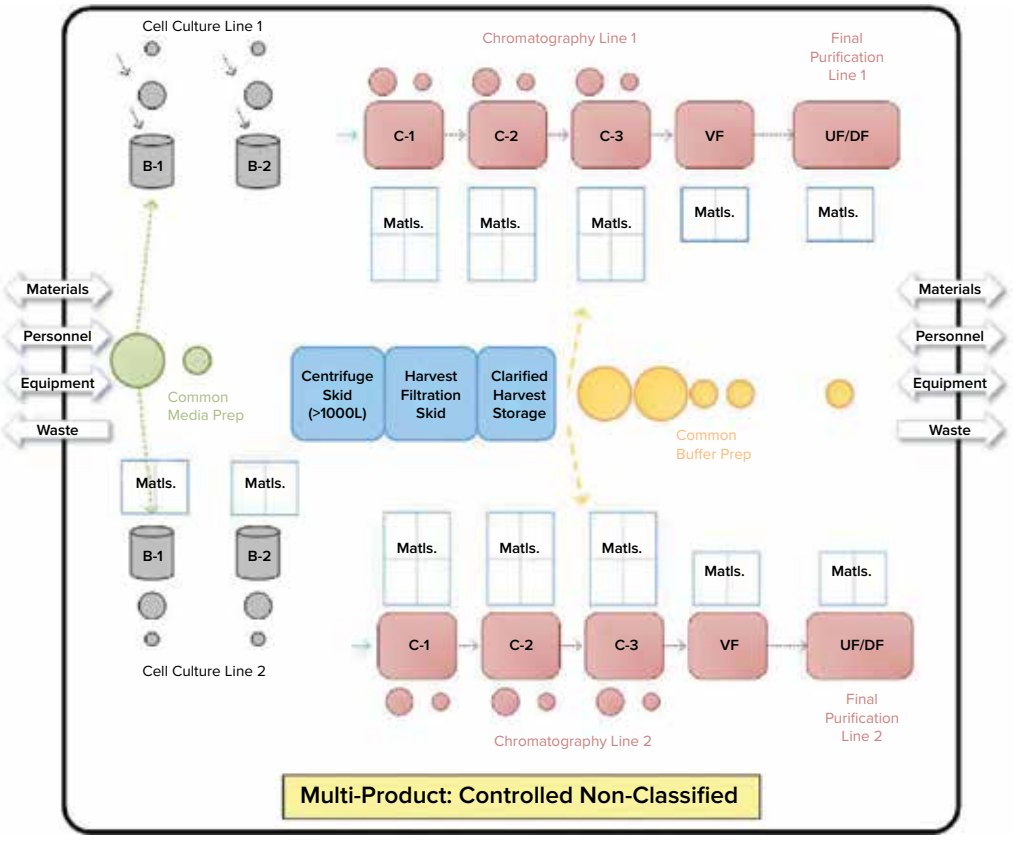


Figure 5: Diagram of Amgen Singapore Biologics Manufacturing Facility. Reprinted from reference 7.

MANUFACTURING AREAS

1. Weigh and Dispense
2. Solution Preparation
3. Logistics Corridor
4. Inoculum Preparation
5. Central Manufacturing Suite
6. Final Purification
7. Equipment Preparation

Facilities of the Future®

Conference and Training

Training **28–29 January** | Conference **30–31 January**
San Francisco, CA

Don't Miss the Industry's Leading Conference on Facilities of the Future®!

New and legacy pharmaceutical facilities must be efficient and cGMP compliant while adopting emerging technologies to improve drug quality. This conference will explore the impact of disruptive technologies and bring together diverse experts to share best practices and benchmark solutions for new and existing facilities.

Topic areas:

- Continuous Manufacturing
- Design and Operations of Cell & Gene Therapy and other Biotech Facilities
- Application of Single Use Technology
- Industry 4.0 / Pharma 4.0
- Innovative manufacturing concepts due to new supply chain requirements
- Artificial Intelligence (AI) in the design, manufacture or operation of Pharma Facilities
- Robotics and Digital Technologies
- Combination Product Manufacturing
- Emerging Technologies
- Industry Trends

Register Today at **ISPE.org/FOF20**

central manufacturing suite concept, where a large number of unit operations are executed in an "open" ballroom suite [7].

The key benefits of this type of approach include projected lower cost per gram of produced protein, increased flexibility for future site implementation, and capital cost savings of hundreds of millions of dollars due to 80% reduction in size [8].

CURRENT TRENDS

In the 2015 BioPlan Associates Top Trends in Biopharmaceutical Manufacturing [9], three of the listed trends were the implementation of SUS, flexible facilities driven by modularity, and continuous biomanufacturing. The following discussion explains how these three facility design drivers, as well as robotics, continue to shape biomanufacturing optimization efforts.

Single-Use Systems

As early as 2006, SUS implementation began to impact facility design and offer flexible solutions [10]. Today, SUS implementation, coupled with proof of closure, has become a key driver of process and facility design that drives flexible solutions [11]. The impact of SUS implementation and the advancement of its regulatory acceptance to support product protection and reduce patient risk have been the focus of numerous industry forums and conferences.

A key focus of the second edition of the ISPE *Biopharmaceutical Manufacturing Facilities Baseline Guide* [12] was to better define current design trends driven by flexibility. The revised Baseline Guide not only established the foundational relationship between facility attributes and system closure but also, for the first time, addressed the relationship between risk assessment, process closure, and layout approach.

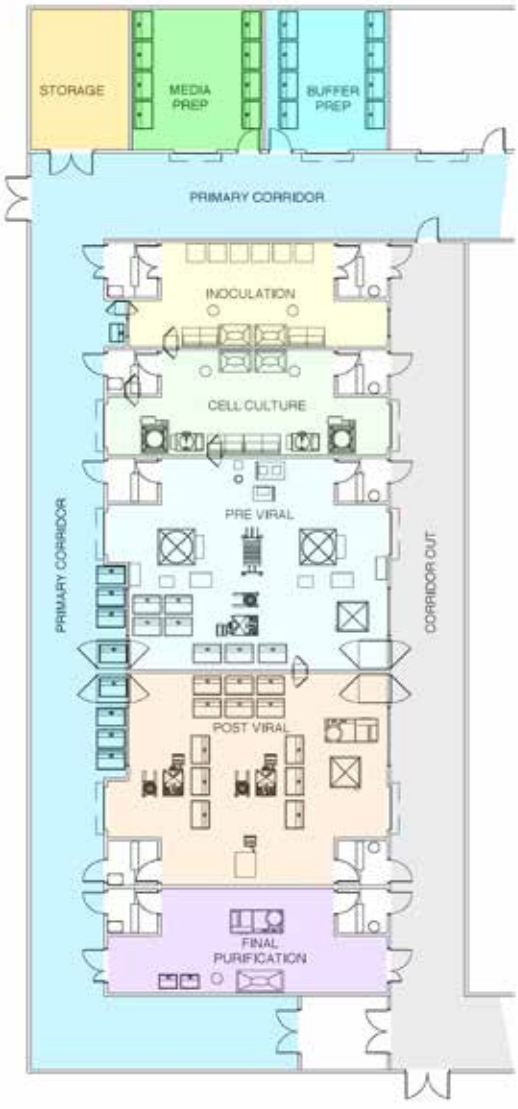
Modularity

Standardization, rapid deployment, and reduced schedule execution are all attributes of the current drivers to investigate modular delivery platforms for manufacturing assets. Over the years, modular approaches, or modules, have been defined from process skids (late 1990s), to prefabricated building segments (late 1990s), to "super-skids" of major equipment and piping components, to the current prefabricated modular cleanrooms. Today, much of the focus is on modular approaches that use forms of prefabricated panel systems or modules that allow for rapid deployment.

The combination of SUS and modularity is driving the next generation of flexible solutions that are primarily being offered for operations focused in the under-2,000-liter-scale operating range for a wide range of product types, including advanced therapeutic medicinal products (ATMPs).

In addition to the ballroom approach already presented, another facility design trend to promote optimized operations is a more segregated layout configuration (Figure 6) [13]. This segregated "matrix" of suites allows for tremendous flexibility between upstream and downstream operations, campaign and concurrent manufacturing, and the ability to conduct short (clinical) and long (launch) campaigns within the same facility [13]. This design approach accommodates both small- and larger-scale manufacturing operations with high levels of flexibility and reconfiguration capability. It also comes with a higher capital cost element due to the increased physical segregation of both environmental and architectural elements.

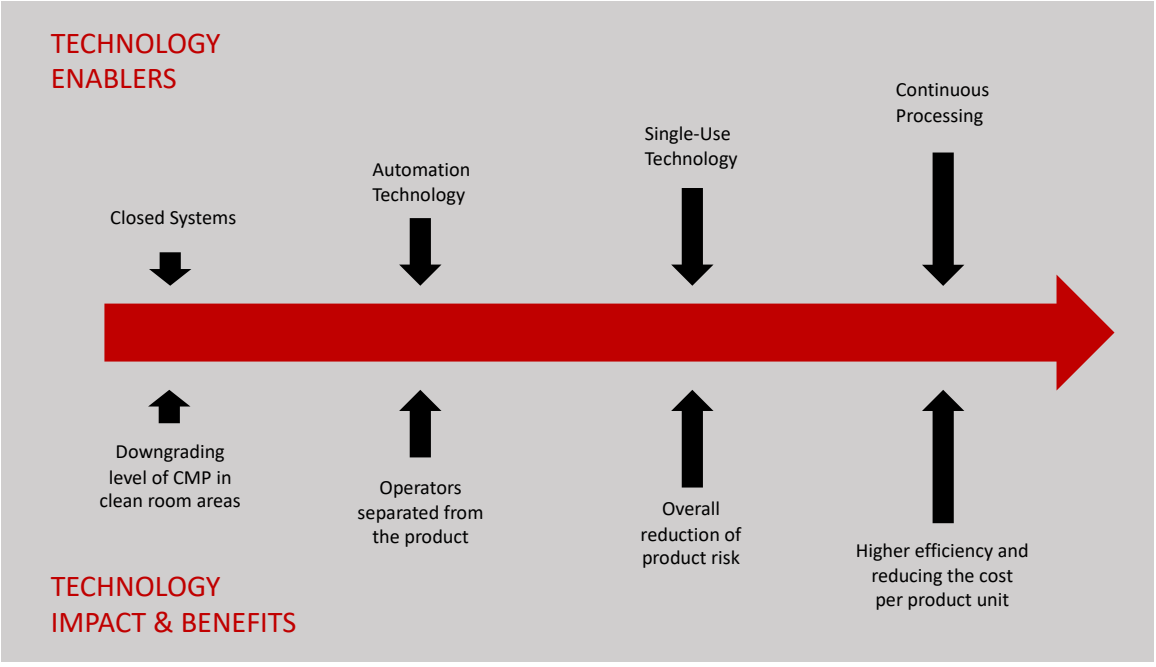
Figure 6: Matrix facility design. Reprinted from reference 13.



Continuous Manufacturing

Continuous manufacturing will increase focus on facility design flexibility. The ongoing movement to advance and incorporate continuous manufacturing into the biotech industry is supported by the FDA [14], which in turn is driving the industry to focus on how the advantages of continuous manufacturing should be defined in facility design attributes. Some of the keys requirements include:

Figure 7: Example of the impact and benefits of enabling technology.



- Smaller equipment and facilities, which would lead to lower capital and operational costs and the potential for modular units
- Increased flexibility in operations
- Integrated manufacturing, which would allow fewer processing steps and simplification in scale-up

These drivers all are in synergy with the pursuit of optimized manufacturing, again being supported by the FDA [15]. But challenges remain as continuous manufacturing technology in biomanufacturing develops. First, this technology is difficult to implement for some unit operations, and a "hybrid" process design could result. Second, there are regulatory concerns around risk—can closed systems be implemented 100%? And, finally, the long history and investment in batch-processing influences the overall design approach.

It is important to understand that implementation of continuous manufacturing is not a given, and it is not the right solution for every company. Because of this, the Parenteral Drug Association (PDA) developed a guided decision process to answer the question of whether to implement SUS, and that process has often been adapted for continuous platforms [16]. For organizations today, continuous manufacturing is not a one-size-fits-all solution.

Robotics

An estimated 80% of errors in pharmaceutical production are due to human error [17]. Risk reduction is a priority in process and facility design today. As higher-level automation solutions move into the use of robotics for drug product and drug substance manufacturing, the industry is taking robotic technology to the manufacturing floor as a major aspect of the Pharma 4.0™ movement.

Current applications include material handling and transfer such as buffer replenishment; compounding activities for toxic materials used in anticancer drugs; picking for kits (syringes, vials, needles, etc.), sampling, packaging, and labeling; and numerous applications in aseptic fill/finish processes.

The combination of these current trends now reflects the mission set forth in the first part of to this article. Enabling technologies (Figure 7) are driving the results and benefits that the industry needs and desires.

PERSONALIZED MEDICINE: THE FINAL FRONTIER?

The increased focus on ATMPs is shifting the flexible facility paradigm even more. As far back as 2011, the industry recognized that future facility design was going to need to move into new directions [18]. The current baseline model defining the majority of biomanufacturing operations for human therapeutics (proteins) is batch-driven. Because advanced therapies target either specific groups of patients or individual patients (personalized medicine), efficient commercial production will not be achieved with the large process volumes and higher titers of traditional biopharmaceutical manufacturing assets. This scale of manufacture and the

1:1 treatment-to-patient nature of autologous therapies mimic hospital lab or compounding pharmacy operations, but the need to produce these therapies for larger patient populations in a safe, pure, and effective manner will require GMP-regulated facilities.

One of the key challenges as ATMPs move along the continuum from development to commercialization is how to ensure these products will meet current GMP guidelines, regardless of whether they are being developed in an academic or commercial environment. All the design and regulatory attributes and trends that have been previously discussed come into play for these facility types [17].

Today, ATMP manufacturing facility design represents the blurring of traditional lines that the industry previously established. These facilities enhance the need for flexible solutions, enabling technologies, and out-of-the-box project delivery: the "perfect storm" of facility optimization. Small-scale, rapid timeline development and execution, and technology innovation will be the attributes driving optimized facility design.

FUTURE STATE

Moving into the next decade, key questions are: Does the enhanced focus on flexibility and optimization in biomanufacturing point to a new paradigm model? Will the future state eliminate our decades-old approach of facility design for many of the new biologic therapeutics?

Large-scale, stirred tank-based, mAb-focused manufacturing assets will be needed for the foreseeable future. They will likely remain a workhorse of the industry and continue to hold a significant place in the manufacturing landscape due to both investment and robust results. But how will the future state look for small-scale single-use platform (<2,000 liter) ATMP-focused manufacturing needs?

Two manufacturing operation models may provide a glimpse into the future state of biomanufacturing. The first is an adaptive approach to contract manufacture in a "one-stop-shop" solution, where equipment suppliers drive innovation and process development solutions targeted at specific client product-process-facility attributes of the enterprise.

Modular, SUS-focused process solutions will be designed around centralized manufacturing support and logistics needs, and will be leased, similar to current contract manufacturing organization–type business models. The flexibility aspect will include in-house supply of raw materials, media and buffer components, QC support, filling and packaging, warehousing, and distribution.

The second model scenario takes the form of modular, flexible GMP units that can be either individually or collectively used to support small-scale ATMP-focused operations. Because of an increasing interest in decentralizing manufacturing operations for smaller-scale operations, these units (which can be rapidly deployed and easily configured) will be developed around specific equipment platforms and can be located at hospitals, research facilities, or commercial-focused incubators. This approach will address concerns over meeting facility-driven GMP requirements and will rely on a GMP-focused operational approach for validated equipment, systems, and facilities.

CONCLUSION

The search for optimized biomanufacturing facility design led us far from where we started in the 1980s. Our future path looks very different as well. We seem to be moving toward smaller facilities with higher output capabilities. The need for lower capital cost requirements remains, along with an increased focus on reduced time-to-deploy delivery models with significant flexibility due to SUS technology. Smaller, faster, and less expensive are the new "normal" for many organizations.

The capital demands on manufacturing organizations continue to be an area of focus to reduce costs. Capital expenditures for manufacturing assets have a direct tie to the cost of goods and the overall financial health of an organization. Today, many companies face tough decisions due to aging facility assets, changing technology demands, increased pressure on speed to market, and the need for agility and flexibility. The traditional path of "build your own asset" is also being challenged with new approaches to manufacturing capability.

Equipment suppliers will continue to move further into the reference frame once solely occupied by design consultancy firms to deliver one-stop-shop facility solutions. This movement is being fueled in part through the numerous marketing authorization application activities in recent months involving organizations such as Thermo Fisher and Pall. The development-to-patient supply chain model may also no longer be just the landscape of traditional biologics manufacturers. Patient-specific commercial manufacturing models will come out of the shadows to occupy a greater piece of the manufacturing landscape. Global regulators define manufacturing control guidelines, and both academic and patient care institutions will become elements of the manufacturing supply chain.

We have come a long way in four decades, and only time will tell where we will be at the end of this decade. However, it is becoming clear that old ways of thinking around facility design and operation will be pushed to the limit.

References

1. Hill, D., and M. Beatrice. "Biotechnology Facility Requirements, Part 1, Facility and Systems Design." *BioPharm International* 2, no. 9 (1989): 20–6.
2. International Society for Pharmaceutical Engineering. *Baseline Guide: Biopharmaceutical Manufacturing Facilities,* 1st ed. North Bethesda, MD: ISPE, 2004.
3. Odum, J. "Looking for the Low-Hanging Fruit: Optimizing Biomanufacturing Operations." Presentation at ISPE Annual Meeting & Expo, November 2016.
4. Palberg, T., J. Johnson, S. Probst, P. Gil, J. Rogalewicz, M. Kennedy, K. Green, and S. Chalk. "Challenging the Cleanroom Paradigm for Biopharmaceutical Manufacturing of Bulk Drug Substances." *BioPharm International* 24, no. 8 (August 2011).
5. Chalk, S. "New Challenges to the Cleanroom Paradigm for Multi-Product Facilities." *BioPharm International* 26, no. 5 (May 2013).

6. Paulino, A. "Transforming Operations with Next Generation Biomanufacturing." Presentation at PDA/FDA Joint Regulatory Conference, September 2017.
7. Odum, J. "Questions Impacting the Future of Flexible Manufacturing of Biologics—The Future of Flexible Manufacturing." Tech Talk webinar. 15 August 2017.
8. Bader, B., M. Greening, and B. Forbes. "Amgen Singapore Next Generation Manufacturing." Presentation at ISPE Annual Meeting & Expo, San Diego, CA, October 2017.
9. BioPlan Associates. "Top 15 Trends in Biopharmaceutical Manufacturing." Contract Pharma website. September 2015. https://www.contractpharma.com/issues/2015-09-01/view_features/top-15-trends-in-biopharmaceutical-manufacturing-497317
10. Galliher, P. "Risk Assessment of Flexible Biomanufacturing Facilities—A Blank Slate Approach." Presentation at ISBioTech Conference, 2012.
11. Estapé, D., A. Walker, S. Orichowskyj, H. Vega, and D. Pratt. "Proof of Closure: Life Cycle of Closed Systems." *Pharmaceutical Engineering* 37, no. 5 (September–October 2017).
12. International Society for Pharmaceutical Engineering. *Baseline Guide Vol. 6: Biopharmaceutical Manufacturing Facilities,* 2nd ed. North Bethesda, MD: ISPE, 2013.
13. Odum, J. "Maximizing Efficiency: Minimizing Operational Interference in Multi-Product, Multi-Phase Biomanufacturing." Accessed 19 August 2019. Tech Talk. https://www.nne.com/techtalk/maximize-efficiency-minimize-interference-in-biomanufacturing
14. US Food and Drug Administration. "FDA Awards $2.5 Million Contract to ChromaTan to Develop Continuous Purification Platform." *FDA Voices.* September 2017.
15. O'Connor, T., S. Lee, X. Yang, and C. Cruz. "Modernizing Pharmaceutical Manufacturing: From Batch to Continuous." *Journal of Pharmaceutical Innovation* 10, no. 3 (March 2015). doi:10.1007/s12247-015-9215-8.
16. Amsler V., K. V. Anderson, M. Munk, and J. Odum. "Do's and Don'ts in Continuous Manufacturing Biotech Facility Design." Workshop at Commercializing Continuous Processing Summit, Boston, MA, January 2018.
17. European Commission. "EudraLex Volume 4: Good Manufacturing Practice (GMP) Guidelines. Part IV: GMP Requirements for Advanced Therapy Medicinal Products." November 2017. https://ec.europa.eu/health/documents/eudralex/vol-4_en
18. James, D. "Therapies of Tomorrow Require More Than Factories from the Past," BioProcess International. March 1, 2011. https://bioprocessintl.com/manufacturing/cell-therapies/therapies-of-tomorrow-require-more-than-factories-from-the-past-312317

About the author

Jeffery N. Odum, CPIP, is the Global Head of Design, Technology, and Standards, Global Biologics for Sanofi. He has over 25 years of experience in facilities design, construction, and commissioning in the biotechnology and pharmaceutical industries. Jeff has authored over 80 articles and four industry reference books on subjects related to project management, GMP compliance, process improvement, and design and construction of biopharmaceutical manufacturing facilities. Jeff served as the North American Education Advisor to ISPE, is Chair of the ISPE global Biotechnology Community of Practice, and is a contributing author to numerous industry baseline and reference guides focused on biotechnology manufacturing, process development, project management, and commissioning and qualification. He is a member of the PDA and ISPE technical training faculties, a Teaching Fellow in North Carolina State University's Biomanufacturing Training and Education Center graduate program, and a Guest Instructor for the North Carolina Community College System BioNetwork Program. Jeff has been an ISPE member since 1995.

APPLYING HOLISTIC CONTROL STRATEGY IN PHARMA 4.0™

By Hans Heesakkers, Christian Wölbeling, Thomas Zimmer, Nuha Al-Hafez, Lorenz Binggeli, Michelangelo Canzoneri, and Lothar Hartmann, PhD

Applying emerging technologies can lead to more robust and flexible manufacturing processes that in turn can help the pharmaceutical industry respond to drug shortages, reduce interruptions in production and delivery of medicines, ensure consistent clinical performance of products, and achieve other benefits. Although some may believe that regulators are averse to the use of emerging technologies in the pharma industry, the previous sentence summarizes the position expressed by representatives of the US FDA during the ISPE Europe Annual Conference in Dublin in April 2019. The ISPE Pharma 4.0™ Special Interest Group (SIG) has designed an operating model as a framework for how digitalization can be applied to ICH Q8–Q12 and named it the "holistic control strategy." This article introduces the strategy and presents two case studies of companies that have started to apply it.

The 20th century was the era of blockbuster pharmaceuticals. Given the nature of homogeneous production in large quantities for a long period of time, the pharmaceutical industry unsurprisingly adopted the principles of mass production. For more than a century, organization, culture, information systems, and resources were optimized to fulfill the rules of Pharma 2.0, which is dominated by a culture of hierarchy and experience-based decision-making and organized by functional silos. In Pharma 2.0, resources are focused on the performance of repetitive tasks, and information systems require many human interventions, prioritizing function over integration. Of course, new technologies were applied during the blockbuster era, but they aimed to fulfill a Pharma 2.0 business case and were not intended to be game changers.

Currently, the pharmaceutical industry is experiencing product differentiation (driven by rapid progress in the areas of biotech, genetics, and treatments for rare diseases) and market segmentation (driven by a larger, aging population and a global market with different regional opportunities and constraints). The industry needs a game changer: Pharma 4.0™.

The section on Pharma 4.0™ operating model elements later in this article offers insights into this desired state. Whereas the elements and enablers of Industry 4.0 might generally apply to all industries, Pharma 4.0™ is distinguished by the need of the pharmaceutical industry and its regulators to safeguard patient safety and health outcomes. This priority requires the alignment of quality control with Pharma 4.0™; additionally, the control strategy must be empowered with the same operating model and technologies used in development and operations. In other words, a *holistic* control strategy is needed.

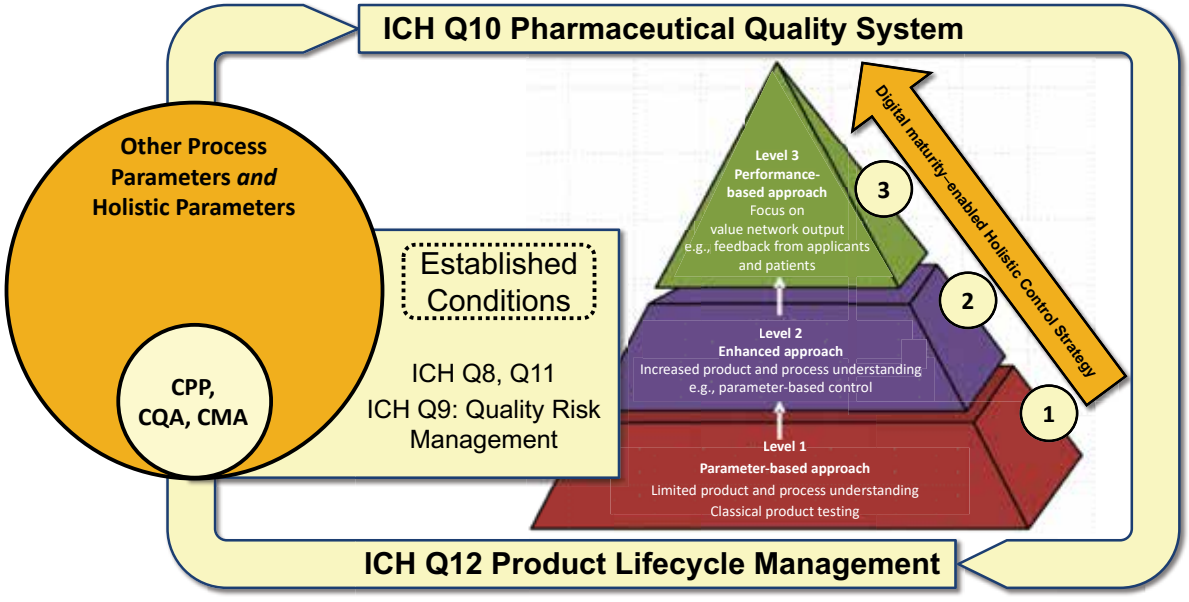
At the dawn of the transition from Pharma 2.0 to Pharma 4.0™, the following hurdles have become apparent:

- The industry is in a hybrid period in which blockbusters and niche products coexist.
- The prevailing Pharma 2.0 culture makes adopting changes difficult.
- The industry's many management layers resist restructuring and adoption of new styles.

Two prerequisites are needed to overcome these hurdles:

- A strong drive and commitment from senior management to fulfill management responsibilities as defined in the pharmaceutical quality system (PQS) in ICH Q10
- A coalition of innovators and regulators to design acceptable roadmaps for the implementation of Pharma 4.0™

Figure 1: The Pharma 4.0™–enabled and ICH-embedded holistic control strategy life cycle. Abbreviations: CMA, critical material attributes; CPP, critical process parameters; CQA, critical quality attributes.



DEFINING PHARMA 4.0™ HOLISTIC CONTROL STRATEGY

ICH Q10 defines "control strategy" as follows [1]:

> *A control strategy is a planned set of controls, derived from current product and process understanding, that assures process performance and product quality. … Every drug substance manufacturing process, whether developed through a traditional or an enhanced approach (or some combination thereof), has an associated control strategy.*

The ICH definition of the control strategy in ICH Q8, Q10, and Q11 [1–3] is the basis for the description of the product, such as the quality target product profile (QTPP). Control of product and process are the main focus.

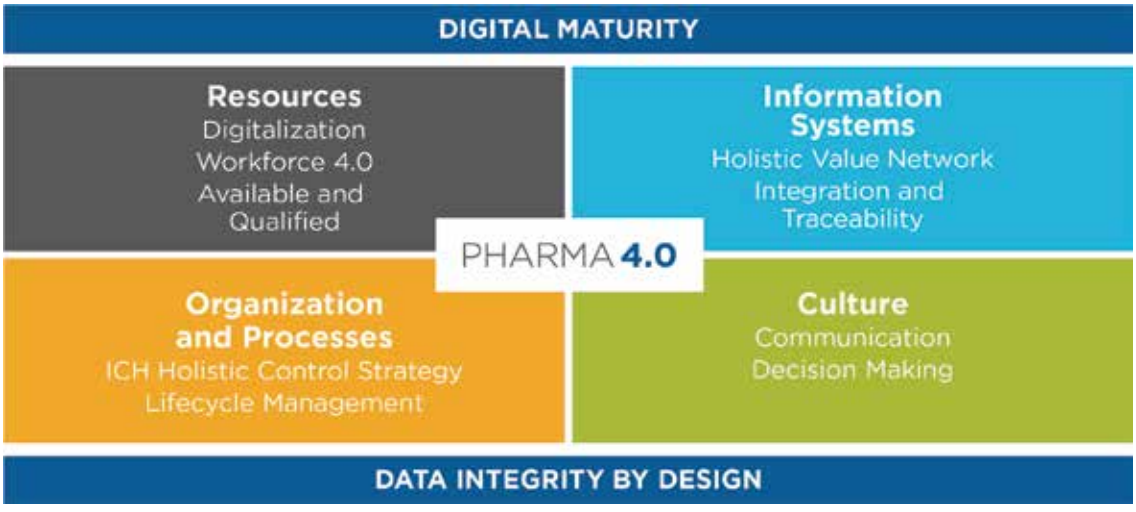
The Pharma 4.0™ term "holistic control strategy" is derived from this ICH definition. The term refers to an integrated approach to product and process life life-cycle management and ongoing change management (see Figure 1). This approach covers both the development chain and commercial manufacturing. Thus, the holistic control strategy targets all stakeholders, from the marketing and manufacturing authorization holders to the patient, including all supply chain parties. The holistic control strategy is enabled by digitalization as the necessary data are managed in real time, fully transparent, and available for sound real-time decision-making, improving quality and manufacturing process efficiency and accuracy. In sum, the holistic control strategy ties regulators, industry members, and patients together in an overall holistic value network structure driven by the Pharma 4.0™ operating model.

ICH guidelines Q8, Q10, Q11, and Q12 [1–4] describe the framework for continuous improvement and product maintenance and product stewardship as part of ongoing ICH Q9–based quality risk management [5]. This is an iterative approach applied throughout the entire life cycle of a product. The holistic approach includes parameters that are decoupled from process variability, going beyond the usual parameters considered during the development of a pharmaceutical product. Specifically, the holistic approach addresses all events that happen throughout the life cycle of the product, as well as the supply chain and patient needs and conditions.

In Figure 1, the authors have adapted the pyramid that the FDA [6–8] uses to illustrate the concept of pharmaceutical quality to show how the main enabler of the Pharma 4.0™ concept, "digital maturity," will scale across three levels:

- Level 1: Product testing–based control (e.g., classic quality control and in-process control testing)
- Level 2: Process-based control (e.g., process verification, automation, real-time release, parametric release, process analytical technology)

Figure 2: ISPE Pharma 4.0™ operating model.



- Level 3: Performance- and patient outcome–based control (e.g., drug availability, drug efficacy, no adverse effects, convenience in application, support for patient compliance)

The method for applying the holistic control strategy depends on the maturity level of a pharmaceutical manufacturer and the market environment; it should also reflect the manufacturer's desired level of aspiration.

PHARMA 4.0™ OPERATING MODEL COMPONENTS

In 2017, the *Pharmaceutical Engineering* article "A Holistic Approach to Production Control" [9] introduced a model that extends ICH Q10 by adding four new elements (resources, information systems, organizations and processes, and culture) and two new enablers (digital maturity and data integrity by design). Full understanding of the holistic control strategy requires knowledge of these six building blocks, which have become the backbone of the ISPE Pharma 4.0™ operating model (Figure 2).

Resources

Resources are defined as an organization's tangible resources, including its workforce (human resources); its machinery, equipment, and tools (physical resources); and the final product.

In Pharma 4.0™, resources are highly adaptive:

- Human resources are distinguished by cognitive flexibility, critical thinking, and creativity, and they require less control by governing bodies and formalized rules. Many recurring decisions are automated.
- Physical resources are designed to process very small series without extensive setup time. Examples of such resources are modular equipment, robotics, and three-dimensional printing.
- The human–machine interface is essential for adaptivity in a hybrid environment of human and physical resources. Virtual, augmented, and mixed reality will enable seamless collaboration during predicted and unpredicted events. A term often used for such a virtualized working environment is "digital twin" [10].

Information Systems

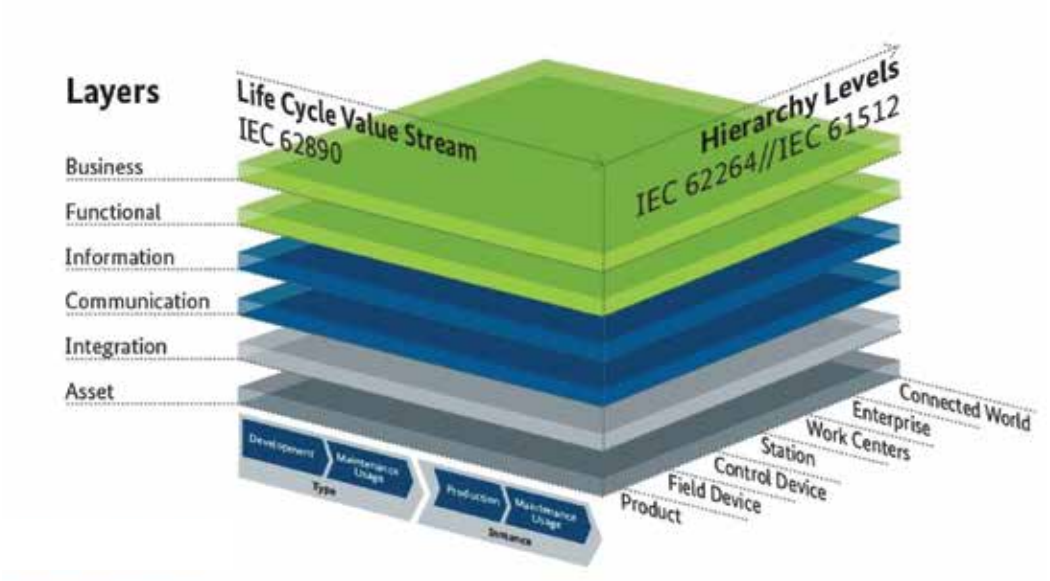
Information systems are socio-technical systems in which information is provided based on economic criteria by both people and information and communication technology. These systems prepare, process, store, and transfer data and information.

Information systems provide one-, two-, and three-dimensional (1D, 2D, and 3D) integration of data:

- 1D integration means the aggregation of information into the decision hierarchy
- 2D integration means the communication of information along the value chain
- 3D integration means the communication of information across the value network (new in Industry 4.0)

Information exchange between value chains that on their own drive toward different deliverables requires a move from a systems-based architecture to a service-oriented architecture. One example of 3D integration is the Reference Architecture Model Industry 4.0 (RAMI 4.0) architecture, which foresees a layered information

Figure 3: The RAMI 4.0 model (Reference Architecture Model Industry 4.0). Source: Graphics Plattform Industrie 4.0 and ZVEI [11]. Reprinted with permission.



structure in which data are the master and systems become services that allow continuous updating to adapt to new business requirements (Figure 3) [11].

Organization and Processes

Organizational structure refers to both a company's internal organization (structure and operational processes) and the company's position within the value network. It establishes mandatory rules that organize collaboration both within the company and externally.

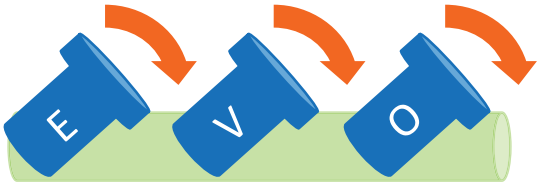
In Pharma 4.0™, empowered value-driven organizations work in Agile processes (Figure 4). Employees are empowered with information that allows them to make operational decisions without a decision hierarchy. Transparency in the value network leaves no doubt that these decisions position the objectives of the network over the interests of an individual silo. At the same time, Agile processes prioritize achieving an early outcome of the right quality and aim to avoid extensive documentation.

Culture

Culture covers the value system within the company and thus describes the "soft" factors of collaboration. Organizational structure and culture are interdependent areas and must be cohesive.

The driving force behind culture is social conformity. When newcomers join an organization, it is mind-boggling how quickly they start conforming to that organization's unwritten cultural expectations. Because cultural "rules" are informal, managers often feel that culture is not (completely) in their control. However, each industry-level transition has required cultural shifts; companies whose cultures do not change may likely fail to move forward.

Figure 4: Empowered value-driven organization (EVO).



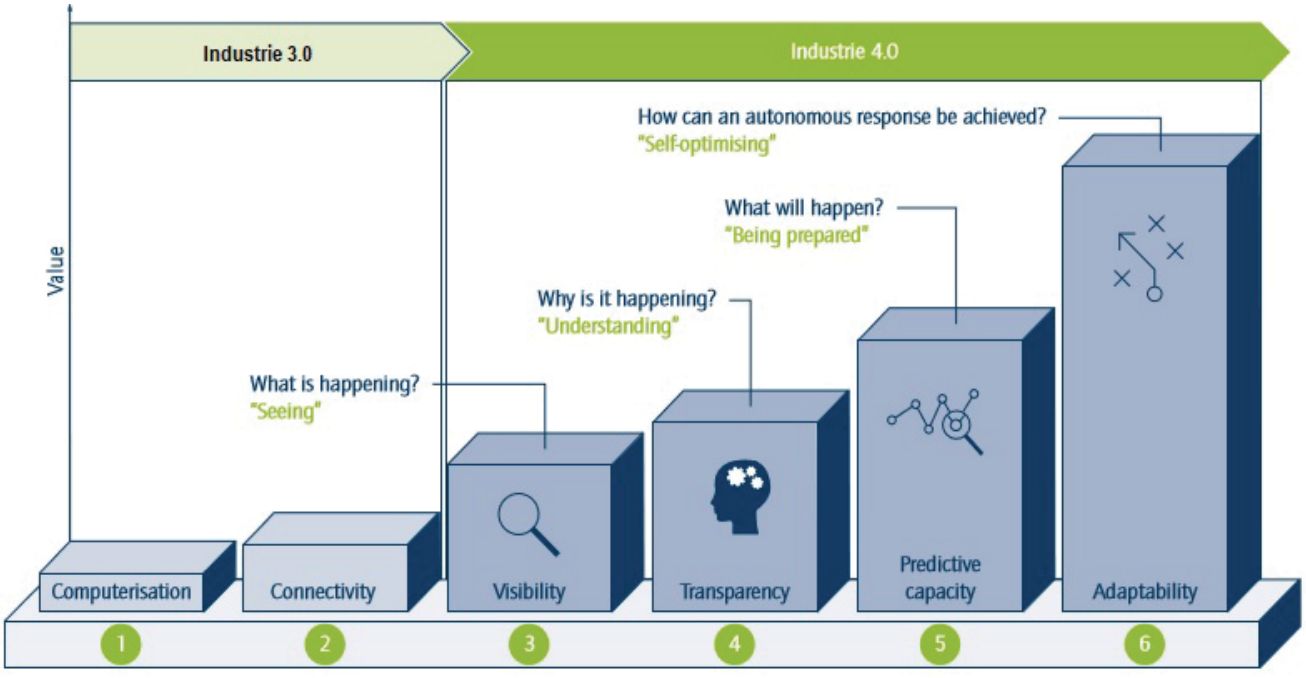
In Pharma 4.0™, people no longer work in a single departmental silo; instead, they interact with different virtual communities, each having their own unwritten cultural norms. Because information exchanges are faster and more accurate than in the past, individuals working close to operations are capable of making decisions without waiting for authorization from others with more seniority or a higher position in the organizational hierarchy.

Digital Maturity

Digital maturity is the stepwise evolution of a current operating model into a Pharma 4.0™ operating model. To move up the digital maturity scale, organizations use an approach that is stepwise in two ways:

- It defines their start and finish points in a maturity index.
- It chooses the process or subprocess that creates a tangible outcome.

Figure 5: Acatech digital maturity index. Reprinted with permission from Acatech [12].



Digital maturity steps can be defined in a maturity index. By leveraging the same index, organizations can learn from other organizations' experiences regarding challenges and outcomes. Within ISPE, the Pharma 4.0™ SIG adopted the Acatech maturity index to also leverage experiences from other industries [12, 13].

- Level 1 of this index is the journey from "paper-based" to database-based operations. "Paper-based" means that electronic files not hosted by database systems do not have the same integrity as "wet ink on paper-based" systems.
- Level 2 is the step from expert systems to integrated systems (i.e., systems integration or service-oriented architecture).
- Level 3 is the 2D integration that allows visibility of information along the value chain. Organizations can see in real time *what* is happening.
- Level 4 uses tools and experience to analyze trends in level 3. It creates transparency about *why* things are happening and unravels the true root causes.
- Level 5 renders level 4 into plannability. Digital systems can predict what will happen, which allows organizations to be prepared.
- In Level 6, automated response technologies adapt processes to reliably generate the right outcome without manual intervention and despite changing input and circumstances.

Figure 5 [12] illustrates the maturity of digital operations in Industry 3.0 and 4.0 operating models. Not every organization needs to move to these models. Moving up the scale can improve a company's performance, but the incentive to move up is largely driven by market forces. For example, an exclusive watch or car manufacturer might not even need to move to Industry 2.0. Similarly, pharmaceutical companies that produce blockbuster products might not have sufficient incentive to adapt the Pharma 4.0™ model. On the other hand, companies moving to niche products or advanced therapy medicinal products might find that Pharma 4.0™ is the only way to sustain their operations.

Data Integrity by Design

Data integrity by design is the information architecture and prospective control of data quality within predefined organizational boundaries.

In Pharma 4.0™, computerized systems are continuously updated and use enormous volumes of data to drive the organization's decision-making. Regulators have already recognized that the focus in the information world is changing from application integrity to data integrity. This shift in focus is enforced at this very moment. Presently, stakeholders are retrospectively verifying data integrity in the existing landscape. The next step will be to prospectively design a data and systems architecture in which data integrity is intrinsic and data reside in platforms of collaborative data, where agreed-upon rules apply.

In such a highly versatile environment, it is impossible to sustain the same validation procedures that were used in Pharma 2.0

and 3.0. New computer system validation procedures must be designed to enable rapid life cycles for computer applications using data in platforms of proven data integrity.

STAKES AND STAKEHOLDERS

Successful industry adoption of the holistic control strategy will involve many stakeholders, including regulators, senior management, standards-setting organizations, and patients.

Regulators

The holistic control strategy requires common understanding and alignment between industry and regulators. In general, to encourage investments in products and process transparency, regulators must shorten approval times for new drugs and for submission of changes and amendments. If the regulatory process is cumbersome, companies will be disinclined to invest in a holistic control strategy.

A holistic control strategy based on a completely digitalized value network has the potential to enable regulators to focus regulatory oversight and shorten product change management approval times. Therefore, the Pharma 4.0™ SIG recommends that industry offer training and education for regulators in the context of a holistic control strategy.

Senior Management

The application of a holistic control strategy offers to the management of a drug manufacturer a new balance between being transparent and being regulated. This can lead to faster approval times for submissions and help senior management fulfill their explicitly required "management responsibilities" as defined in the ICH Q10 PQS system.

Industry leaders and regulators should acknowledge that the proposed approach is not about camaraderie or companionship. Clear rule-setting can help maintain appropriate boundaries in the relationships between companies and regulators.

To ensure transparency, companies and management must get rid of functional silos and replace hierarchies with empowered cross-functional teams operating within value-driven organizations.

Standards-Setting Organizations

A holistic control strategy can only be effective if regulatory authorities agree to uphold common technical and regulatory standards. Trade wars, trade barriers, and unharmonized systems are the enemies of progress.

Standards-setting organizations such as PIC/S and ICH can develop frameworks for a holistic control strategy enabled by digitalized and integrated systems. Additionally, interagency initiatives by national health authorities such as the US FDA or European Medicines Agency, together with national competent authorities in the European community, could establish respected frameworks on a smaller scale.

Social media can play a major role in influencing key stakeholders to agree to develop common technical standards as business enablers.

A holistic control strategy promises to create more industry transparency and better oversight for patients and consumers as well as regulators.

Patients and Consumers

The roles of patients and consumers in disease prevention and management are rapidly expanding as individuals are using digital tools to connect with other stakeholders in the healthcare system. Notably, a holistic control strategy promises to create more industry transparency and better oversight for patients and consumers as well as regulators. Patients are already seeking transparency in product pricing. In the future, patients may also directly demand that companies share data about, for example, medication risks; the reliability of quality and production; quality, safety, and efficacy rankings; and benchmark comparisons of products and companies. Statistics in connection with field alerts and recalls will be public as well, and patients will be able to use end-user devices to verify the authenticity of medicines, and much more.

CASE STUDIES

Merck Healthcare KGaA: Augmented Reality

The biopharma industry is faced with increasing complexity in terms of new manufacturing technologies, portfolio delivery, health authority regulatory requirements, and cost pressure. Therefore, digitalization is a critical element for the future of the biopharma industry (and other industries). With that in mind, the healthcare business sector at Merck Healthcare KGaA, in Darmstadt, Germany, and Mollet del Vallès, Spain, has begun its digital journey to cover the entire value chain. In manufacturing, augmented reality initiatives were kicked off in 2019 across the whole network, including at the state-of-the-art pharma packaging center in Darmstadt, to address some of these challenges.

Augmented reality is a great add-on tool for complex processes to help employees manage the daily operations in a standardized mechanism. It is used in the pharmaceutical industry in digital operations where accurate and paperless processes are deployed. At the Merck facilities, it is being used in devices such as hands-free smart glasses and mounted tablets with heads-up display interfaces and voice or touch controls (Figures 6 and 7).

Figure 6: A worker at Merck Healthcare KGaA, Darmstadt, Germany, demonstrates use of hands-free smart glasses. Reprinted with permission from Merck.

Figure 7: A worker at Merck Healthcare KGaA, in Mollet del Vallès, Spain, uses a mounted tablet with a heads-up display interface and touch control. Reprinted with permission from Merck.

The purpose of using augmented reality within Merck's facilities and operations is to bring the right information to the right employee at the right time across multiple device types, and to foster proactive decision-making. Augmented reality will help overcome variability in operations. Variability is known to be reliability's first enemy, and by using augmented reality tools, Merck expects to improve reliability; specifically, the main augmented reality functionalities affect quality, safety, production, personnel, and data.

Implementing and deploying augmented reality to reduce variability accelerates the pace of operations at Merck Healthcare KGaA in Darmstadt. Augmented reality can be used in several applications such as changeovers, maintenance, line clearance, cleaning activities, and training. It will increase the quality of operations significantly, save time, ensure a reliable quality of the tasks, support on-time technical problem-solving, and increase productivity and efficiency to deliver positive results. Additionally, the data produced from the augmented reality applications can be used to continuously improve processes.

Overall, an augmented reality system in the manufacturing area is a digital driver for quality, efficiency, and standardization. Augmented reality enables employees to master increasingly complex machines and workflows.

Sanofi: Applying BITMAP

Recently, the challenge for organizations of managing knowledge efficiently and effectively has noticeably increased due to the volume of data, information, and knowledge as well as the pace at which data are produced. Also, organizations may learn at a slower speed than is potentially possible because tacit knowledge is difficult to capture and make accessible to everyone who needs it.

Recognizing that this situation influences how innovation is managed, Sanofi decided to experiment with new ways for people to connect and share and access knowledge. The goal is to leverage existing internal and external knowledge, connect experts internationally, and improve the creation of both incremental and breakthrough ideas related to manufacturing processes in research and development and industrial affairs.

In the age of Industry 4.0, digital technologies become increasing important for managing the amount of data and information produced in an organization, and for using advanced analytics (e.g., machine learning) to create knowledge that makes us smarter. For example, digitalization helps predict manufacturing processes, assess the impact of manufacturing process parameters on product quality and quantity, and, ultimately, provide a holistic view and understanding of how those parameters influence each other during the life cycle of a drug. Digitalization can also help with company-wide sharing of information as people use digitized workflows to perform daily activities and routines.

Biologics Innovation and Technology Management Process (BITMAP) is a concrete example of how Sanofi has used digital technologies to help in the field of knowledge management. BITMAP is composed of three elements: people, digitized business processes/workflows, and a smart IT platform.

Sanofi is a global organization. When a worker is interested in how the company is addressing a specific issue, that worker might have no idea who to contact. BITMAP connects people across the company to all topics that are internally addressed. A smart search engine and digitized workflows have thus helped Sanofi employees to be more efficient and effective in managing and exchanging knowledge and ultimately enable innovation for manufacturing technologies in biologics.

References

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. "ICH Q10 Pharmaceutical Quality System." Effective June 2008. https://www.ema.europa.eu/en/ich-q10-pharmaceutical-quality-system
2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. "ICH guideline Q8 (R2) on Pharmaceutical Development." August 2009. https://www.ema.europa.eu/en/ich-q8-r2-pharmaceutical-development
3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. "ICH Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)." May 2012. https://www.ema.europa.eu/en/ich-q11-development-manufacture-drug-substances-chemical-entities-biotechnologicalbiological
4. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. "ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management." 2018. https://www.ema.europa.eu/en/ich-q12-technical-regulatory-considerations-pharmaceutical-product-lifecycle-management
5. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. "ICH guideline Q9 on Quality Risk Management." November 2005. https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-3.pdf
6. US Food and Drug Administration. "Guidance for Industry. Process Validation: General Principles and Practices." January 2011. http://www.fda.gov/downloads/Drugs/Guidances/UCM070336.pdf
7. US Food and Drug Administration. "Guidance for Industry. Q8, Q9, and Q10: Questions and Answers (R4). ICH Revision 1." November 2011. https://www.fda.gov/downloads/Drugs/Guidances/UCM210822.pdf
8. US Food and Drug Administration. "Guidance for Industry. PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance." September 2004. https://www.fda.gov/downloads/drugs/guidances/ucm070305.pdf
9. Herwig, C., C. Wölbeling, and T. Zimmer. "A Holistic Approach to Production Control: From Industry 4.0 to Pharma 4.0." *Pharmaceutical Engineering* 37, no. 3 (May–June 2017): 44–49.
10. Whytock, A. "The Digital Twin: Creating Efficiencies in a Virtual World." *Pharmaceutical Engineering* 44, no. 4 (July–August 2019). https://ispe.org/pharmaceutical-engineering/july-august-2019/digital-twin-creating-efficiencies-virtual-world
11. Grangel-Gonzáles, I., L. Halilaj, G. Coskun, S. Auer, D. Collarana, and M. Hoffmeister. "Towards an Administrative Shell for Industry 4.0 Components." 2016. University of Bonn, Germany, Festo AG & Co. KG, Germany. https://arxiv.org/pdf/1601.01556.pdf
12. Schuh, G., R. Anderl, J. Gausemeier, M. ten Hompel, and W. Wahlster, eds. *Industrie 4.0 Maturity Index: Managing the Digital Transformation of Companies (Acatech Study).* Munich, Germany: Herbert Utz Verlag, 2017. https://www.acatech.de/wp-content/uploads/2018/03/acatech_STUDIE_Maturity_Index_eng_WEB-1.pdf
13. Heesakkers H., S. Schmitz, U. Kuchenbrod, C. Wölbeling, and T. Zimmer. "The ISPE PHARMA 4.0 Operating Model's Pharma-Specific Maturity Index." *Pharmaceutical Engineering* 39 no. 3 (May–June 2019): 40–45.

About the authors

Hans Heesakkers is Managing Director of Circuition Life Science Consultants and Co-Chair of the ISPE Pharma 4.0™ SIG. He has 30 years of experience in the life sciences industry, 20 years of experience in business process reengineering and IT projects, 15 years of experience in manufacturing and supply chain management, and 15 years of experience in the areas of clinical development and investigational products. He has been an ISPE member since 2004.

Christian Wölbeling is Senior Director, Global Accounts, at Werum IT Solutions based in Lüneburg, Germany, part of the Körber Medipak Systems Group. He holds a master's degree in mechanical engineering. With more than 25 years of experience working in life sciences manufacturing IT, Christian has had significant experience in all GMP-related processes. He has broad involvement with ISPE as Pharma 4.0™ SIG Founder and Chair, GAMP® MES SIG Co-Chair, ISPE GAMP® member at large of the European Steering Committee, Knowledge Network Council Co-Chair, PAT & Lifecycle Control Strategy CoP Steering Committee member, and D/A/CH Affiliate board member. He has been an ISPE member since 2001.

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 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.

Nuha Al-Hafez is the Head of Connected Health, Global Healthcare Operations, Connected Health and Devices, at Merck. She has worked in the biopharmaceutical industry for more than 25 years in operations and quality in innovation, generic, and CMO sectors. Nuha was previously with Teva Canada and Patheon and joined Merck in 2014. She has covered various functions in local and global roles in quality control, quality assurance, R&D, process development, technical project management, quality risk management, product quality management, and external supplier quality including CMOs and suppliers. Nuha has been an ISPE member since 2019.

Lorenz Binggeli has been working in quality management for computerized systems (CS) at B. Braun Medical AG, Switzerland since 2003. He was previously an IT/ SAP consultant for B. Braun and other companies. Binggeli has experience with numerous GxP projects for CS from enterprise to manufacturing levels. As of 2012, he worked for two years as a CS compliance subject matter expert for a manufacturing site at the B. Braun company headquarters at Melsungen, Germany. He is the owner of the Swiss quality system processes for the life cycle of CS, documentation, and data. The risk- based control of information flows is among the key elements in those processes. Lorenz has been an ISPE member since 2003.

Michelangelo Canzoneri joined Sanofi in 2008 as a Laboratory Head in R&D Upstream Process Development for Biologics. He moved to the role of Head of Technology and Innovation Therapeutic Proteins in the Biologics Platform, Industrial Affairs (IA), and then to the IA Manufacturing Excellence, Factory 4.0 team as Digital Operations Leader and a product owner for digital products. Within his current role, iCMC Digital Transformation Leader, he translates and executes the strategic vision for digitalization of the global CMC space covering the R&D/IA value chain from early stage to postlaunch product life-cycle management. Michelangelo graduated with a degree in chemical/bioprocess engineering and obtained a Dr. rer. nat. degree in biotechnology from the University of Bielefeld. He is a University Professor at the Frankfurt University of Applied Sciences and a Guest Lecturer at MIT. Since 2016, he has chaired the ISPE Special Interest Group on Biotechnology. He has been an ISPE member since 2016.

Lothar Hartmann, PhD, obtained his diploma and PhD in technical chemistry from the Technical University of Berlin. He joined Hoffmann-La Roche in 1988 and served in numerous functions in the global Quality Department. Lothar acted as Head of Pharmaceutical Quality Systems and External Relations and Knowledge Management. In 2011, he became Head of Quality at a large Johnson & Johnson site before he became an independent consultant with PhACT. Lothar has served in numerous organizations such as APIC/CEFIC (Vice Chair), European Biopharmaceutical Enterprises BioManufacturing Working Group (Chair), and PDA (Board of Directors, Quality Systems Interest Group Chair). Currently, he heads PDA's Global Interest Group on Quality Systems and is actively involved in ISPE's Pharma 4.0™ SIG. Lothar was part of the Expert Working Group of ICH Q7a. He has been an ISPE member since 2002.

A HOLISTIC CLEANROOM CONCEPT:

Higher Quality and Greater Flexibility

By Ute Schleyer

As the pharmaceutical industry balances demands for small-batch and blockbuster products and encounters new regulations, there is a need for efficient and safe production technologies that can meet stringent quality and safety requirements for the aseptic filling of drugs. Looking forward, manufacturers should anticipate future format, packaging, and filling needs, and seek technologies with sufficient built-in versatility. This article explores a promising holistic cleanroom concept for high-quality aseptic processing of drugs.

Aseptic fill-and-finish processing faces special challenges. On the one hand, demand is increasing for small-batch products to treat rare diseases; on the other hand, blockbuster drugs require large batch sizes. To meet divergent product requirements, pharmaceutical companies need flexible manufacturing systems that enable individual line setup for product changeovers.

Additionally, new and revised guidelines updating global regulatory requirements for process safety are expected in the near future. For example, Annex 1 of the EU GMP Guide "Manufacture of Sterile Medicinal Products"—which is considered the most important European regulatory standard for the manufacturing of sterile pharmaceutical products—is under review and being updated. In its current draft version, Annex 1 states that the expected result of microbiological findings within isolators and restricted access barrier systems (RABSs) is 0 CFU recovered, and "all critical surfaces that come into contact with sterile materials should be sterile" [1]. There is also a trend in visual inspection to increase requirements regarding detection of particles [2].

CONVENTIONAL TECHNOLOGIES

To date, two technologies for high-quality aseptic processing of drugs have stood out: isolators and RABSs. It is important to differentiate between these systems because they offer different types of product protection.

Isolators are completely sealed units, entirely "isolated" from the outside environment. They undergo extensive decontamination that results in constraint levels of adaptability and efficiency.

RABS technology involves barrier and dynamic airflow separation between the environment and the drug product. Compared with isolators, RABSs offer advantages of faster setup, efficient product changeover, and variability. As such, RABSs are appropriate for manufacturing operations with several products and short downtimes.

A NEW ALTERNATIVE

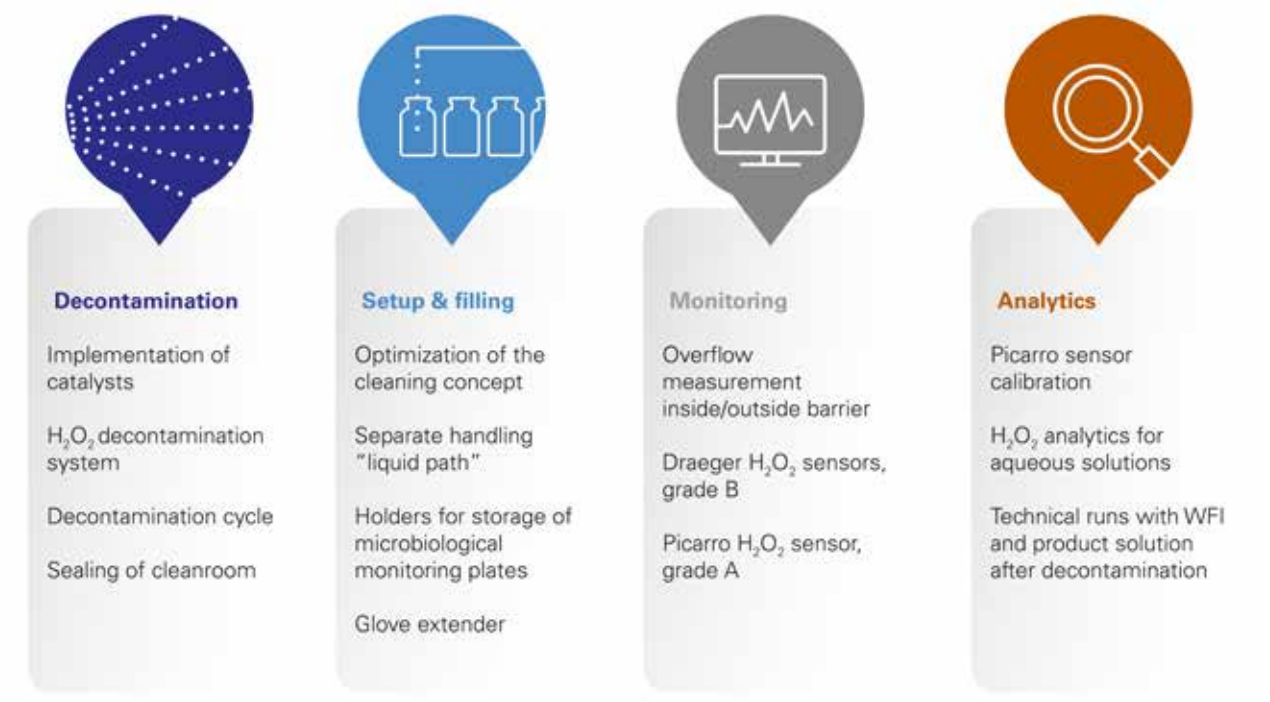
The starting point for the new technology described in this article was a passive open RABS with closed doors that provides a high level of aseptic control. Thus, the barrier surrounding a grade A clean area is open at the top and the bottom toward a grade B area and is supplied with laminar air from the ceiling of the cleanroom. The barrier can be opened for installation of huge format parts at the beginning of setup. During filling, interventions are only allowed through built-in gloves. Any opening during filling will result in immediate termination of the batch and the discarding of all open units within the barrier.

To improve the already high level of aseptic control, Vetter decided not to convert the existing RABS lines in isolator lines. Instead, the benefits of both conventional solutions were taken to create an alternative, Vetter Cleanroom Technology (V-CRT). Based on a passive open RABS, automated hydrogen peroxide (H_2O_2) decontamination, already well established within isolator technology, plays the most important role in this concept. Being a holistic concept, the technology is not limited to decontamination and its directly linked systems. It also includes setup and filling, and monitoring as well as analytics (Figure 1).

Decontamination

Decontamination is the core element of the holistic cleanroom concept. With automated H_2O_2 decontamination, unwieldy processes such as formaldehyde fumigation are replaced and sources of error in manual decontamination are minimized. Automated

Figure 1: In a holistic cleanroom concept, all working steps around aseptic filling such as decontamination, setup, filling, monitoring, and analytics are considered.



H_2O_2 decontamination also provides greater protection from microbiological contamination than wipe-and-spray disinfection. H_2O_2 is an effective decontaminant because it removes critical microorganisms in grade A areas. In addition, it is practically residue-free because the solution quickly breaks down into water and oxygen.

A system of stainless steel pipes built into the cleanroom walls and ceiling aerosolizes the H_2O_2 solution into class ISO 5 and 7 cleanrooms through dual-substance jets inside and outside of the barrier. To enable tightness during decontamination, the cleanroom is sealed gas-tight using inflatable door gaskets.

After the cleanroom is sealed, H_2O_2 decontamination can begin. Thanks to the permanently installed nozzles, decontamination of the entire cleanroom can work automatically and autonomously. For aerosolization of H_2O_2, the HVAC system is switched off and reactivated after the prescribed reaction time; laminar airflow flushes the entire cleanroom. Implemented catalysts enable rapid H_2O_2 degradation, and a HEPA filter prevents particles from entering the room.

After start of the entire decontamination cycle, the cleanroom area of 144 m^3 is ready for use in less than 2.5 hours.

Setup and Filling

Before the automated H_2O_2 decontamination can begin, the cleanroom is carefully prepared and machine surfaces are wiped clean. With the holistic cleanroom concept, manual cleaning prior to H_2O_2 decontamination can be optimized. Manual cleaning is reduced to a minimum, positively influencing downtimes and overall equipment effectiveness (OEE) times.

In the meantime, offline cleaning and steam sterilization of machine parts are performed (Figure 2). When isolator technology is used, gas-tight wrapped agar plates are brought into the barrier after cleaning of the filling suite. Therefore, when the holistic cleanroom concept is applied, storage holders in the barrier are implemented to avoid later transport from grade B to grade A. The concept also adopts Vetter's RABS process: First, barrier doors are closed. Next, equipment parts that are not product-touching and cannot be transported in a sterile box are installed within the barrier. Therefore, defined barrier doors are allowed to be opened. Gloves are then installed, and the remaining equipment parts are brought into the barrier using sterile boxes. Before any equipment parts are brought into the cleanroom, they are steam-sterilized in an autoclave. The preparation of the manufacturing line behind

Figure 2: Steps in a holistic cleanroom concept.

closed barriers in an aseptic environment further enhances the degree of purity achieved through the system. As a last part of the initial setup step, glove spreaders are installed. Then, the decontamination cycle can begin.

To prevent H_2O_2 uptake of the equipment in contact with the product (liquid path), as a final process step of installation, the second aseptic setup is performed after the decontamination cycle is completed (Figure 2). Installation starts after an H_2O_2 concentration of less than or equal to 0.5 parts per million (ppm) is reached.

Monitoring and Analytics

In addition to monitoring and analytics done as a part of the aseptic filling process, a holistic cleanroom concept requires specific methods to help make certain both products and employees are fully protected from H_2O_2. Thus, the sensors inside and outside the barrier track several variables. H_2O_2 decay is measured within the cleanroom in grade B areas by means of two Polytron sensors within the parts per million levels, and in grade A areas by means of a Picarro sensor down to the parts per billion levels. A flow meter continuously measures the airflow out of the barrier area into the ambient cleanroom air to allow for overflow from environment A to environment B. Product impact can be assessed by H_2O_2 analysis for aqueous solutions. H_2O_2 concentrations in water for injection (WFI) or other product solutions can be verified in the lab.

READY FOR TOMORROW'S CHALLENGES

The holistic cleanroom concept is associated with high reliability and reproducibility. Another significant advantage is speed. Depending on the size of the cleanroom, the entire decontamination cycle starting with conditioning of the cleanroom and followed by decontamination (aerosolization), exposure, and aeration can be completed in less than 2.5 hours. Appropriate catalysts and a highly effective ventilation system enhance H_2O_2 degradation and lead to short decontamination cycles. Preparation for production and aseptic setup of the cleanroom can begin immediately. Shorter downtimes streamline processes and improve OEE.

V-CRT optimizes existing production processes by making them more versatile and efficient. Furthermore, it mitigates the risk of microbe carryover from grade B to grade A areas, while still enabling rapid changeover. The contamination recovery rate for cleanrooms operated by V-CRT is notable. Since V-CRT was commissioned in early 2017, no germs have been detected in grade A environments, which fully meets the requirements in the current Annex 1 draft [1].

The holistic cleanroom concept can be used for new cleanrooms and machinery. The methodology can also be applied to traditional RABS cleanrooms to improve microbial decontamination and cleanroom control. Pharmaceutical and biotech companies can clearly benefit from such technologies.

References

1. European Commission. "Targeted Stakeholders Consultation on the Revision of Annex 1, on Manufacturing of Sterile Medicinal Products, of the EudraLex volume 4: Consultation Document." Accessed 22 October 2019. https://ec.europa.eu/health/sites/health/files/files/gmp/2017_12_pc_annex1_consultation_document.pdf
2. European Pharmacopoeia. "New Chapter on Visual Inspection for Visible Particles." Accessed 4 November 2019. https://www.gmp-compliance.org/gmp-news/european-pharmacopoeia-new-chapter-on-visual-inspection-for-visible-particles

About the author

Ute Schleyer studied biology, with a focus on microbiology, at Goethe University Frankfurt. After receiving her PhD with honors, she spent four years as a Lab Supervisor at the Institute of Biotechnology based in the research center Forschungszentrum Jülich, one of the largest interdisciplinary research institutions in Europe. In 2007, she joined Vetter as a Manager of Aseptic Production. In 2008, she was promoted to Production Manager for the manufacture and filling of sterile drug products, which included single-chamber and dual-chamber filling lines, and in 2016, she was appointed Project Manager in the Site & Plant Development department. In this position, she is responsible for supporting pharmaceutical engineering projects, including V-CRT. Ute has been an ISPE member since 2014.

WOMEN IN PHARMA® EXPANDS ITS GLOBAL REACH

Inaugural ISPE Women in Pharma® Event Held in India at the 2019 ISPE South Asia Pharmaceutical Manufacturing Conference

By Caroline Rocks

Since its inception at the ISPE 2016 Annual Meeting & Expo, Women in Pharma® (WIP) has been rapidly growing. In the US and Europe, the society has held numerous WIP events at local Affiliates, Chapters, and Annual Meetings & Expos, and it is now establishing a presence in Asia. On 27 September 2019, the inaugural Women in Pharma® event in Asia—a panel discussion on the "Influence of Culture Across Countries and Organizations in Achieving Gender Diversity"—was held as part of the 2019 ISPE South Asia Pharmaceutical Manufacturing Conference in Bangalore, India, with a full house of more than 200 participants.

The panel consisted of both women and men working for manufacturing companies, service providers, and regulatory agencies, representing different countries and career stages. This diversity of perspectives was evident in an insightful discussion.

The panelists were:

- David Churchward, GMP Inspector, UK MHRA
- Ranjana Pathak, President and Global Head of Quality, Medical Affairs and Pharmacovigilance, Cipla
- Richi Sethi, Bioprocess Systems Specialist, Merck Life Sciences
- Aditi Thakur, Acting Quality Assessment Lead, US FDA/CDER/OPQ/OPF
- Frank Verni, Compliance Officer, US FDA/CDER/OC/OMQ
- Frances (Fran) M. Zipp, President and CEO of Lachman Consultant Services, Inc., and Chair, ISPE International Board of Directors
- Moderator: Caroline Rocks, Senior Program Manager, AbbVie

SESSION PROCEEDINGS

Zipp opened the session by offering background information about the ISPE Women in Pharma® initiative and details on its various aspects, including Mentor Circles and travel grants. She issued a call to action to the audience to encourage their women colleagues to become part of this initiative.

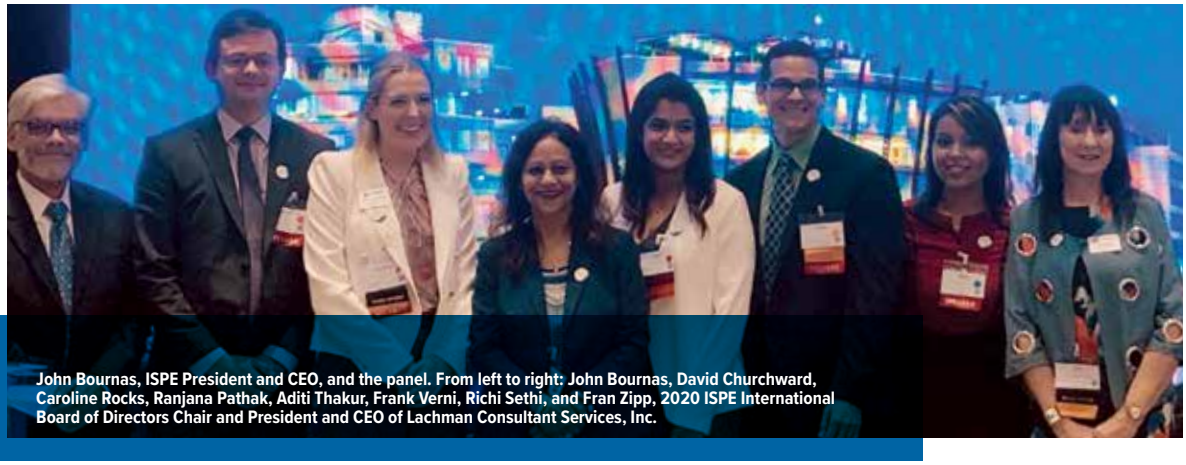
Pathak shared insights about working in the US and India as a woman leader, including distinctive aspects of her experiences in each country.

Thakur spoke about her own career journey from studying and living in India to moving to the US, and how some aspects were unplanned, such as moving from her initial career as a chemist in research and development to joining the FDA.

Sethi shared the challenges associated with unconscious bias that she experienced at the beginning of her engineering career and asked the audience to be more aware of this issue for women engineers who are just starting out.

Both Pathak and Zipp followed up, emphasizing that although the industry has made tremendous progress in achieving gender diversity since they started their careers 30 years ago, challenges persist. Women in the industry still need encouragement and empowerment.

Churchward shared his perspective on how diversity and culture can impact conduct in compliance or inspection. Teams of empowered and diverse individuals can facilitate critical thinking and reduce bias. This enables robust decision-making based on quantitative risk management to ensure product quality, while



John Bournas, ISPE President and CEO, and the panel. From left to right: John Bournas, David Churchward, Caroline Rocks, Ranjana Pathak, Aditi Thakur, Frank Verni, Richi Sethi, and Fran Zipp, 2020 ISPE International Board of Directors Chair and President and CEO of Lachman Consultant Services, Inc.

also contributing to an "enabling environment" for personal development. Churchward reflected that this approach is also applicable to inspection teams; specifically, the skills and perspectives used to assess compliance will differ as teams operate in different cultural environments.

Verni emphasized that when you limit the degree of diversity in a workplace, you lose an immense untapped pool of talent, skills, and experiences. A diverse workforce increases creativity and productivity. And, "it will reduce fear and grow a strong quality culture that will in turn benefit the company in a multitude of areas. As an added bonus, it will also boost the company's reputation among a variety of stakeholders."

Zipp shared her perspective on the unique challenges working parents encounter in a manufacturing environment, and how to overcome them. "These days, work demands more than a 9-to-5 commitment. Therefore, you need backup plans. Ask people for help—needing people does not make you needy! I raised my three children for the most part alone, and I was most grateful for the support of family, friends, and coworkers," she said. "Also, be realistic and make choices that you can live with—if you want a job that requires you to travel, accept that you will need help with household items and childcare. If you cannot accept that or afford that, find another role."

KEY FACTS ABOUT THE WIP EVENT IN INDIA

- 200+ attendees
- Regulatory and industry panelists
- Representatives of Europe, the US, and Asia
- Women and men attendees
- Early career, midcareer, and C-suite

ADVICE ON BALANCE

The panelists agreed that it was challenging to achieve the correct work-life balance. They shared some advice on how they use flexible working hours to balance work and family commitments.

"You have to be honest with yourself and recognize that you only have a finite amount of time and energy to split between your work life and personal life," said Verni. "You have to focus on what your goals are and ultimately what makes you happy. Whether it's becoming a director or spending more time with your family, embrace what makes you happy and pursue it."

"Work-life balance is about what you choose and what is important to you," Zipp stated. "No choice is perfect, and you are the only one who can judge your decisions."

When the audience was invited to ask questions and share comments, Deva Puranan, Head of Global Quality Investigations for Mylan, raised the important point that a successful career requires support and encouragement not only from your organization but also, and even more so, from friends and family. He attributed his own career success to the strong support he receives from his wife and family.

BECOME INVOLVED IN WIP

Go to https://ispe.org/women-pharma for more information, including a toolkit to organize your own Affiliate/Chapter WIP event and WIP iSpeak blog posts. If you would like to get in touch directly with the WIP Committee, email wip@ispe.org or join our online community.

About the author

Caroline Rocks is Senior Program Manager, Operations, AbbVie, and serves on the 2019–2020 ISPE International Board of Directors.

ISPE BRIEFS

ISPE Special Interest Group Formed for Cloud Services

A new ISPE Special Interest Group (SIG) has been formed under GAMP® to address the increasing use of cloud services. A conversation with Michael Osburn, Head of Quality at Cornerstone OnDemand, and Judy Samardelis, IT Quality Director at Thermo Fisher Scientific, who are leading the new SIG, provides some details.

Why has this SIG been formed?

The industry is increasingly relying on cloud services to reduce IT footprints with on-premise data centers, while increasing storage capability requirements as manufacturing and R&D create vast amounts of data that cannot be stored on premise. The SIG was formed to create tools and guidance for use throughout the industry.

What are the key drivers/objectives of the SIG?

We are aligning GAMP® principles with industry best practices, providing case studies and guidance.

What regions are represented by SIG members?

The group includes life sciences companies, consulting organizations, and industry suppliers, including Microsoft and Amazon Web Services, with regulators across the world participating.

What are the hot topics being addressed?

One hot topic involves defining supplier quality agreements aligned with the recent GxP working group paper, "Application of SOC 2+ Process to Assessment of GxP Suppliers of Services," published in *Pharmaceutical Engineering* (July–August 2019).

Another priority is to review the technical controls of the ISPE *GAMP® Good Practice Guide IT Infrastructure Control and Compliance*, 2nd edition, and align with industry best practices.

What are the main challenges with these topics?

The primary challenges are changing the current industry quality assessment practices and processes on how cloud services should be evaluated and maintained throughout their life cycles.

What is the expected output of the SIG, and what is the time frame?

Expected outputs include providing a case study on the evaluation of a SaaS provider and providing a quality agreement template for publication in *Pharmaceutical Engineering* for industry use.

—Anthony Margetts

Wider Distribution Opportunity for Some PE Articles

Pharmaceutical Engineering is piloting an open-access program to allow greater access to some of the great content published in the magazine. Several articles from each issue will be available for viewing by any visitors to the PE Online site. Most of the magazine will remain "locked" as an exclusive ISPE member benefit.

Opening access to some PE content offers authors the opportunity to indicate interest in having a wider distribution for their articles. Selections for open access are made by the Senior Director, Editorial, in consultation with the *Pharmaceutical Engineering* Committee as needed.

Please indicate in your submission if you would like us to consider your article for open access. While we cannot promise that every open access status request will be approved, we will consider author requests.

If you have questions about open access, please contact Susan Sandler, Senior Director, Editorial, at ssandler@ispe.org

We'd like to feature your Chapter, Affiliate, CoP, or other ISPE group in upcoming ISPE Briefs.

Share highlights from training programs, conferences, social events, or other activities in an article of 250 to 400 words. We welcome photos (300 dpi or >1 MB). Send submissions to Susan Sandler, Senior Director, Editorial, at ssandler@ispe.org

ISPE®

Aseptic Conference and Training

Evolution in Aseptic Processing: Flexible and Reliable Solutions

CONFERENCE **2–3 March 2020**
TRAINING **4–5 March 2020**

Bethesda North Marriott Hotel
and Conference Center
North Bethesda, MD

Featured Keynote Speaker

David Doleski
Compliance Head for Biologics Quality Operations, Sanofi and former Deputy Director (Acting), Office of Process and Facilities, FDA

Training Courses*

4-5 March 2020
Cleaning Validation Principles
Pharma Water Generation
Process Validation, Biotech Manufacturing
Aseptic Processing & Annex 1

**Separate registration is required.*

Register at ISPE.org/Aseptic20

Topics to be discussed
Advanced Therapy Medicinal Products (ATMPs) • Alternate Transfer Technologies • Aseptic Processing Science & Technology • Cell Therapy Scale-Out Planning • Containment Technologies for Cytotoxics • Legacy RABS - Based Facilities • Facility Design & Expansion Case Studies • Formulation-Filling for Viral Vectors • High-Speed Syringe Filling Expansion • Robotic Applications in Aseptic Processing • Small-Scale/ Clinical Manufacturing • Standardization of Extractables Testing • Sterile Connectors & Materials Transfer

A Systems-Based Approach to DIGITAL DESIGN AND OPERATION

By Robert H. Peeling, CEng, FIChemE, Charles M. Gordon, PhD, Martin R. Edwards, PhD, John A. Henderson, CChem, PhD, and Sean K. Bermingham, PhD

The Advanced Digital Design of Pharmaceutical Therapeutics (ADDoPT) project [1] is a recently completed UK-based design manufacture and supply chain research collaboration. This collaboration catalyzed work to define a system for top-down, knowledge-driven design and operation for drug products and their manufacturing processes.

Through a dedicated technical facilitation process, ADDoPT consortium members identified a need for, and developed, information flow for digital design and manufacture of pharmaceuticals, which can help the pharmaceutical industry adopt new technology and build the necessary innovation and leadership capacity to realize the potential of Industry 4.0 and similar initiatives around the world.

INDUSTRY 4.0 AND DIGITALIZATION

The worldwide transformation of manufacturing through the increasing use of digitalization has been christened "the Fourth Industrial Revolution" or "Industry 4.0" [2, 3]. Properly harnessed, digitalization has the potential to transform the future of manufacturing in all sectors, although progress varies widely across industry sectors and countries. The influential UK government–sponsored 2017 "Made Smarter Review" [4] highlighted that UK industry in general is not taking advantage of a rapidly growing capability in industrial digitalization technology; therefore, the review's authors recommended technology adoption and supporting the innovation and leadership necessary for the country to realize Industry 4.0's potential.

Attitudes and digital readiness vary considerably across industrial sectors [5, 6]. For example, in the oil and gas industry, process technologies and manufacturing processes are well developed [7], and modeling for optimization and control systems is an established practice to minimize production variations based on technology licensor, engineering, and operational constraints. In contrast, the operating context in pharmaceutical product manufacturing is very different. Absolute production volumes are relatively small, unit product costs and values are high (reflecting upfront development or acquisition cost, scale-up risks, and other factors), and products are typically produced in relatively short-run production campaigns with frequent product changeovers. Additionally, because the pharmaceutical industry has a large asset base for batch manufacturing that will persist for several decades, it's important to maximize batch process value and quality and to build robustness into emerging flexible manufacturing solutions.

In the oil and gas industry, the impact of feedstocks on process and product quality is established and understood, and integrated digital approaches exist for plant design and operation. Conversely, because end-to-end pharmaceutical product manufacturing is complex, such links may not be readily established, and quality-critical links can differ between products. Unlike products in the oil and gas industry, each new pharmaceutical product is, in effect, a novel design and requires process optimization on production scale; also, although individual steps may be modeled, integrated digital approaches are not commonly available. With process-scale experimentation at an absolute premium, pharmaceutical manufacturers need to derive the necessary process insight, predictive models, and capacity to ensure quality in new ways.

In fact, pharmaceutical manufacturing technologies have not changed significantly in over 40 years. Though manufacturers are data-rich, they have yet to fully realize and pursue the potential of advanced process modeling and analytics to transform decision-making in process design and control. Process and product development are still predominantly based on a make-and-test approach, which requires long development cycles, nonrobust scale-ups, and inefficient processes. The industry has tolerated these limitations during the "blockbuster drug era," but as this era ends [8], and as the need to realize the benefit of personalized

medicines increases, new approaches are necessary. Furthermore, these approaches may open new possibilities such as holistically linking solid form, active pharmaceutical ingredient (API) physical properties, and drug product formulation and manufacture [9].

As the pharmaceutical industry increasingly uses outsourcing/offshoring to reduce costs, it faces associated supply chain risks and mitigation costs. Personalized medicines require a shift from one-size-fits-all products and manufacturing processes toward greater flexibility in both. Regulators such as the US FDA and the European Medicines Agency (EMA) support quality by design (QbD) [10], an approach that aims to ensure the quality of pharmaceutical products by employing statistical, analytical, and risk-management methodologies in the design, development, and manufacturing of these products. A goal of QbD is to ensure all sources of variability affecting a process are identified, explained, and managed through appropriate measures. This enables the finished product to consistently meet predefined characteristics from the start, ensuring it is right the first time. Current QbD approaches tend to be experimentally driven and therefore data-hungry and resource-intensive. Their uptake is further limited at present because it is generally not practical to extrapolate beyond experimental boundaries, and so there is limited opportunity to transfer knowledge and understanding gained to other scales.

To address these risks and costs, the pharmaceutical industry is exploring solutions such as flexible manufacturing and advanced process modeling and control; however, unlike other industries, such as oil and gas, the pharmaceutical industry does not currently routinely embed these approaches.

ADVANCED DIGITAL DESIGN

ADDoPT was established in response to challenges faced by the industry worldwide. The 12 collaboration partners included four multinational pharmaceutical companies (AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline [GSK], and Pfizer), three technology-based small- to medium-size enterprises (SMEs) (Process Systems Enterprise [PSE], Perceptive Engineering, and Britest), and five specialist academic and research organizations (Universities of Leeds, Cambridge, and Strathclyde; Cambridge Crystallographic Data Centre; and the Science and Technology Facilities Council's Hartree Centre).

Consortium members worked across the pharmaceutical value chain to define a system for top-down, knowledge-driven digital design and control for drug products and their manufacturing processes. The aim was to integrate a wide range of predictive models and gain insight from industrial case studies at the four major pharmaceutical companies, allowing more targeted future experimentation, a better understanding of risk, and therefore better design and scale-up for robust products and processes.

Digital design combines research insight and qualitative and quantitative mechanistic modeling to provide links between raw materials, manufacturing processes, and product performance to meet patients' needs. It spans all unit operations, processes, and procedures during the manufacture of pharmaceutical products

Personalized medicines require a shift from one-size-fits-all products and manufacturing processes toward greater flexibility in both.

and their impacts, both upstream for product efficiency and process design, and downstream on product performance. ADDoPT's objective was to "create virtual medicine manufacturing systems to make sure they are effective and efficient before creating them in the real world" [11].

The consortium determined at the outset that to ensure a consistent and effective approach to digital design and manufacture of pharmaceutical products, an overarching system-based approach would be required to manage and combine information flows from the many facets of modeling and (where still necessary) experimentation. This information flow map becomes a significant enabler for guiding adoption of industrial digitalization technology, aligning with the Made Smarter Review recommendations and generally emerging trends in the global pharmaceutical sector.

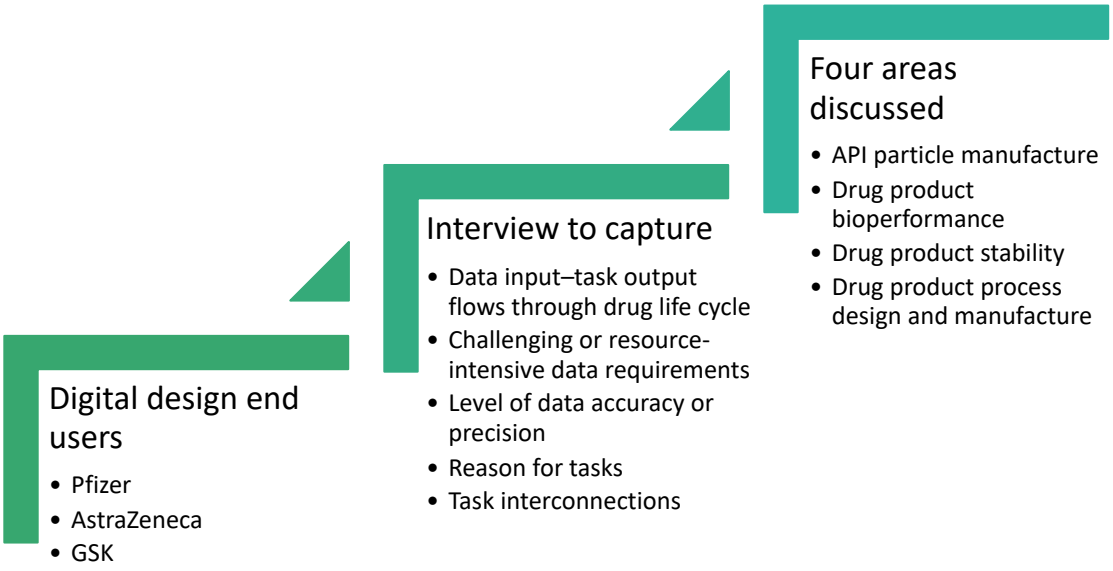
SYSTEMS FRAMEWORK–BASED INNOVATION

Technology- and knowledge-driven partners worked within ADDoPT to advance the current state of process modeling and control for pharmaceutical processes, and to advantageously combine and integrate technologies based on a systems framework–based approach to understand and address the pharmaceutical industry's needs. One benefit may be to stimulate systems thinking [12] in pharmaceutical product and process development. By replacing the typically linear approach to development, the industry can potentially reduce risk; for example, a systems framework–based approach might prevent a repeat of the 1998 polymorphism issue that led to Ritonavir being temporarily withdrawn from the market [13].

CURRENT BEST PRACTICES AND AREAS FOR DEVELOPMENT

Three ADDoPT industrial partners from the pharmaceutical industry (AstraZeneca, GSK, and Pfizer) were interviewed by Britest and PSE to establish to what extent digital modeling approaches are currently part of process development routes to introduce new therapeutic products (see Figure 1). The study's scope comprised API particle manufacture and formulation of immediate-release oral dose products, and it explored links between manufacturing process development and

Figure 1: Pharmaceutical manufacturer interview structure.



bioperformance and stability. To keep the size of the study manageable, API synthesis was excluded.

Generalized conclusions from the three companies interviewed can be summarized under three categories.

- **Current practice:** Workflows are primarily experimentally driven, progress is sequential (meaning, influenced by launch timeline), output is rarely used to revise earlier process steps to ultimately deliver a better result, and a large amount of confirmatory experimental work is undertaken to manage risk.
- **Current influence of digital design techniques:** These techniques—which are in development and not yet in mainstream use—are used to confirm, explain, or fit experimental data. They are not integrated into the overall product and process design approach.
- **Opportunities provided by digital design techniques:** First, task and decision-making flows are similar across the companies, which allows for identification of common tasks and/or decisions points. A standardized approach could streamline progress within organizations and make regulatory reviews more efficient. Second, data and information transfer points could be coordinated between business functional groups. Third, de-risking may potentially become more efficient than current practices. By using digital design techniques, manufacturers could build in an iterative approach to achieve a more robust overall process; identify risk sooner, which would enable the defining of mitigation strategies; and support better management of work and experimental timelines, as modeling could focus on promising and relevant operating windows.

To capture impressions from solution providers, the three SME businesses (Britest, PSE, and Perceptive Engineering) were also interviewed. The topics discussed with each company varied according to the nature of their solutions, and are outlined next.

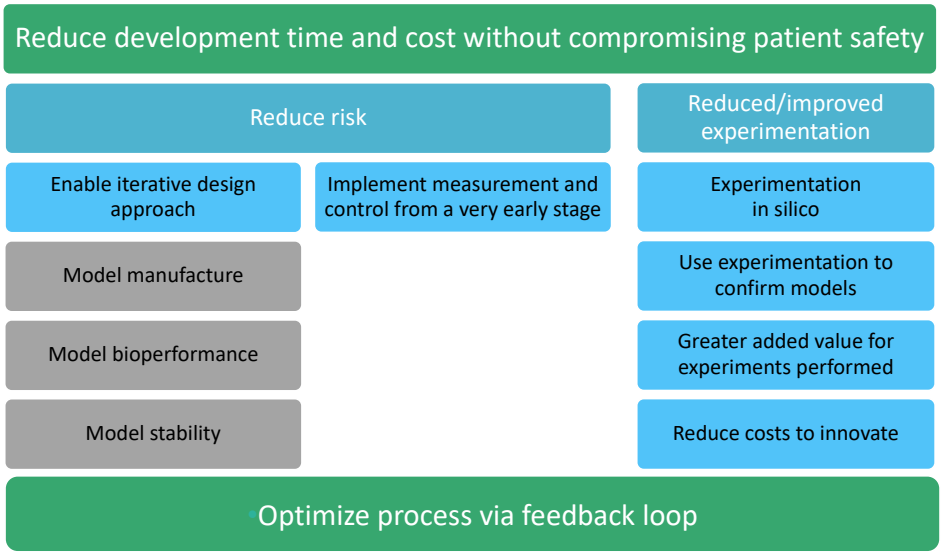
For PSE and Britest, interviews addressed three main topics: (a) the business model for interacting with clients in the pharmaceutical industry; (b) the current status of tools that support ADDoPT-relevant key unit operations; and (c) the current and potential opportunities for the use of tools for biopharmaceutical/formulation design/drug product stability applications.

The interviews with a representative of Perceptive Engineering covered a series of questions:

- Where in the development life cycle do you normally engage with the client?
- Where in the life cycle would you like to engage?
- What is the normal pattern/program for a project?
- In the modeling process, what data do you need/get? What data would you like to get?
- How can you interface to a model process without actual plant data to build a control strategy?
- Can you provide feedback and add value to the clients' development process?

From these interviews, common themes and conclusions emerged. Service providers usually become involved with clients only after key directional decisions are made, which limits the value that service providers can add for the client. Service providers are engaged with/by research and development, rather than the manufacturing communities (although some localized progress

Figure 2: Digital design information flow requirements.



has occurred). Digital design approaches developed for the pharmaceutical sector have significant potential for applications in other high-value product sectors.

INFORMATION FLOW REQUIREMENTS

Commercially launching a new pharmaceutical product is a complex and lengthy process, which involves nearly all of the organization and typically extends into the supply chain, particularly if parts of production have been outsourced to contract manufacturing organizations.

The goal of ADDoPT is to significantly streamline and expedite this complex process while enhancing (or at least not compromising) patient safety. Therefore, any approach to digital design and manufacture must consider not only the end-to-end pharmaceutical manufacturing process but also the wider system, including product design and performance.

Clearly, many groups, and people from many functions and disciplines, must share information effectively. Therefore, those devising a digital approach should focus on information flow instead of a linear, project plan–based workflow. The difference lies in the promotion of systems thinking rather than ticking off a list of discrete deliverables.

Successfully harnessing new digitally enabled approaches is not just a matter of technical implementation; it involves a fundamental paradigm shift for the pharmaceutical industry, moving away from its traditional experimentally based approach to a new design-and-make framework. Just as new enabling modeling and control platforms are designed to be integrated across the pharmaceutical workflow, product and process design and control decisions must consider all relevant upstream and downstream impacts and dependencies, rather than merely seeking a local optimum. For instance, API crystallization might conventionally be optimized to deliver a given average particle size, but simply replicating this specified value from one batch to another does not necessarily ensure trouble-free downstream processing.

There is growing recognition of the need to characterize materials more richly, and to analyze the connection between molecular and material properties at one end through to process and product performance at the other. Developments in statistical and mechanistic modeling approaches, the ability to harness big data, and effective cross-industry collaboration over matters such as the emergent manufacturing classification system [14] can all help put the pieces of the puzzle together.

Committing to a digital (in silico) approach offers many potential benefits. By using in silico experimentation, the pharmaceutical industry can speed up timelines and consider all or a larger subset of a system's factors, while minimizing and better directing the set of practical experiments required to validate the digital model. An in silico approach to design of experiments also reduces risk by eliminating the practical cost and time constraints that currently lead us to limit experiments to the subset of variables considered most likely to prove critical; in digital experiments, we can routinely

explore all potentially critical variables. In silico modeling makes a more broadly applicable QbD approach practical and resource-efficient while also minimizing the quantity of API required for experiments in which the API is difficult to produce or obtain.

NEW WAYS OF THINKING AND WORKING

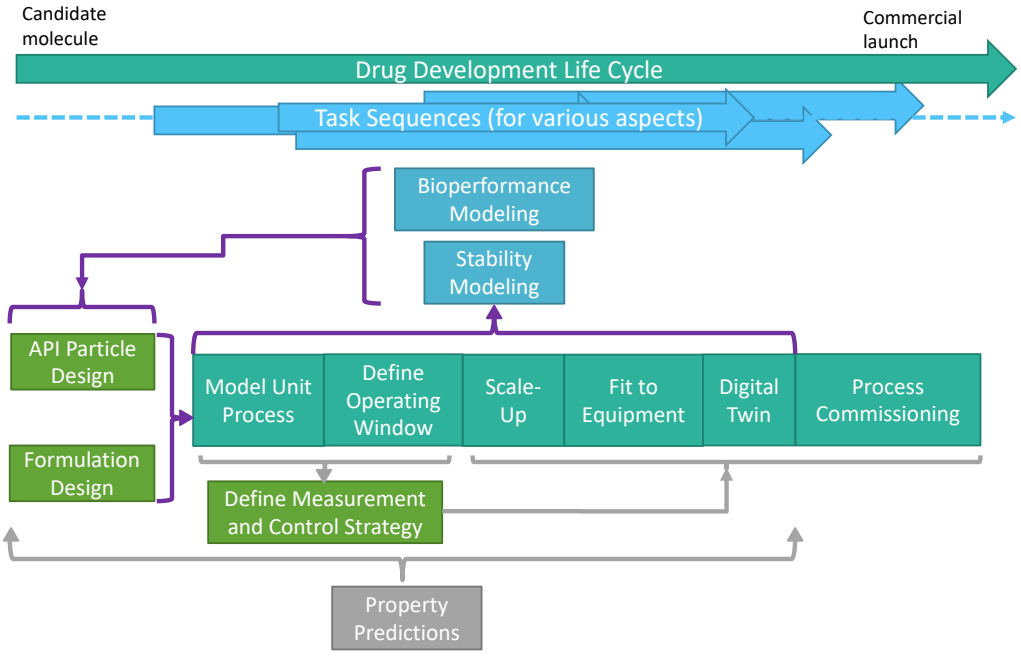
The pharmaceutical industry needs to integrate process development with considerations of patient safety, efficacy, and manufacturability. If this is done successfully, the result will be optimized, more consistent, and more robust products from the outset. A holistic approach helps manufacturers first determine the product performance attributes required and then design the process to deliver the required product. Figure 2 summarizes the overall requirements for a successful information flow for digital design and manufacture of pharmaceutical products.

Understanding the overall manufacturing chain as an interconnected system calls for fundamentally different ways of thinking and working. Along with new technical competencies (how to use the tools and technologies), the holistic approach also includes a broad range of people factors, such as aspects of change management (e.g., critical mass awareness and acceptance of new approaches), knowledge and skills development in the current and future workforce, and overcoming any (usually unintended) silo behaviors between functions and supply chain connections, including geographical challenges of global manufacturing organizations.

To succeed with a digital approach, the organization must implement a substantial cultural change that supports the move from old habits (using modeling to explain experimental results) to new (using models to ensure practical outcomes and identify experiments to verify outcomes). To succeed, the organization's approach to recruitment and training must change, so it can develop scientists and engineers capable as experimentalists *and* modelers, rather than perpetuating two separate communities.

Successful information flow must also highlight key risk-assessment hot spots, business and route decision points, and the information requirements for facilitating them. Digital design enables much earlier integration of measurement and control strategies in equipment design, with the aim of achieving more robust, controllable manufacturing processes. In turn, early understanding of measurement and control enables the development of a manufacturing process "digital twin," where mechanistic system models are

Figure 3: Generic information flow for digital design of manufacturing process.



used to enable dynamic simulation of the whole process, not merely individual steps. Such an approach embodies the principles behind QbD, making it part of the "way things get done," rather than an additional consideration to discuss during filing.

ADDoPT INFORMATION FLOW ARCHITECTURE

In the ADDoPT approach, understanding of the entire pharmaceutical information flow process begins when software developers and users answer the following questions together:

- Which specific tasks, operations, and decisions are addressed by digital modeling?
- What is the level of model fidelity? What are the model's assumptions and limitations? Are those assumptions and limitations appropriate to the application scope?
- What data are required to run a model? What are the outputs? (These matters are key to managing interfaces between different modeling components.)
- Where does the modeling need to be applied? Who will be applying it, and what skills do they need?

Answers to these questions provide the conceptual framework within which developers and users can co-create solutions that anticipate the upstream and downstream impacts of design decisions and best fit the needs of the industry.

Britest's existing whole-process understanding tools were used to help developers and users address the questions in a structured way and ensure mutual communication and comprehension of the issues and potential solutions. In developing the information flow, some simplifying constraints have been imposed to maintain a manageable scope. The starting point is a small molecule API with a synthesis route defined elsewhere that will be delivered as a solid oral dose. The requirements defined in Figure 2 are addressed by the overall information flow structure for digital design (Figure 3).

The overall drug development life cycle runs from selection of the candidate molecule to commercial launch, including the project timeline and stage gates (e.g., first through third clinical trials). The task sequences are the individual tasks required to obtain the deliverables necessary for the project stage gates. These sequences are usually carried out by separate groups within the organization. The key task sequences are illustrated, with interconnecting information flows indicated by brackets and arrows. For example, in Figure 3, the defining steps are API particle design and formulation design, which together encompass product design. Here, the requirements for efficacy, stability, and patient safety should come together with consideration of manufacturability to deliver a whole-process design running through the information flow. This, in turn, feeds back to the bioperformance and stability areas, enabling product design to be reassessed and optimized in a "virtuous cycle" enabled by extensive use of modeling at all points.

The strategy for measurement and control is informed by and supports the process design. Modeling underpins everything to provide physical property estimates for all models employed in all preceding task sequences.

The information flow can be documented as an interactive

The pharmaceutical industry needs to integrate process development with considerations of patient safety, efficacy, and manufacturability.

flowchart with hyperlinks so it's easy to jump from task to task. An e-learning solution (Articulate Storyline) facilitates layering information from a high-level overview to increased depth and detail, and provides web-enabled output, which is ideal for dissemination. To allow greater flexibility in exploring the link between available models and tasks, a visual relational database interface (SharpCloud) has been interwoven with the e-learning solution.

Implicit within the information flow requirements is the desire to make the information flow more practical for implementation by annotating clear explanations and descriptions of alternative models that could be used to achieve tasks identified, and to signpost training, support, and service providers who can help industrialists put them in practice. In an in-house implementation, this documentation could be expanded to include contact details for subject matter experts. Thus, information flow development has become confluent with the development of an ADDoPT online Digital Design Guide, within which it will ultimately be embedded as a primary piece of the publicly available project.

DISSEMINATION AND EXPLOITATION OF THE ADDoPT INFORMATION FLOW

The ADDoPT information flow has been developed to be general in application for the global pharmaceutical sector. In this form, it is an aid for SMEs to position services supporting digital design and manufacture. For pharmaceutical companies, and the contract research and manufacturing organizations in their supply chains, it will provide a resource for introducing researchers to the value and opportunities of digital design and modeling. These outputs will be generally accessible through publications and an open-access website [1].

For implementation within individual organizations, further work will be required to tailor the information flow to the organization's needs. Customization is required to adapt language and tasks to different business processes, cultures, and priorities, and will also consider the different models used, including special models developed in-house.

It is believed that an independently facilitated process will be the most efficient way for a business to develop a bespoke information flow to realize the advantages of digital design and manufacture while incurring minimal disruption during changeover. Within ADDoPT, Britest has already used the methodology to deliver bespoke, visually accessible frameworks for the application of digital model tools to two of the major pharmaceutical partners in the ADDoPT project.

CONCLUSION

The ADDoPT consortium has developed information flow for digital design and manufacture of pharmaceutical products. This innovation will help the global pharmaceutical industry implement the Made Smarter Review's recommendations regarding technology adoption, innovation, and leadership, which have been identified as essential to realize the potential of the Industry 4.0 revolution.

The generic information flow developed is a template that can be customized to meet individual organizational needs. This is best done via an independently facilitated workshop-based process identifying existing modeling capability and gaps. Similar information flows for digital design and manufacture will be applicable outside the pharmaceutical industry, and the pharmaceutical information flow can act as a template of this digital-enabling approach for other areas of manufacturing.

References

1. "ADDoPT—Advanced Digital Design Transforming Pharmaceutical Development and Manufacture." Accessed 1 September 2019. https://www.addopt.org
2. Wright, I. "What Is Industry 4.0, Anyway?" Engineering.com. Published 22 February 2018. https://www.engineering.com/AdvancedManufacturing/ArticleID/16521/What-Is-Industry-40-Anyway.aspx
3. Baur, C., and D. Wee. "Manufacturing's Next Act." McKinsey and Company. Published June 2015. https://www.mckinsey.com/business-functions/operations/our-insights/manufacturings-next-act
4. UK Department for Business, Energy and Industrial Strategy. "Made Smarter Review." Updated 1 November 2017. https://www.gov.uk/government/publications/made-smarter-review
5. Kane, G. C., D. Palmer, A. H. Phillips, D. Kiron, and N. Buckley. "Aligning the Organization for Its Digital Future: Findings from the 2016 Digital Business Global Executive Study and Research Report." Deloitte Insights. Published 26 July 2016. https://www2.deloitte.com/insights/us/en/topics/emerging-technologies/mit-smr-deloitte-digital-transformation-strategy.html
6. Confederation of British Industry. "Embracing Digital in Every Sector." Published April 26, 2016. https://cbicdnend.azureedge.net/media/2559/embracing-digital-in-every-sector_cbi-survey-findings.pdf?v=20190822.1
7. Accenture Consulting. "The Digital Oil Company: Getting Ahead of the Energy Transition." Published 2017. https://www.accenture.com/gb-en/_acnmedia/pdf-58/accenture-the-digital-oil-company-getting-ahead-of-the-energy-transition.pdf
8. Van Eck Securities Corporation. "Drug Patent Expirations: $190 Billion Is Up for Grabs." Published 3 March 2016. Market Realist. https://marketrealist.com/2016/03/drug-patent-expirations-190-billion-sales-grabs
9. Ticehurst, M. D., and I. Marziano. "Integration of Active Pharmaceutical Ingredient Solid Form Selection and Particle Engineering into Drug Product Design." *Journal of Pharmacy and Pharmacology* 67, no. 6 (10 February 2015):782–802. doi:10.1111/jphp.12375
10. US Food and Drug Administration. "Pharmaceutical Quality for the 21st Century—A Risk-Based Approach Progress Report." Published May 2007. https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm128080.htm

11. McCubbin, I., and Medicines Manufacturing Industry Partnership. "Handing Over the Helm of MMIP" [blog post]. Association of the British Pharmaceutical Industry. Published 15 February 2017. https://www.abpi.org.uk/media-centre/blog/2017/february/handing-over-the-helm-of-mmip

12. Ollhoff, J., and M. Walcheski. "Making the Jump to Systems Thinking." The Systems Thinker. Accessed 1 September 2019. https://thesystemsthinker.com/making-the-jump-to-systems-thinking

13. Bauer, J., S. Spanton, R. Henry, J. Quick, W. Dziki, W. Porter, and J. Morris. "Ritonavir: An Extraordinary Example of Conformational Polymorphism." *Pharmaceutical Research 18,* no. 6 (2001): 859–866. doi:10.1023/A:1011052932607

14. Leane, M., K. Pitt, G. K. Reynolds, N. Dawson, I. Ziegler, A. Szepes, A. M. Crean, R. D. Agnol, and the Manufacturing Classification System Working Group. "Manufacturing Classification System in the Real World: Factors Influencing Manufacturing Process Choices for Filed Commercial Oral Solid Dosage Formulations, Case Studies from Industry and Considerations for Continuous Processing." *Pharmaceutical Development and Technology* 23, no. 10 (2008): 964–977. doi:10.1080/10837450.2018.1534863

Acknowledgments

The ADDoPT collaboration was initiated by the Medicines Manufacturing Industry Partnership (MMIP) and partially funded under the Advanced Manufacturing Supply Chain Initiative, a UK Department of Business, Energy and Industrial Strategy initiative delivered by Finance Birmingham and Birmingham City Council. The authors are grateful to colleagues from across the ADDoPT consortium for their input to workshop sessions and various helpful discussions in the development of the approach described herein.

About the authors

Robert H. Peeling, CEng, FIChemE, is a chemical engineer and Fellow of the Institution of Chemical Engineers. A Senior Innovation Specialist at Britest Limited, he uses the experience of a professional lifetime spent in design, operations, and engineering research management roles, in organizations such as Johnson Matthey Vertec, Synetix, and Tioxide UK Limited, to bear on assessing the risks of new technical innovations and new ways of working arising from Britest studies and collaborations.

Charles M. Gordon, PhD, joined Britest Limited as a Senior Innovation Specialist in 2011, having previously worked as a reaction engineer in API process development for Pfizer UK. He has a degree in chemistry from the University of Oxford and a PhD in inorganic chemistry from the University of Nottingham. Following postdoctoral research at the University of Würzburg, Dublin City University, and Queen's University Belfast, he was awarded a Royal Society of Edinburgh British Petroleum Research Fellowship during a six-year lectureship in the School of Chemistry at the University of Strathclyde. Charlie uses his mix of industrial and academic experience to support effective cross-partner communication in a range of innovation activities, as well as supporting Britest users through training and technical facilitation.

Martin R. Edwards, PhD, is a Senior Innovation Specialist at Britest Limited and has spent more than 25 years in the chemical industry, leading product and process research and development teams at ICI, Zeneca, Avecia, and Fujifilm Imaging Colorants. His experience is primarily in polymers, dispersions, UV-curing resins, toners, and inks. He has a degree in chemistry and a PhD in physical organic chemistry, both from the University of Cambridge. Martin is skilled in translating outputs of collaborative research into practical tools and methodologies for use by industrialists.

John A. Henderson, CChem, PhD, is Technical Communications Specialist at Britest Limited. He is a Chartered Chemist with an honors degree in applied chemistry from the University of Strathclyde and a PhD in polymer science from the University of Durham. John's career encompasses roles in industrial research and development, management, training, and knowledge transfer activities. As Research and Development Manager for Chemdal Limited (later BASF) polyacrylate superabsorbents, John was responsible for several international process and product transfers and technical representation to major clients. He has also worked extensively in UK/EU collaborative innovation and coordination actions and knowledge transfer programs.

Sean K. Bermingham, PhD, has been Head of Process Systems Enterprise's Formulated Products business unit since 2010 and previously was Global Head of Consulting. He is responsible for strategic business development, product management, and services delivery for the pharmaceutical, food, consumer good, specialty, and agrochemical industries. Sean is one of the founders of the Systems-Based Pharmaceutics Alliance with Eli Lilly, GlaxoSmithKline, Pfizer, and Roche. He was also the lead for the £20.4 million ADDoPT Digital Design project with partners including AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, and Pfizer. Sean is a chemical engineer with an MSc in chemical engineering and a PhD in crystallization from Delft University of Technology and an executive MBA from Imperial College London.

EVALUATION OF VISUAL INSPECTION IN PARENTERAL PRODUCTS

Using the Attribute Agreement Analysis Method

By Sambhujyoti Das

According to US Pharmacopeia (USP) Chapter <790>, "all parenteral products should be essentially free from any visible particles" [1]. This is the first and foremost requirement stated in all pharmacopeia for any injectable product. However, yielding absolutely particle-free injectable products is virtually impossible under real-life manufacturing conditions. Hence, inspection of each and every filled and sealed product unit before the unit is taken into labeling or packaging is mandatory [1].

The visual inspection process is the final step in this scenario to ensure finished products in the marketplace are particle free. USP Chapter <1790> includes a critical requirement to qualify the visual inspection system and demonstrate the consistency of inspection processes throughout the product life cycle [2].

VISUAL INSPECTION PROCESS METHODS

In the visual inspection process, both manual and automated inspection methods are fundamentally based on the optical characteristics of filled units. Irrespective of the method of inspection, the visual inspection process is always probabilistic rather than definitive. For this reason, the simple pass-fail criterion in evaluation of visual inspection process has drawbacks.

Knapp and Budd have provided a statistically justified method to evaluate visual inspection processes [3], but this method also has limitations. Specifically, the Knapp method is useful for determining rejection zone efficiency (RZE), reject/accept/gray (RAG), and so on, but it falls short for detailed multidimensional analysis.

The attribute agreement analysis method (or 3A method) of evaluation offers a statistically based, practical technique with comprehensive analytical capability. This method not only identifies the efficiency of visual inspectors or the overall visual inspection process, but also evaluates the misclassification rates (unit-wise and inspector-wise) and the estimated accuracy range of inspectors with a 95% confidence interval (CI). The 95% CI is chosen because it is the most commonly used interval with a significant level of confidence.

Using the 3A method, one can identify the borderline defective units (or gray-zone units). These analyses help pinpoint the need for retraining or improvement opportunities in the visual inspection process. Table 1 summarizes the differences between the pass-fail, Knapp, and 3A methods.

APPLYING THE 3A METHOD

The calculations associated with the 3A method are straightforward. They can be done manually, although the use of commercially available statistical software simplifies the tasks. Also, the graphical representations generated by software or a spreadsheet are useful in interpreting data.

Scenario

Let's consider a scenario in which 100 known vials are to be inspected by three visual inspectors (in the evaluation study). These 100 vials include 20 defective vials (of known defects) and 80 defect-free vials. The defective (bad) vials contain both particulate defects (e.g., fragments of glass, metal, elastomeric materials)

Table 1: Comparison of 3A method with other evaluation methods.

	Pass-Fail	Knapp	3A
Applicability	Largely for manual inspection; limited applicability to automated inspection	Applicable to automated inspection; can be used for manual inspection	Applicable to manual inspection; can be extended to automated inspection
Number of inspection trials	Not defined or not fixed	Relatively large (i.e., generally 10 inspection trials per inspector)	Relatively small (i.e., generally 3 inspection trials per inspector)
Statistical validity of evaluation approach	Not valid	Statistically valid	Statistically valid
Analysis of test results	Not standardized; depends on evaluators or organizations	Standardized approach, one- or two-dimensional (e.g., RZE and RAG)	Standardized approach, multidimensional
Causal analysis of misclassification (good rated bad or vice versa)	Not possible; misclassification only attributed to inspector error	Not possible; misclassification only attributed to inspector error (or inspection machine error)	Possible to attribute error to either inspectors or inspected units (vials)
Extrapolation of test results	Not possible	Not possible	Accuracy of inspectors can be manipulated with 95% CI to estimate possible accuracy range in future inspections
Extent of data analysis	Low to moderate	Moderate	Comprehensive
Identification of improvement needs in inspection process	Limited to inspector training	Capable of identifying need for inspectors' training or inspection machine optimization	Facilitates designing of need-specific training for inspectors and identification of improvement opportunities in the inspection system

Table 2: Partial record of visual inspection trials showing data for 10 out of total 100 vials.*

ID of Vial	*Std. Vials*	*FIRST INSPECTION TRIAL*			*SECOND INSPECTION TRIAL*			*THIRD INSPECTION TRIAL*		
1	G	G	G	G	G	G	G	G	G	G
2	B	B	B	B	B	B	B	B	B	B
3	G	G	B	G	B	G	G	G	G	G
4	G	G	G	G	G	G	G	G	G	G
5	G	G	G	G	B	G	G	G	G	G
6	G	G	G	G	G	G	G	G	G	G
7	G	G	G	G	G	G	G	G	G	G
8	B	B	B	B	B	B	B	B	B	B
9	B	B	B	B	B	B	B	B	B	B
10	G	G	G	G	G	G	G	G	G	G

*G denotes a good vial, B denotes a bad vial, and the blue, black, and green figures denote inspector 1, 2, and 3, respectively.

and nonparticulate defects (e.g., cracks, inappropriate seals). Defective vials are selected from production rejects that have been removed from product lots. Alternatively, the re-creation of equivalent defects in a controlled laboratory is also acceptable [2]. The defect-free (good) vials are also selected from actual product lots. All 100 test vials are standardized by expert inspectors prior to the start of evaluation. The standard vials are assigned identification numbers, and information about their conditions (categorization as good or bad vials) is concealed from the inspectors under evaluation. In this evaluation study, three visual inspection trials

Table 3: Equations, values, and results for calculations.

Calculation	Equation	Values	%
Overall accuracy	$\left(\frac{\text{Total number of inspections that match the standards}}{\text{Total number of inspections}}\right) \times 100$	$\left(\frac{862}{900}\right) \times 100$	95.8
Overall error rate	$\left(\frac{\text{Total number of inspections that do not match the standards}}{\text{Total number of inspections}}\right) \times 100$	$\left(\frac{38}{900}\right) \times 100$	4.2
Good units rated as bad	$\left(\frac{\text{Total number of good units rated as bad}}{\text{Total number of good units inspected}}\right) \times 100$	$\left(\frac{33}{720}\right) \times 100$	4.6
Bad units rated as good	$\left(\frac{\text{Total number of bad units rated as good}}{\text{Total number of bad units inspected}}\right) \times 100$	$\left(\frac{5}{180}\right) \times 100$	2.8
Inspector accuracy rate	$\left(\frac{\text{Number of correct matches by the inspector}}{\text{Number of inspections done by the inspector}}\right) \times 100$		
	Example for inspector 1	$\left(\frac{280}{300}\right) \times 100$	93.3
Unit-specific error rate	$\left(\frac{\text{Number of incorrent matches on the specific unit}}{\text{Number of inspections done on the specifc unit}}\right) \times 100$		
	Example for vial 11	$\left(\frac{8}{9}\right) \times 100$	88.9
Good units rated as bad by inspector	$\left(\frac{\text{Number of good units rated as bad by the inspector}}{\text{Number of good units inspected by the inspector}}\right) \times 100$		
	Example for inspector 1	$\left(\frac{17}{240}\right) \times 100$	7.1

were conducted independently on three different days. The results are shown in Table 2.

Calculations for Analyzing Inspection Results

After completing three visual inspection trials by three inspectors and recording observations in Table 2, the following data are used to begin outcomes analysis:

- Total number of inspections = Total number of vials inspected (100) × Number of inspection trials (3) × Number of inspectors (3) = 100 × 3 × 3 = 900 total inspections
- Total number of good vials inspected = Number of good vials (80) × Number of inspection trials (3) × Number of inspectors (3) = 80 × 3 × 3 = 720 good vials inspected
- Total number of bad vials inspected = Number of bad vials (20) × Number of inspection trials (180) × Number of inspectors (30) = 20 × 3 × 3 = 180 bad vials inspected

From those data, several calculations are run. These calculations and the results are shown in Table 3.

Using these calculations, we can then determine upper and lower bound CIs for inspector accuracy rates on good units with a 95% CI (α = 0.05) [4]:

$$\text{Lower bound value} = \frac{1}{1+\frac{n-x+1}{x}F_{2(n-x+1),2x,\alpha/2}}$$

$$\text{Upper bound value} = \frac{\frac{x+1}{n-x}F_{2(x+1),2(n-x),\alpha/2}}{1+\frac{x+1}{n-x}F_{2(x+1),2(n-x),\alpha/2}}$$

where

x = number of correct matches with good units by the inspector
n = total number of good units inspected by the inspector
$F_{v1,v2,\alpha}$ = F distribution table value with v1 and v2 degrees of freedom at alpha (95%) level of confidence

Example for inspector 1:

$$\text{Lower bound value} = \left(\frac{1}{1+\frac{240-223+1}{223}F_{2(240-223+1),(2\times223),0.05/2}}\right)\times 100$$

$$= 88.9\%$$

$$\text{Upper bound value} = \left(\frac{\frac{223+1}{240-223}F_{2(223+1),2(240-223),0.05/2}}{1+\frac{223+1}{240-223}F_{2(223+1),2(240-223),0.05/2}}\right)\times 100$$

$$= 95.8\%$$

Note: It is best to use statistical software to calculate the exact CI because the formulas are complex. For manual calculation, a relatively simple normal approximation method can be used. The formulas are as follows:

$$\left(p \pm Z_{1-(\alpha/2)}\sqrt{\frac{p(1-p)}{n}}\right)\times 100$$

where

$p = \frac{\text{Number of correct matches with good units by the inspector}}{\text{Total number of good units inspected by the inspector}}$

$Z_{1-(\alpha/2)} = 1.96$ for 95% CI

n = total number of good units inspected by the inspector

Graphical Tools to Interpret Trial Data

The data obtained from inspection trials can be graphically illustrated by using a spreadsheet application or commercially available statistical software.

The first report (Figure 1) shows the overall accuracy of the visual inspection process (95.8%). The overall process complies with the minimum acceptance for accuracy of 95% (a justifiable limit).

Figure 1 also compares the individual accuracy of the three inspectors. Inspector 1 had an accuracy rate of 93.3%, which is below the acceptance accuracy limit. Hence, inspector 1 needs to be retrained.

A point of concern related to the "misclassification rate" in Figure 1 is the presence of defective units rated as good units (bad rated good). Units misclassified as good may cause health risks to patients and are therefore unacceptable from the GMP perspective. The misclassifications might have been due to a specific inspector's errors, or they might be borderline cases for which it is difficult for any inspector to differentiate between good and bad units.

Figure 2 can be useful to interpret misclassification rates. A low rate of accuracy overall and across all inspectors indicates the need to improve the effectiveness of visual inspection procedures, arrangements, or training.

Figure 1: Overall and inspector-specific accuracy rates of visual inspection process.

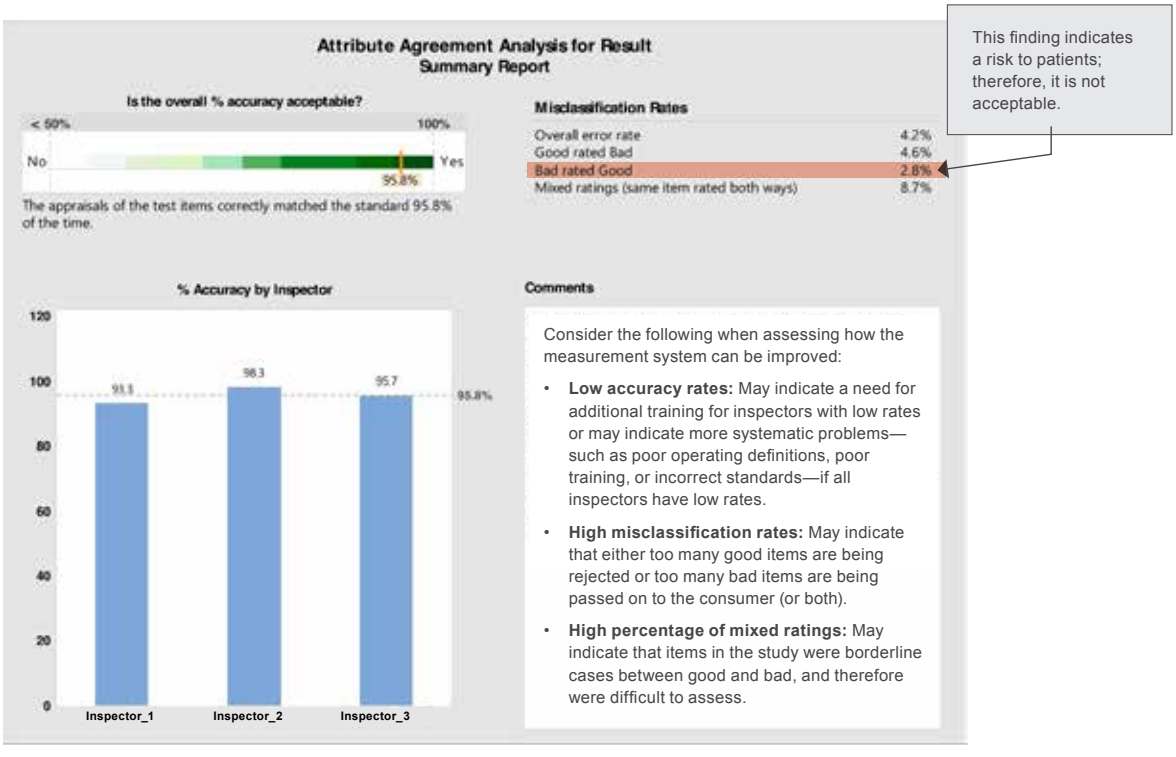


Figure 2: Graphical representation of misclassification rates.

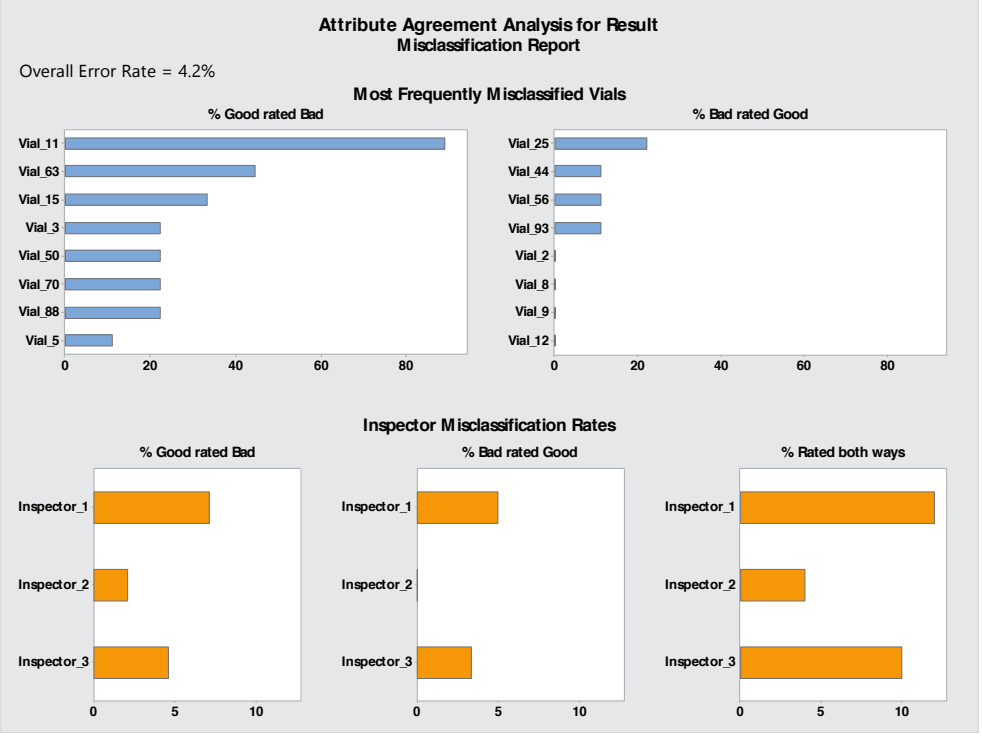
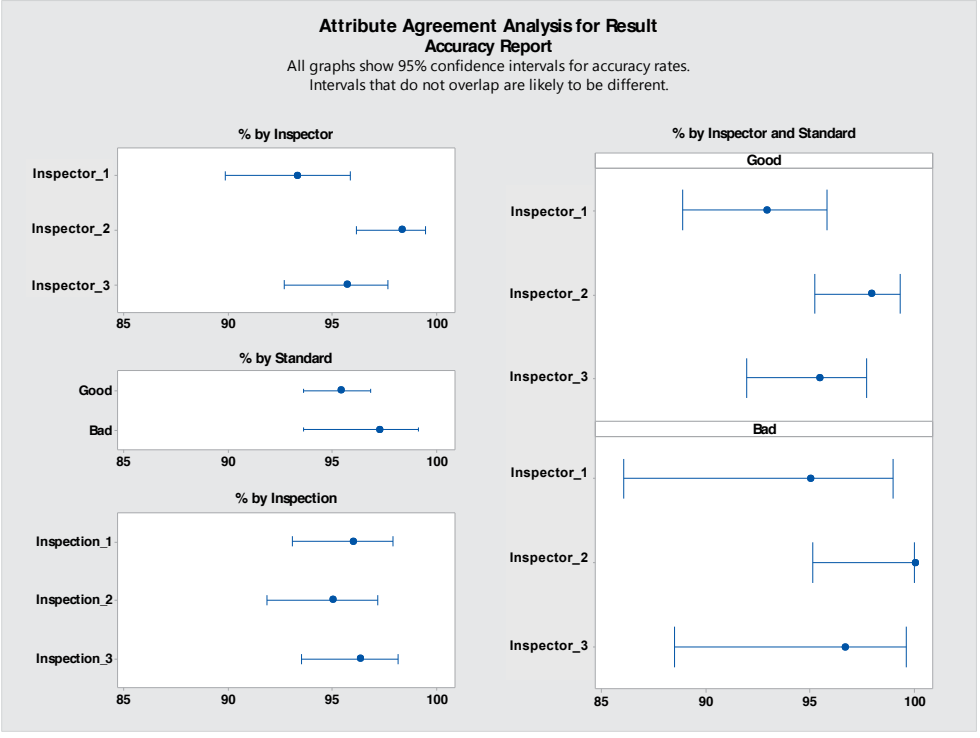


Figure 3: 95% CIs for visual inspection accuracy rates.



The attribute agreement analysis method (or 3A method) of evaluation offers a statistically based, practical technique with comprehensive analytical capability.

The top section of Figure 2 shows the unit-specific (vial-specific) misclassification rates. It is evident that vial 11 has been misclassified 88.9% times across all inspectors. This is indicative of a borderline case. The evaluators (expert inspectors) should reinspect the borderline vial to identify the discrepancy and preferably replace it with a prominent good vial in future inspection trials. The misclassification rates of other vials are less than 50% and can be attributed to errors by the inspectors. The bottom portion of Figure 2 shows that inspectors 1 and 3 have misclassified bad vials as good (which is a patient safety risk). Based on this finding, those two inspectors require further training regarding proper classification.

Finally, Figure 3 shows results with 95% CIs. In this figure, the "% by Inspector and Standard" section is the main focus. An expected accuracy limit of not less than (NLT) 90% is reasonable. (A higher acceptance limit, such as NLT 95%, can be assigned for requalification of more experienced inspectors.)

An expected accuracy limit of NLT 90% means there is a 95% confidence level that the estimated "% Accuracy" of an inspector will not be less than 90% in any future inspection. However, the acceptance criterion (point estimation) for "% Accuracy" of an inspector is NLT 95% in this evaluation method.

Figure 3 shows lower bound interval values of less than 90% for inspectors 1 and 3, especially for distinguishing defective units (bad vials). Therefore, to improve the estimated range, both inspectors should undergo more extensive training to improve consistency.

CONCLUSION

The 3A method provides an effective way to evaluate the accuracy of a visual inspection system for parenteral products. It can be used in initial and periodic qualification of visual inspectors. Because the core principle of visual inspection in parenteral products is the same for both manual and automated processes, this method can be extended to automated or semiautomated visual inspection systems as well. Furthermore, the multidimensional analysis of inspection trials provides an in-depth understanding of the visual inspection process and inspectors' capabilities. The interpretation of 3A method test results helps capture weaknesses in a visual inspection program and in turn supports formulating improvement initiatives.

References

1. United States Pharmacopeia. USP Chapter <790>: Visible Particulates in Injections.
2. United States Pharmacopeia. Chapter <1790>: Visual Inspection of Injections.
3. Knapp, J. Z., and G. W. Budd. "Excerpts Taken from the PDA 2005 Annual Conference Paper Presented by Julius Z. Knapp and Gerald W. Budd: Part III: Reject Zone Efficiency and the Sampling Inspection Implementation of Standard Procedures for Visual Inspection: NIST Traceable Automated Contaminating Particle Measurements, Using the NIST2-ParticleVision™ System." Phoenix Imaging Ltd. website. http://www.mib-lights.com/wp-content/uploads/2013/10/Part-III-Reject-Zone-Efficiency-and-the-Sampling-Inspection-by-Knapp-and-Budd.pdf
4. Morisette, J. T., and S. Khorram. "Exact Binomial Confidence Interval for Proportions." *Photogrammetric Engineering & Remote Sensing* 64, no. 4 (April 1998): 281–283. https://pdfs.semanticscholar.org/8622/a48e1c0b38ceaa294c6dd2610714281dfd95.pdf

About the author

Sambhujyoti Das is Assistant General Manager of Quality Assurance at Fresenius Kabi Oncology Ltd. He's responsible for quality- and regulatory compliance–related supports to the company's manufacturing units in India (Standard Solutions) and South Africa. He has more than 15 years of professional experience in pharmaceutical quality assurance and validation, earned a master's degree in pharmacy, and is a certified Lean Six Sigma black belt. He has been an ISPE member since 2013.

INDEX

CLASSIFIEDS

ARCHITECTS, ENGINEERS, CONSTRUCTION

CRB
1251 NW Briarcliff Parkway
Suite 500
Kansas City, MO 64116
+1 816-880-9800

EI Associates
8 Ridgedale Avenue
Cedar Knolls, NJ 07927
+1 973-775-7777

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

ASEPTIC ANALYZERS

Picarro, Inc.
3105 Patrick Henry Drive
Santa Clara, CA 95054
+1 408-962-3900

BUSINESS SERVICES

UBM Sinoexpo
7/F, Cheng Kai International Mansion
No. 335 Hong Qiao Road
Shanghai 200030, China
+86-21-33392533

INFORMATION TECHNOLOGY

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

Kneat Solutions
Unit 7, Castletroy
Business Park
Plassey Park Rd
Limerick, Limerick, V94
KW28, Ireland
+353-61-203826

SOFTWARE SIMULATION AND PROCESSING SYSTEMS

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

VALIDATION—MANUFACTURING

ValGenesis, Inc
395 Oyster Point Boulevard
Suite 228
South San Francisco, CA 94080
+1 510-445-0505

VALIDATION—SERVICES

CAI
652 N Girls School Road
Indianapolis, IN 46214
+1 317-271-6082

Ellab
303 E 17th Avenue
Suite 10
Denver, CO 80203
+1 303-425-3370

SPIRAX SARCO
Charlton House
Cheltenham
Gloucestershire, GL53 8ER,
United Kingdom
+44 (0)1242 521361

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

PE ONLINE'S FIRST YEAR

ISPE's online site for *Pharmaceutical Engineering* was launched a little over one year ago, in November 2018. Here are some statistics about the site's success during its first year.

Total Pages Viewed

293,000

Total Visitors

131,000

TOP ARTICLES VIEWED

#1 Design Considerations for WFI Distillation Systems Part 1 (15 April 2016)

#2 Continued Process Verification, 3rd Stage of FDA Process Validation Guidelines (26 February 2019)

#3 Biopharmaceutical Manufacturing Process Validation and Quality Risk Management (May/June 2016)

#4 Data Integrity in the Trenches: A Look into Quality Control Lab (January/February 2019)

#5 EU Clinical Trials Application Process (7 June 2016)

Electronic Bowie Dick Sensor

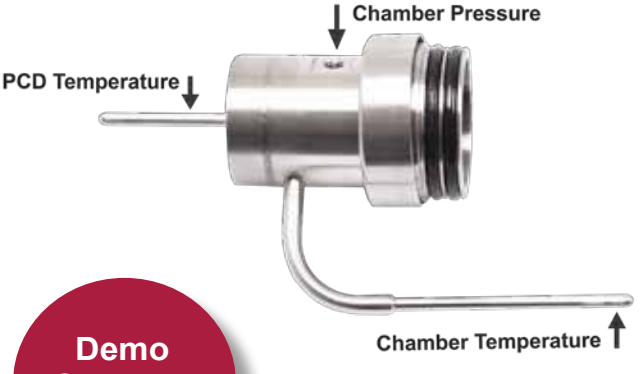
Validation & Monitoring Solutions

ISO 11140-4 Compliant

- Electronic Documentation of Tests & Reports
- Advanced Sterilization Analysis
- CFR 21 Part 11 Compliance with Audit Trails
- Clear Pass/Fail Test Report Results
- Intuitive Software with Database Integrity

VALIDATION • MONITORING • CALIBRATION • ON-SITE SERVICES

- Interchangeable Process Challenge Device for Subsequent Test Cycles
- Compact Size with +/- 0.05°C Accuracy
- Up to 1,000 Cycles between Calibrations
- Critical Parameter Verification of Pre-Vacuum Sterilization Processes



Demo Systems Available!

For more information contact:
usa@ellab.com | 303.425.3370

ellab.com

INTEGRATED SOLUTIONS FOR **CELL & GENE THERAPY**

CAI delivers customized integrated solutions for every phase of your project to help you achieve operational excellence and accelerate speed to market.

Our experts in Cell and Gene Therapy have the knowledge and experience to help advance your product from development through clinical and into commercial production.

- » Facility & Process Design
- » Project Management
- » Commissioning & Qualification
- » Technology Transfer
- » Process Validation
- » Operational Readiness
- » Human Performance
- » Quality & Regulatory

CAI

WHEN YOU NEED TO MEET A HIGHER STANDARD™

cagents.com