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A CULTURE OF INNOVATION

George Scangos, CEO of Vir Biotechnology, on corporate culture, its role in innovation, and the war against infectious disease

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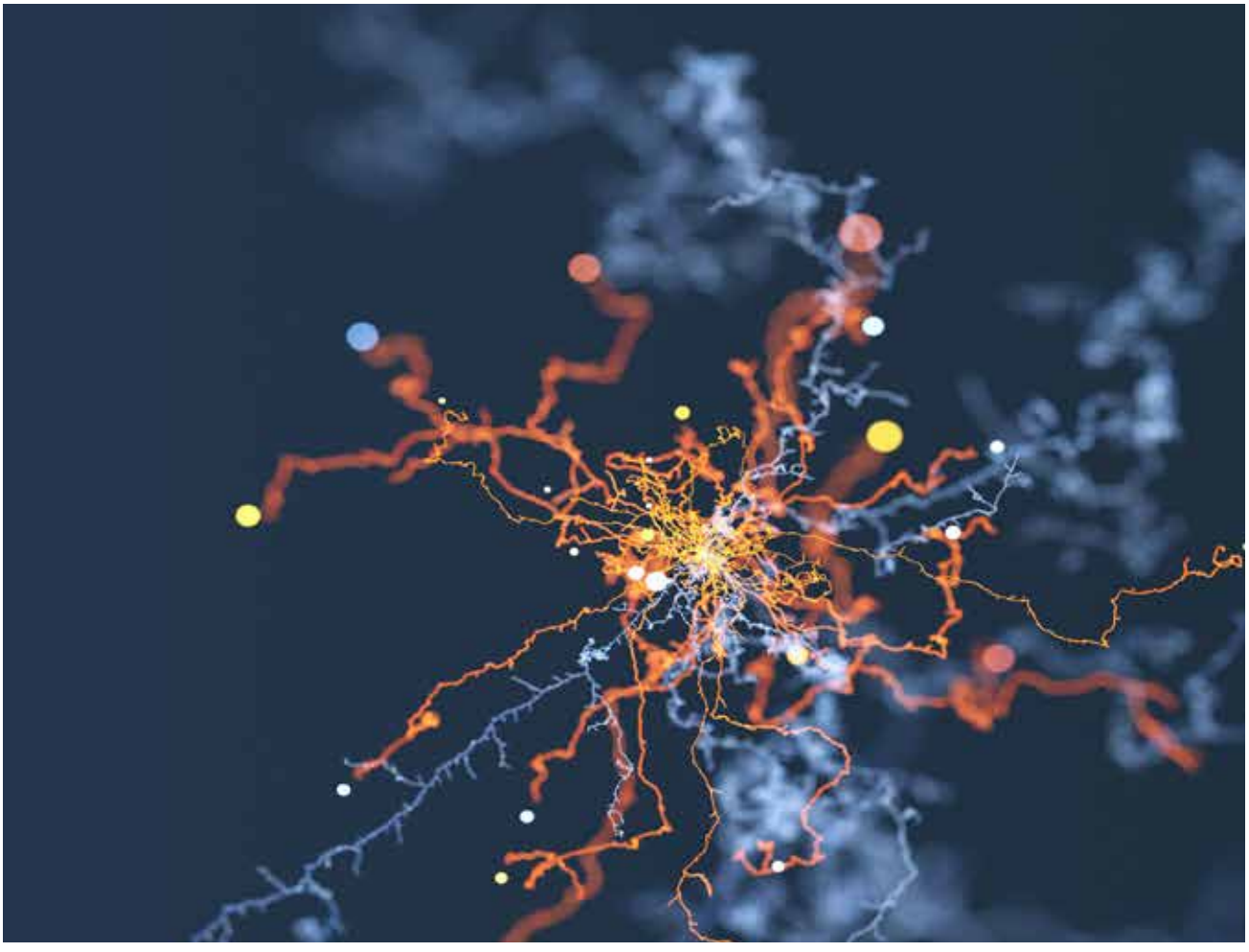

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A CULTURE OF INNOVATION

A corporate culture that supports creative thinking can help pave a road to innovation. Free people from fear and encourage them to do their best and you'll have an environment for accomplishing great things, according to George Scangos, who has led Biogen and other pharma companies. In a recent conversation with PE, Scangos shared his approach to building a culture of innovation and provided updates about his latest endeavor, Vir Biotechnology, whose mission is the war on infectious disease.

ON THE COVER An abstract image illustrates the culture, connection, and communication, that spark innovation.

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SPECIAL SECTION: YP 2018 HIGHLIGHTS

This year, ISPE Young Professionals held over 60 events in 15 countries, drawing more than 2,000 attendees—an amazing testament to the growth of the YP community. This Special Section details the success of these global activities and the IYPC's exciting work over the past year.

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Welcome to the New *Pharmaceutical Engineering* Online


Susan Sandler

In November, ISPE introduces PE Online, a new web-based reading platform for *Pharmaceutical Engineering*. It is your central place for PE content, including information on trends, developments, technology, and scientific research. PE Online is part of the main ISPE website, providing easy access to PE and other important ISPE information, including member benefits, conferences, training, and Guidance Documents. PE Online's responsive design is compatible with any device, to give you an optimal reading experience.

What's on the site?

PE Online contains all the content found in the print magazine—including current issue articles—plus the popular iSpeak blog and an extensive PDF archive of past issues. One helpful new feature will allow you to search for specific content by topic. In addition to posting some content before it's available in print, we also plan to include online-only exclusives and add feature content with whitepapers from ISPE partners.

Is PE Online for ISPE members only?

Access to all content on PE Online continues to be a benefit for ISPE members only. The new site may offer limited "open access" to nonmembers for some articles we deem important to the industry. In this way we'll be able to spotlight PE content and draw attention to ISPE's research and technical discussions. Open-access content also introduces PE and ISPE to more people around the world.

How can you submit an article to PE Online?

We welcome content submissions from our members. Instructions for submitting content are on the new site. Our user-friendly information page should help answer your questions: www.ispe.org/pharmaceutical-engineering/about/submit-article.

Will ISPE continue to publish print PE?

Yes, you will continue to receive the print version of PE six times a year as part of your ISPE membership.

Is print PE changing?

We are updating the print magazine's design with a more modern look to make it easier to read and enjoy. You'll see some of this same design online: clean, crisp, and very easy to read and search. PE will continue to publish technical and other content in both print and online, even as it expands to include more types of content. The newest addition, ISPE Briefs, provides short articles about Chapter and Affiliate events and other ISPE news.

Can you still access PE on the app or flip book?

As part of our transition to PE Online, the app and flip book have been discontinued. All PE online content is available at the PE Online site.

The new online site and updates to the print magazine are part of ISPE's mission to improve and enhance your member benefits. Please let us know what you think about PE Online and the updated print PE magazine: ssandler@ispe.org.

We look forward to PE's growth in 2019 and wish you a happy and peaceful holiday season.

—Susan Sandler, Editorial Director, *Pharmaceutical Engineering*

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SIX SIGMA QUALITY AND CONSORTIA

Lawrence Yu

Disclaimer: This article contains brief, abridged, and informal synopses of remarks from a US FDA regulator during the 2018 ISPE Continuous Manufacturing Workshop proceedings in June 2018. This content has not been vetted by the agency and does not represent official guidance or policy of the FDA.

Six Sigma is an approach for pharmaceutical manufacturing quality that can help to eliminate drug shortages and recalls and improve performance issues. Lawrence Yu, PhD, Deputy Director, Office of Pharmaceutical Quality, FDA Center for Drug Evaluation and Research (CDER), provided an overview of key factors around the move to Six Sigma quality in pharma manufacturing in his presentation "The Future of Pharmaceutical Quality" at the 2018 ISPE Continuous Manufacturing Workshop opening plenary session. The Workshop took place in Arlington, Virginia, on 6–June. The sidebar "How Global Consortia are Advancing CM" features highlights from another presentation during the opening plenary session.

Six Sigma is defined as "a disciplined, data-driven approach and methodology for eliminating defects (driving toward six standard deviations between the mean and the nearest specification limit) in any process—from manufacturing to transactional and from product to service."[1]

The path to Six Sigma in pharmaceuticals, Yu said, is being driven by certain factors that are unique to the industry. These include economic factors that favor quality, and increased emphasis on performance-based regulation that can give the pharma industry greater flexibility in managing and improving quality. Continuous manufacturing and process analytical technology (PAT) play important roles; continuous improvement and operational excellence are also needed.

ECONOMIC DRIVERS

Quoting FDA CDER Director Janet Woodcock, Yu noted that "The fundamental problem we identify is the inability of the market to observe and reward quality. This lack of reward for quality can reinforce price competition and encourage manufacturers to keep costs down by minimizing quality investments."[2] This makes manufacturers vulnerable to quality issues, leading in some cases to product recalls and supply disruption.

PERFORMANCE-BASED REGULATION

Yu defined performance-based regulation as a regulatory approach that focuses on desired, measurable outcomes rather than prescriptive processes, techniques, or procedures regarding how those results are to be obtained.

At the Nuclear Regulatory Commission, for example, performance-based regulatory actions focus on identifying performance measures that ensure an adequate safety margin and offer incentives to improve safety without formal regulatory intervention by the agency.

Pharmaceutical regulation should similarly be designed to improve the performance of individual and organizational behavior in ways that protect and promote public health, he said. This will give the industry enough flexibility to manage and improve quality on its own. Advances in machine learning, big data, and other Pharma 4.0 technologies that can measure and analyze processes in real time will further encourage performance-based regulation.

EMERGING TECHNOLOGIES

Yu talked about improving quality through PAT[3] and continuous manufacturing. Both will help with the move toward Six Sigma. A quality by design (QbD) approach and willingness to embrace new technology are also necessary.

The impact of Industry 4.0, which is based on cyber-physical systems (linking real objects with information-processing/virtual objects and processes via information networks such as the internet), will gradually affect pharma manufacturing in personalized medicine, artificial intelligence, and other areas. "It is coming," he said.

"There are many new answers we have to face with emerging technology but I'm very pleased with the progress we are making," Yu observed.

—continued on page 10

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QUALITY BY DESIGN

QbD is a systematic approach that emphasizes product and process understanding and process control based on sound science and quality risk management. QbD is another step on the path to Six Sigma quality. Tools for QbD include prior knowledge, risk assessment, design of experiments (DOE) and data analysis, and PAT tools.

Yu explained that QbD objectives are:

- To achieve meaningful product quality specifications that are based on assuring clinical performance
- To increase process capability and reduce product variability and defects by enhancing product and process design, understanding, and control
- To increase product development and manufacturing efficiencies
- To enhance post-approval change management[3]

Yu compared quality by testing (QbT) and QbD: QbT has acceptance criteria based on data from one or more batches; testing must be done before they can be released. QbD has acceptance criteria based on clinical performance; testing may not be necessary to release batches.

It is not enough to comply with the FDA to achieve total quality, however. "We need to decouple acceptance criteria from process variability," Yu noted.

CONTINUOUS IMPROVEMENT AND OPERATIONAL EXCELLENCE

Citing the McKinsey & Company book *Flawless: From Measuring Failure to Building Quality Robustness in Pharma*, Yu discussed "the challenge of shifting mindsets across industry that has focused predominantly on compliance rather than on truly knowing the root causes and effects on quality issues."[5]

He defined a culture of quality as an environment in which employees not only follow quality guidelines but also consistently see others taking quality-focused actions, hear others talking about quality, and feel quality all around them. The four essentials for quality are:

- Maintaining a leadership emphasis on quality
- Ensuring message credibility
- Encouraging peer involvement
- Increasing employee ownership and empowerment

CONCLUSION

Yu said that consumers and patients deserve Six Sigma quality products with minimal risks of shortages or recalls. The pharma industry can get there by following the five steps discussed in his presentation:

- The market observes and rewards quality
- Regulatory quality oversight becomes performance-based, not management-based
- Pharma develops and adopts emerging technologies
- Pharma adopts pharmaceutical QbD
- Development of continuous improvement and operational excellence

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How Global Consortia Are Advancing CM

Douglas B. Hausner

A group of global consortia has given new meaning to the term "collaboration" in the pharma industry. Populated by academia and industry, and increasingly governments and regulators, consortia work together to develop and share advanced manufacturing technology.

Douglas B. Hausner, PhD, Associate Director of the Rutgers University/C-SOPS consortium, talked about consortia's contributions to the development of continuous manufacturing (CM) technology during the opening plenary session at the 2018 ISPE Continuous Manufacturing Workshop.

Consortia are already making a significant contribution to pharma technology, he noted. "Most of this is not about the future—it is about where we are and where we are going," Hausner said.

HISTORY OF CONSORTIA

All consortia interact and collaborate with industrial sponsors and share information with each other. "It is a community of practice, an attempt to harmonize our approach." Or, for a more colorful take, Hausner suggested, academic consortia are "a sandbox where new tech is incubated with adopters, vendors, regulators, and students."

One example of a consortium that helped develop CM solid-dose technology is C-SOPS, a consortium that included participation by early adopters Vertex, Janssen, and Lilly. The C-SOPS team was involved in the Prezista CM process development, the first CM approval for batch to continuous. C-SOPS has also conducted work for the FDA and other major pharmaceutical companies. Other projects are underway.

High visibility for a consortium like C-SOPS is very helpful since it allows the development to be seen, and lets regulators interact and ask questions; this can help to move the technology along more quickly, he noted.

TRENDS AND FUTURE DIRECTION

International collaboration is the focus of the consortia model, and consortia are seeing government investment by EU nations and now by the United States. (See the sidebar for background on some of the more active consortia.) Academia is working as development partners on emerging technology for manufacturers.

—continued on page 12

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—continued from page 10

As activity has expanded, so has the interaction both directly and indirectly with regulators, Hausner noted.

Look for more interactions among consortia, international collaboration, and dialogue with regulators on advanced manufacturing technology, Hausner predicted. Continuous bio will be the next area of emphasis, and integration of advanced pharma manufacturing with the Internet of Things and Industry 4.0 are coming trends. Consortia are also looking to move to an advanced manufacturing model that could adapt to other advanced manufacturing processes beyond CM.

CURRENT CONSORTIA

Hausner gave a brief overview of some of the most active consortia:

C-SOPS (Engineering Research Center for Structured Organic Particulate Systems)
https://www.csops.org/

- Established 2006
- Headquarters: Rutgers University, with partner schools: Purdue University, New Jersey Institute of Technology, and University of Puerto Rico at Mayagüez
- Focus on solid dose/direct compression
- Spinoff company: Integra Continuous Manufacturing Systems
- Participant in commercial development activities: Prezista

Novartis–MIT Center for Continuous Manufacturing
https://novartis-mit.mit.edu/

- Established 2008
- Two-party partnership: Novartis and MIT
- Focus on end-to-end CM approach
- Spinoff company: CONTINUUS

CPAC (Center for Process Analysis & Control)
http://cpac.apl.washington.edu/

- Established 1984
- Center at University of Washington
- Focus on PAT and process control
- Pharma is one of many focus industries

CMAC Future Manufacturing Research Hub
https://www.cmac.ac.uk/

- Established 2011 in the United Kingdom
- Focus on API and crystallization
- ISPE FOYA winner
- University of Strathclyde is the hub; British partner universities are Bath, Cambridge, Imperial, Leeds, Loughborough, and Sheffield
- Active government funding support

SSPC (Synthesis and Solid State Pharmaceutical Centre)
https://www.sspc.ie/

- Established 2013 in Ireland
- Broad focus on API, crystallization, solid dose
- Headquartered at University of Limerick; seven schools total

RCPE (Research Center Pharmaceutical Engineering)
http://www.rcpe.at/en/home-en/

- Established 2008 in Austria
- Focus on end to extrusion
- University of Graz is a shareholder
- Spinoff companies: five

PSSRC (Pharmaceutical Solid State Research Cluster)
http://www.pssrc.org/

- Established 2018
- Headquarters: University of Ghent (Belgium); participants include researchers from the universities of Cambridge (United Kingdom), Copenhagen (Denmark), Düsseldorf (Germany), Graz (Austria), Helsinki (Finland), Leuven (Belgium), Lille (France), Lisbon (Portugal), Ljubljana (Slovenia), and Otago (New Zealand).
- Focus on solid dispersions, solid dose

NPTE (New Pharmaceutical Technology and Engineering Institute)
http://sinseizai.com/english/index.html

- Based in Japan
- Focus is broad, particle technology
- Joint industry-academia group, industry driven

—continued from page 10

He closed his presentation by listing future directions for continuous manufacturing:

- Understand and control raw materials
- Develop modular and flexible manufacturing platforms
- Strengthen collaborations among industry, regulatory agencies, and academia
- Evolve regulatory oversight standards

—Susan Sandler, Editorial Director

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FROM CONCEPTS TO REALITY

Meet Young Professional Richi Sethi

Richi Sethi, a Design Engineer for Biocon, India's largest biopharma company, knows that process engineering involves constant adaptation. "We have to be very dynamic," she explained. "People want to try new things, and we have to be on the forefront."

Sethi took her own advice recently and responded enthusiastically when introduced to ISPE. "A colleague introduced me to Caroline Rocks (Senior Process Engineer, Global Engineering, AbbVie, and incoming Director on the ISPE International Board). She provided a very good initiation into an organization with which I look forward to getting more involved."

This willingness to grow reflects Sethi's approach to her vocation. While she's currently working as a design engineer, Sethi remarked that she'd "be more than glad to move onto a more managerial role" in the future. "I would also like to be more actively involved in the ISPE India Affiliate and share my experience and learnings in the industry with others who are new to it," she added.

Sethi, who holds a master's degree in biomedical engineering from the prestigious Indian Institute of Technology (IIT) Bombay, was "fascinated by science" from an early age, although engineering was not her original plan: She wanted to be a doctor. An amusing anecdote illustrates her turning point.

"My mother was unwell and needed to go to the hospital. The closest one was a general hospital—not very privileged. Patients all around us were bleeding, vomiting. 'My God!' I thought. I left my mother in the waiting room and ran outside to get some fresh air. Moments later, I fainted. Finally, after 15 minutes, people managed to get me back inside. We were there to care for my mother, but I was overwhelmed. I told her, 'I definitely cannot be a doctor.' And that was the end of it."

While her medical aspirations may have evaporated that day in the hospital, she began a four-year bachelor of engineering program at Panjab University, studying a wide range of subjects including tissue culture, bioprocess design, cell culture, and bionanotechnology. That led directly to her two-year master's program at IIT, where she specialized in nanotechnology and biomedical technology. During the second year of the program, however, Sethi made another career pivot.

"In my second-year project phase, I realized nanotech research was not my cup of tea, not only because I grew less interested in the research angle, but also since this field lacked 'Vitamin M' (money) and a proper facility—at least in India at that time. I had a strong desire to apply what I'd learned [in biomedical technology] and wanted to be on the front lines."

Near the end of her postgraduate study she learned of an opportunity at Biocon. "Biocon was looking for people with an engineering mind who could solve real-life problems," she said. Sethi described her start at the company as an ideal fit, but challenging nonetheless. "It was a totally different ball game—out of college and into the industry. Fortunately, I had a mentor. He's my boss now. He made the transition very smooth for me."

As a Biocon process engineer and assistant manager, Sethi works closely with her department to go from concepts to reality. "We lead the way. We build the processes for how to manufacture a drug at production scale using GMP. We need to build the facility itself, ensuring that it meets GMP qualifications. We have to consider market demands as well as regulatory requirements, and how our facility can respond to them."

Asked to recall a particularly important moment in her time at Biocon, Sethi recalled an intense, 10-day FDA audit focused on the manufacture of biosimilar mAbs. A capacity expansion was underway, and the project was being executed by her department. At the end of the audit, the drug earned FDA approval, and her team was "on top of the world." She said that "years of planning, design, and execution gave rise to the facility as it stands today. It gives a sense of achievement and satisfaction to see the facility being attested at par with the best in the world by none other than US FDA—even greater so because we were the first to get there in the entire world. Our hard work paid off. Our process worked, and that brought a concept to reality at production scale. We were joyful, and this served as a morale booster to aim for and attain greater heights."

Sethi is excited about the growth of the pharma industry in India. Asked about the upcoming India Conference in Mumbai (15–17 October 2018), she commented, "It's a great initiative to ensure

quality and compliance to accepted regulatory standards. India, as an actively growing manufacturer of pharmaceuticals, is an ideal choice for this conference."

Sethi's generation of engineers work in an exciting era of rapid, transformational change. "Over the past 10 years we've gone from manual systems with operators to an increasingly automated production system," she said. "Now when I talk to vendors, everything is automated. We want minimal operator intervention." Sethi described this shift as a "dynamic" change with which "efficiencies have gone up, downtime has decreased, and yield has increased." She explained that with less operator intervention and fewer hands on the process, there has been a notable reduction in sterility issues and batch losses due to error. "There is absolutely no human intervention" in many aspects of the process, Sethi remarked.

Of course, with this level of automation, the importance of good up-front design is emphasized. "We must have a detailed qualifications procedure. Each and every sequence has to be right at the beginning. Intense testing early on pays off at the end, and ultimately, that's better for patients."

The patient benefits afforded by these more efficient manufacturing systems are multifaceted, Sethi explained. "Now, with the ease of automation, we can modify batches by adjusting settings and alarms. It's an aspect of machine learning—the system is so smart." Automation is transforming all aspects of manufacturing—right down to automated hoists and other equipment in facilities, she continued.

> Our hard work paid off. Our process worked, and that brought a concept to reality at production scale.

That kind of dynamism—the ability and willingness to adapt to change—seems inborn in Sethi. From that moment in the hospital when she realized that her path led not to medicine but to engineering, she's made a career out of responding to change. She's found a way to bring intellectual curiosity and a passion for science to the front lines of the pharmaceutical industry.

—Paul J. Cumbo, MLitt, MS

AERATION EQUIPMENT
in Aerobic Fermentation Processes

Travis McGarrah


Travis McGarrah

A wide range of pharmaceutical products is produced using two complex fermentation processes. Anaerobic fermentation takes place in the absence of oxygen, and aerobic fermentation requires oxygen, supplied via blower and compressor systems, to yield microorganisms and produce the desired product. This article examines the role of aeration equipment in aerobic fermentation, considerations when designing aeration systems, and compressor features that contribute to reliable plant production.

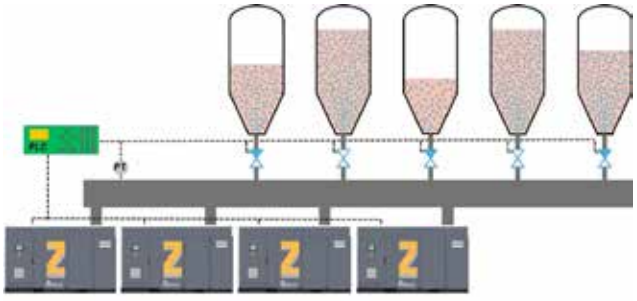
COMPRESSORS IN AEROBIC FERMENTATION

To begin, we will identify the differences between a blower, single-stage compressor, and typical two-stage screw compressor, and discuss their uses in fermentation applications.

A blower is a machine that supplies high volumes of air at pressures typically under 20 psi(g).* A compressor produces air at higher pressures and typically at lower volume. Single-stage screw compressors are designed to operate between 25 and 60 psi(g); two-stage compressors are typically designed for pressures above 100 psi(g). Large-scale production of pharmaceuticals is carried out in deep fermentation tanks that require pressures between 25 and 45 psi(g).

It is not uncommon for the air supply in fermenters to be normal plant or instrument air that has been compressed to approximately 100 psi(g) for use in other areas of the plant. The actual pressure required to aerate fermentation tanks is usually much lower, however—roughly equal to the pressure of the liquid column height in the tank. It may seem convenient to use instrument air that is already available, but it can lead to unintended electricity costs. For example, a tank that is 60 feet deep and filled with liquid that has a density similar to water will only require air at ~25 psi(g) to overcome the tank liquid pressure.

Figure 1: Aerobic fermentation system with a common header and multiple compressors



* Pounds per square inch (gauge): Air pressure measured relative to ambient atmospheric pressure.

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Table A: Energy costs for 200-cfm airflow at varying pressures

Pressure, psi(g)	Flow, cfm	Power, kilowatts	Energy cost per year*
25	200	26	$20,820
45	200	37	$29,471
100	200	53	$42,792

*Assuming 8,000 hours per year at $0.10 per kilowatt-hour

We recommend having aeration equipment that is dedicated to the fermentation process and sized appropriately for process needs. Energy savings from supplying only the required air pressure can be quite significant in continuous applications.

Why is this important? The electrical cost for operating compressor equipment continuously can be quite high. Compressing air to 100 psi and then throttling it down to 25 psi is a large and unnecessary expenditure of energy. In general, we recommend having aeration equipment that is dedicated to the fermentation process and sized appropriately for process needs. Table A shows the energy required to produce air at these pressures vs. instrument air that was compressed to 100 psi for a flow of 200 cubic feet per minute (cfm).

As Table A shows, energy savings from supplying only the required air pressure can be quite significant in continuous applications. The cost for a single-stage, oil-free compressor producing 200 cfm is in the range of $50,000 for a complete package, including filtration and an aftercooler (heat exchanger). Depending on actual energy costs and operating hours, simple payback of a dedicated single-stage compressor would be 3–5 years. This could potentially be reduced even further if a smaller air compressor were purchased.

The compressor system supplies air to the fermentation tank using an aeration device such as a sparger, perforated tubing, or diffuser system, typically installed at the bottom of the tank to allow oxygen to disperse as it rises through the liquid. Additional agitators may be used to distribute air bubbles evenly throughout the liquid in the tank.

Oxygen content is monitored with dissolved oxygen (DO) probes, since the level of DO required varies throughout the fermentation process, depending on desired growth or reaction rates. To meet this variable demand, the compressor system must able to produce varied amounts of airflow. This can be achieved by using multiple units that are turned on or off as needed, load/unload control, or variable-frequency drives (VFDs) to control compressor operating speeds. The VFD approach saves energy, but more importantly, allows for the tightest control of DO levels. This not only ensures that the required oxygen demand is always met, but it can also improve production yields by providing the ideal oxygen level for all process steps.

To achieve the most functional outcome, it is important to select a compressor system that can meet the maximum and minimum expected flow demand without any gaps between the two. Screw compressors have a turndown ratio—the ratio of maximum to minimum flow—that is approximately 3:1 when run with a VFD. Drastic variations in flow demand may require compressor systems that utilize several smaller machines, while more constant demand can be handled with fewer or even one machine. A fermentation system with a common header and multiple compressors is shown in Figure 1.

DO control in fermentation tanks is managed with a closed proportional–integral–derivative (PID) loop that has an output to control the total required flow from the compressor system. The standard method is to have the header system supplied with a fixed pressure setpoint, with valves for each fermentation tank controlled for respective vs. required DO levels. More advanced control functions based on system flow and flow to each tank can also be implemented to reduce header pressure and energy consumption.

DESIGNING AERATION SYSTEMS

An often-overlooked consideration in aeration systems is the plant design itself. As discussed, it is common practice for multiple fermenters to run from a common "header" pipe that supplies air to each tank. Although this is acceptable, liquid levels may vary from one tank to the next. When this is the case, the compressor system will have to create enough pressure to operate the deepest tanks, even though the others require less pressure when aerated individually. This can result in unnecessary energy costs that could have been avoided by separating systems based on expected liquid levels. To combat unnecessary energy use, tanks with roughly the same system pressure requirements should be on a common header system; tanks with large variable pressure needs should have dedicated aeration equipment.

There are several factors to consider when justifying the extra equipment required for this setup. The required flow to each tank and the pressure difference between tanks must be significant enough to have a reasonable payback period. Considering the example given earlier, if we have one tank that requires 200 cfm at only 25 psi(g) and another that requires 200 cfm at 45 psi(g), then a separate sys-

tem would save ~$9,000 per year in energy. This would require an additional compressor whose cost is ~$50,000, yielding a payback of < 6 years. Factoring in the extra maintenance costs of the second compressor, equal to 3% of the capital cost per year, gives a slightly longer payback of ~6.5 years.

FEATURES FOR RELIABLE OPERATION

The compressor equipment should have several features to meet fermentation process requirements.

Equipment reliability: A backup compressor for each header system should always be in place, since unreliable equipment can lead to multiple machines down and a system unable to meet oxygen demands. Although nonfunctioning equipment is most often the result of extreme conditions or unexpected circumstances, the cost of unusable end product(s) may be greater than the compressor equipment investment.

Energy efficiency: As we have seen, single-stage equipment designed for the lower operating pressures of fermentation tanks can greatly reduce operating costs. VFD equipment further improves this efficiency to accommodate variable oxygen demands at various stages of fermentation.

Controllability: A supervisory control and data acquisition (SCADA) or distributed control (DCS) system in the plant should be able to operate compressor equipment seamlessly, varying the speed as the system requires. Compressors that utilize integrated controls can perform this function while they monitor critical parameters, making sure the equipment is protected while being controlled remotely.

CONCLUSION

In summary, aeration is a critical element for producing pharmaceuticals via aerobic fermentation processes. Consideration should be given to the system layout, control scheme, and compressor equipment to ensure that fermentation tanks always have a reliable source of air to meet the oxygen demand. Following these guidelines will ultimately lead to the smooth, reliable plant production at the lowest possible operational cost.

About the Author

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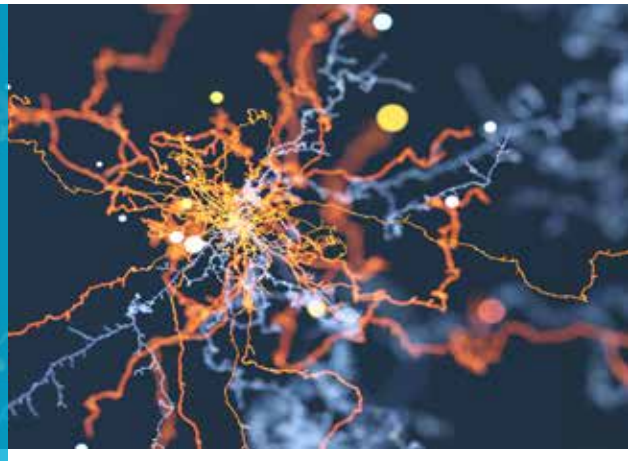
A CULTURE OF INNOVATION



A corporate culture that supports creative thinking can help pave a road to innovation. Free people from fear and encourage them to do their best and you'll have an environment for accomplishing great things, according to George Scangos, who has led Biogen and other pharma companies. In a recent conversation with PE, Scangos shared his approach to building a culture of innovation and provided updates about his latest endeavor, Vir Biotechnology, whose mission is the war on infectious disease.

Innovation is a goal of pharmaceutical development, but without a culture to support it, innovation may be elusive. Develop a good culture and you lay the groundwork for good people to do their best work, which will bring new ideas forward. This approach is one that George A. Scangos, PhD, has followed in the cultures he has built or contributed to in leadership roles at organizations including Biogen, Exelixis, Inc., and Bayer Biotechnology.

His latest venture—which takes innovation in pharma development to new ground—may sound more like an **ad**venture: a biotech company on a quest to treat and even vanquish infectious disease, with an approach that eschews traditional development models for something very different. Vir Biotechnology, Inc., headquartered in San Francisco, California, is "using breakthroughs in immune programming to manipulate pathogen-host interactions. The company will take a multi-program, multi-platform approach to applying these breakthroughs, guided by rigorous science and driven by medical need."[1]

Pharmaceutical Engineering recently talked with Scangos about his philosophy toward corporate culture, how it contributes to an environment that supports innovation, and about the exciting developments at Vir.

CULTURE RULES

"Culture is huge for any company, not just pharma companies," Scangos said. "It impacts productivity, the view of the people toward the company and themselves, and whether they are willing to go the extra mile. People should feel good about the company, they should feel that it is doing something worthwhile, that they are doing something worthwhile, and that they are working with colleagues who value them."

Creating and sustaining a positive culture will support an innovative environment. "Innovation is critical to the industry," Scangos said, noting that most innovative ideas may at first be considered farfetched. "You need to be able to distinguish ideas with merit from those that don't have merit. Leadership needs to be able to do this." But leaders need to do this in a manner that means people are not afraid to put forth innovative ideas.

Scangos saw the effects of what he called "destructive elements" of culture in some of the organizations he has worked with. Key among them: an environment in which employees are afraid to make a mistake. "Fear of making mistakes is a natural human fear but if you are not making mistakes, you are making safe decisions. You can't make a great organization by making all safe decisions."

Risk taking is an important part of the work that pharma companies do, and people should be encouraged to take responsible risks, he said. "If you take a calculated, thoughtful risk and it doesn't work, that should be celebrated—not punished. Part of what distinguishes really great companies is that they can distinguish between really good risks that did not work out and bad decision-making that did not work out."

HIERARCHY AND CULTURE

Other dangers can be hierarchy and bureaucracy. Process and some organizational structure are important and necessary to run a business, especially one that operates in a regulated industry, he noted. And the type of pharma company can have an impact on the amount of organizational structure that is needed: for instance, a GMP manufacturing plant making commercial product requires


George Scangos

standard protocols rigidly applied, while process science organizations have room for the flexibility to try new things.

But too much hierarchy and bureaucracy can sometimes let people lose sight of the fact that everyone in the organization has a voice. "We all have a job to do, a skill set, families, and lives outside of the company. Everyone needs to be treated with respect, from the janitor to the CEO—we're all just people." He acknowledged that "it's easy to say that as a CEO, harder to say when you are further down [in the hierarchy], but people should not be afraid to speak up. That kind of candor is really important."

The threat of bureaucracy that grows tends to happen in the middle levels of a company, demonstrated by proliferating committees and meetings that may not be needed. "People can spend too much time sitting in meetings and not enough time actually working." Balancing the need for structure with the need to make sure people have time to do productive work is important. This can be more challenging in a larger organization, since they need more controls and organizational structure.

A related issue is productivity, which bureaucracy can impact. "People need to value their own time and value themselves. Ask yourself, what are you doing hour to hour and day to day to make the best use of your time? I remember earlier in my career that there were times when I thought something was a waste of time, that I could be doing something productive or fun instead. People need to think in those terms—is what you are doing really the best use of your time and your talent? If not, do something different."

Scangos felt that there was some success in making changes with these cultural elements during his time at Biogen, but he emphasized that the care and feeding of culture is a never-ending endeavor. "Changing culture isn't something you do and it's done. Culture is something you do and keep doing, and you work on it over time."

MAKING CHANGE HAPPEN

Communication is another important component of a good culture. To illustrate this, Scangos relayed the story about adding video to his quarterly CEO calls with Biogen employees. Initially these were voice-only calls, and the IT staff encouraged him to try a video option so employees could see him. However, the first attempt resulted in a crash with many employees logging in to view the call. "People said, 'Those IT guys are going to get in trouble now. What are you going to do?'" What he did was support another attempt at implementing video on the next call. "The video worked like a charm, and during the call I thanked the IT people for going out on a limb and trying to make things better." The message conveyed—that it was OK to try something new and not have it work, without fearing repercussions—is powerful, he noted.

Changing an existing culture can be more difficult than establishing one in a start-up such as Vir, Scangos said. "In large pharma companies with many employees, it is hard to deviate from the mean. A start-up is small, and it can and does deviate from the mean—which could be better or worse. Biotech companies are self-selecting aggregates of people. Given a sound strategy, financial strength, and talented staff, this will attract more good and like-minded people. In a company like Vir, we have the opportunity to start out with really high quality and build the culture as we want it." But a new culture's organization still requires care and feeding. "Culture

Managing Culture When You're Not the CEO

You don't have to be the CEO to improve the culture—and innovation and productivity—around you. If you're managing a division or a department, you can affect three areas of culture: in your department or division, managing up (your relationship with your supervisor is a cultural relationship), and managing your peers.

For mid-level managers, the issues are no different from those faced by a CEO, Scangos said. "You must manage people, treat them well, and treat them with respect. Strike a balance between not overmanaging and paying enough attention to be sure they are doing their jobs well; if they are and they need help with an issue, get them the help they need. If they are not doing their jobs well, then you need to deal with that."

"Managing up," or managing your direct supervisor, is the second place where a mid-level manager can affect culture. You may not think this is an important component, and Scangos acknowledged that he did not think so either at a point earlier in his career. "My view was that I should do my job as well as I could, do it really well, go home, and feel like I'd done as well as I could. If I did well, the company would recognize and reward me appropriately, and if I didn't, I'd suffer the consequences."

A good relationship with your boss is also part of succeeding at work. Scangos advised speaking candidly, but warned "not all bosses tolerate that, so you need to be a little careful. Figure out how to best deal with your boss. In most cases, supervisors of people appreciate if you point out something that can help them do their job better and make them look better. No one is truly resistant to good ideas—but they may resist how those ideas are broached."

Finally, mid-level management is also about cultural interactions among peers. Beware the insecurity that can come as individuals rise in the organization; for instance, some may feel challenged by younger peers who are moving up. Building relationships with your peers is a part of managing the culture around you.

What can you do if the culture above you does not align with the culture you favor? "All you can do is make sure that the sphere of influence you have has the culture that is most productive, and your group does its work as well as it can," Scangos said. Politics, competition for advancement, even bad behavior happen. Despite these challenges, "do your job as well as you can, treat your people well, and have good relationships with your boss and with your peers."

establishes itself if you don't work at it. Even in a start-up it takes effort to make it one that you like and is productive. It's easier to start from scratch and build it."

VIR'S CULTURE OF INNOVATION

Starting from scratch and building a culture—along with a different approach to developing pharma solutions—is part of Scangos's current role as CEO and Director at Vir. The company launched in January 2017 with the goal of developing drugs to fight and prevent a range of infectious disease. Hepatitis B, tuberculosis, and influenza are among its initial targets.[1]

At the time of its launch, Vir defined its approach as a new one in biotech, using multiple platforms and a lack of a technology-specific approach, with initial funding support from ARCH Venture Partners and the Bill & Melinda Gates Foundation, among other sources. ARCH Venture Partners' co-founder Robert Nelsen developed the concept for Vir and led its formation.[1] Since the launch, Vir has built a pipeline through acquisition and partnerships, including acquiring Humabs BioMed SA, Bellinzona, Switzerland, and initiating partnerships with Alnylam Pharmaceuticals, Inc., and Visterra, Inc., and leading academic research institutions including Harvard and Stanford Universities.[2] The most recent addition is an agreement to partner with Brii Biosciences, a start-up in China[3] that has expertise and financial backing, Scangos said.

Vir's different approach—and its mission—are what appealed to Scangos. "When I left Biogen, I really did not know what I wanted to do next or if in fact I wanted to do anything. Vir intrigued me. Bob Nelsen, the founding VC (venture capitalist), had the vision and saw the opportunity. There is such a need for better treatment for viral, bacterial, fungal—all infectious disease. A lot of pharma companies have decreased their work in this area or left this altogether. Many start-ups are underfunded and narrowly focused. So there was an opportunity for a company with a big vision and solid funding to attract really good people, and to make a difference. The vision and incredible need attracted me.

"I saw this as an opportunity to make a difference in the lives of tens or hundreds of millions," Scangos said. "This will be the last thing I will do in my career. The opportunity to make lives better for millions of people is a great last endeavor."

Vir's approach does not focus on any one physiology or technology, but on the broad war against infectious diseases. "A lot of startups start around a technology and disease X; you form a company, work

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on disease X, and then figure out what else the technology is good for. I would not have gone to a startup like that."

Vir's approach of using science, biology, and immunology advances to create novel and new approaches to battling infectious disease will help to arrest hepatitis B, tuberculosis, and even the flu, which kills thousands. "We need to do better" in fighting these diseases, Scangos said. Antibiotic-resistant bacteria are another growing challenge and those are also on Vir's hit list.

There is "incredibly powerful new technology to interrogate cells and populations of cells to determine changes that would cause them to be refractory to infection. Look at the host side of the equation, to augment the immune system or enhance it, not just looking at bacteria. There's a lot of insight already in how to do this, and more is coming every day. Not all antibodies are created equal: How they work, how to manipulate them to maximize their effectiveness, is moving forward rapidly. We can use this information to make the next generation of compounds with a reasonable chance of efficaciousness" to fight disease in a way that the previous generation could not. With Vir's vision and the state of science, "there is a reasonable chance of succeeding."

"Vir started with the strategy of wanting to cure or treat serious infectious disease. So we assembled what we think is the best set of tools to go after these diseases. We have a pretty diverse array of technology: CMV (cytomegalovirus) platform for vaccine vector, siRNA (small interfering RNA) collaboration with Alnylam. Those aren't random. If we're going to approach these diseases, we need a set of tools with a serious chance of success. Hep B is a tough, clever virus, effective at countering the immune system. Almost certainly an effective treatment will require a combination product. We will develop our own compounds and may combine them with compounds from other companies—it's not like we have all the answers."

Where does culture come into what Vir is building? It may be just another tool in the Vir toolkit, as Vir is already partnering with multiple external companies and organizations; relationship building is key to the work that is underway.

Scangos cited the acquisition of Humabs as an example. "They are really good at what they do but we must pay attention to them and make sure they don't feel distant from us. Collaborations with other biotech companies, with the Gates Foundation—we need to spend time on those relationships." Ultimately, these partnerships "bring in technology and expertise that we're way better off for [having]." This will continue to help as multiple manufacturing modes will be brought forward, including work with viral factors, antibodies, and siRNA. "We need more expertise in process development and manufacturing than most companies of our size."

That so many diseases are problems outside of western Europe, the United States, and Japan presents both an opportunity and a challenge, especially in dealing with regulatory agencies around the world. "If we have something to treat hep B, TB, or prevent flu deaths—most governments should be interested in getting this to their people." One recent step forward: Vir's Humabs subsidiary has, in collaboration with the US National Institutes of Health, produced a single monoclonal antibody called mAb114[4] to treat Ebola virus disease. This experimental treatment is being administered to Ebola patients in the current outbreak in the Congo as part of a first-in-human trial.

As to whether Vir's work will impact how other pharmaceutical companies view fighting infectious disease, Scangos noted that those companies are under different constraints from Vir, with global manufacturing and complex legal issues. "We have a freedom that they don't have to focus on innovative science and medicine." Vir does not have the depth of expertise in commercial manufacturing so "we have to do what we do well. We'll have to work with partners to make products available around the world. At the right time, we will establish some of those partnerships."

For now, Vir's focus is on "generating data, moving programs forward, demonstrating some value and potential. At some point we will be able to combine what we do well with some of the larger companies."

The Vir approach agnostically embraces new technologies with the potential for impact. "For Vir, we have our own R&D but are aggressively looking on the outside for interesting new things. As things change and new technology emerges I would hope we will be on top of them and get access to them.

"Vir is still a relatively new start-up. We have some exciting programs with meaningful potential, and we will be bringing a number of things into clinical development over the next months. We hope to get some human data in the relatively near future. We're excited—we're starting a number of research programs as well. We're in a great period at Vir. No start-up goes from start to success in a straight line, but we've got the resources and people to have some staying power."

—Andre Walker, BSChEng, CPIP, and Susan Sandler,
Editorial Director, *Pharmaceutical Engineering*

About the author

Andre Walker is a consultant with over 30 years of experience providing engineering and technical support for manufacturers of biopharmaceuticals, medical devices, and consumer products. He has led teams supporting every aspect of manufacturing operations including facilities, utilities, maintenance, metrology, technical support, label and pack, qualification, and process validation. A Past Chair of ISPE's Board of Directors, he is currently the 2018 Biopharmaceutical Manufacturing Conference Chair.

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SINGAPORE
Biopharm's Global Hub

Our May-June cover story on the rise of biopharmaceutical manufacturing in Asia noted that "Biopharmaceuticals are booming … buoyed by enhanced regulations, an influx of venture capital, a culture of innovation, and government support."[1] While that report focused principally on China, Indonesia, and South Korea, in this issue we look at another key player in the region: Singapore.

In June 2000, Singapore launched a national initiative to become a global hub for biomedical sciences (BMS). Within 15 years, the island nation had been named one of the world's most innovative countries, boasting a robust industrial ecosystem that fuels drug development, clinical studies, manufacturing, and health care delivery.[2–4] Singapore has also become one of the most prosperous nations on the planet, with a per capita GDP well above most developed countries, a low unemployment rate, a AAA credit rating,[5] and the number-one ranking on the World Economic Forum's Global Enabling Trade Report 2016.[6]

Pharmaceutical Engineering's 2016 profile of the ISPE Singapore Affiliate described "a global commerce, finance, and transportation hub" with a "world-class" pharmaceutical and biotechnology industry.[7] The pharmaceutical sector's manufacturing output has tripled since then,[8] highlighting the country's rapid development.

In this article, *Pharmaceutical Engineering* garners the perspectives of four regional industry experts: ISPE Singapore Affiliate President Joseph Micsko, Affiliate Vice President Shanshan Liu, Past Affiliate President Pierre Winnepenninckx, and ISPE International Board Chair Tim Howard.

MULTINATIONAL PLAYERS

Micsko, Operations Director, PSC Biotech, described the country's current biopharmaceutical landscape as a geographically consolidated mix of multinational companies, including AbbVie, Alcon, Amgen, GlaxoSmithKline, Kaneka, Lonza, Merck Sharp & Dohme (MSD), Mundipharma, Novartis, Pfizer, Roche, Sanofi, and Shire. Many are housed in the city's Tuas Biomedical Park, a collection of manufacturing facilities in a 300-hectare footprint, and the nearby Biopolis, a complex of seven biomedical research buildings completed in 2004. Despite the dense development, Micsko remarked that "there have been no major FDA or EU regulatory observations" to date.

Nigel Cheong, Head, Biomedical Sciences, Singapore Economic Development Board (EDB), offered a keynote presentation on the Singapore biopharmaceutical industry at the August 2017 ISPE Singapore Affiliate Conference.[9] It described the country as "a leading bio-cluster in Asia," with more than 50 manufacturing plants employing over 18,000; more than 50 R&D centers and over 2,000 private sector researchers; and more than 30 leading regional headquarters, with over 7,600 employees.

The presentation also highlighted some recent "first-in-Asia" biologics investments in Singapore, including Amgen's introduction of the world's first commercial-scale "next-generation" single-use facility, Novartis's state-of-the-art biotech production for large- and small-scale volumes as well as its technological competence center, and AbbVie's campus for combined biologics and small-molecule production.

Finally, the keynote outlined an "ecosystem of suppliers, solution providers, research institutes and academia" that creates an environment conducive to growth in the region's biopharmaceutical industry. This includes elements that provide integrated analytics technology such as process control systems, sensor systems, and process analytics. Bioprocess technology and capabilities both upstream and downstream complete the "ecosystem." On the research and academic front, there are multiple elements of the Singapore A*Star—the Agency for Science, Technology, and Research—along with institutions such as Nanyang Technological University, Nanyang Polytechnic, the National University of Singapore, the Singapore University of Technology and Design, and the Singapore Institute of Technology.

As of May 2018, biopharma's growth has been notable. According to the EDB, biomedical manufacturing in Singapore had grown 17.7% from the previous year. Within the cluster, the pharmaceutical segment grew 19.2%.[10]

AN IMPORTED INDUSTRY

The city's pharmaceutical manufacturing complex has been growing since 1972, when GSK established an amoxicillin facility there.[11] "You could say the 'pharma boom' came in 2006 and 2007, with much biological investment," said Winnepenninckx, CEO and Founder of No Deviation Pte, Ltd. He came to Singapore in 2008 as a process engineer working on a new vaccine facility with Belgium-based GlaxoSmithKline (GSK).

Affiliate Vice President Liu, former Senior Technical Expert, Global Engineering, with Novartis Singapore Pharma Manufacturing Pte, Ltd., noted that Singapore's pharmaceutical industry started with an imported foundation. "Singapore is very unique, with much knowledge from Europe and the USA," she said. "Today, Singapore is developing its own R&D."

This had some implicit advantages, as the industry was "mostly already mature, with pilots and R&D that came from somewhere else. Singapore was on the 'receiving side' of the knowledge," Winnepenninckx said. Liu noted, however, that the island nation is seeking more industrial autonomy. "We are building on a solid foundation, but this can hamper innovation on some levels. We need to focus on our own local development; Singapore wants to build its own industry," she said.

Despite its roster of big industry names, "Singapore is quite new on the whole for biopharma industry, and this brings some challenges," Micsko said. Efforts to develop the workforce have included training programs in North America and Europe. "And Singapore is a training hub, where expats come and train the local workforce. But that's a double-edged sword. There's a desire to build up the local workforce, but you have largely expat leadership making key decisions for facilities here. The problem is that shifting away from expat leadership will lose some of that experience and expertise."

The path toward a more autonomous internal workforce is to use these programs to develop high-level local leaders, he said.

CHALLENGES AND OPPORTUNITIES

One challenge for Singapore is that "there are very few complete products here—although MSD has filling and packaging—and no substantial local market. Products produced locally are sent somewhere else in the world as part of the supply chain," Winnepenninckx said.

Another hurdle, the attrition of human resources, is an ongoing concern, he continued. The rapidly developing financial industry, for example, draws capable people out of the pharma sector. "Many manufacturing sites need manpower. Besides, the high cost of living doesn't help the situation."

The pharma sector's rapid technological innovations—artificial intelligence, machine learning, 3D printing—also raise concerns about the readiness of the country's young, conservative (i.e., risk-averse) workforce to embrace those changes. "We use risk-based approaches," and sometimes we're maybe a little more conservative than we need to be," Micsko said.

Singapore has several advantages that work in its favor. It was ranked ninth on *Forbe*'s 2018 "Best Countries for Business" list,[12] and second only to Hong Kong on the Heritage Foundation's 2018 "Index of Economic Freedom."[13] Micsko also emphasized the island nation's enviable position as the hub of Southeast Asia. "You can get anywhere within a two- to four-hour flight. It's easy to fly to Thailand, China, India; it's very accessible."

Quality of life is another asset, said Winnepenninckx. "It's very stable on several levels. There's a stability of politics here, sure. But you've also got to consider that we have no typhoons or earthquakes here … things that can be issues in other Asian countries. It's also a very stable climate, and there's not a lot of seasonal change."

This is a plus for manufacturers, he continued. "For example, while it's true that the humidity creates a high operating cost per square meter, this is offset by other factors." If companies build the right way on the front end (planning for humidity, for example) they'll be well positioned for efficient operations because there are fewer shifting elements. It's warm and humid, but that beats dealing with constantly shifting temperatures, or the natural disasters endemic to other parts of Asia. This is why despite the high cost of living, "There is a good pool of people from places like India and China who are attracted to Singapore. The population is very well educated," Winnepenninckx noted. Micsko also praised the country's determined young workforce. "People here like to work hard. Many operations run 24/7," he said.


Timothy Howard


ShanShan Liu


Joseph Micsko


Pierre Winnepenninckx

SMART CITY

BMS is a major pillar of the Singaporean economy, said Tim Howard, Vice President of Asia Operations for Commissioning Agents International. "The country has a keen interest in being a biotech leader. Singapore has invested in its workforce of the future through state-sponsored programs intended to establish a technically strong workforce for the Singapore biotech industry."

Winnepenninckx said, "It's a smart city. They've reduced the cost of production, implementing and promoting operational excellence. And it's all condensed in roughly 20 square kilometers." This creates some real operating efficiencies. There's a condensed pool of knowledge, which fosters a culture of communication and collaboration. The drawback is the previously mentioned competition for people, he explained. The Biopharmaceutical Manufacturers' Advisory Council has helped with agreements that prevent employee poaching among competing companies.

"The beauty is that Singapore is a part of PIC/S," he continued, referring to the Pharmaceutical Inspection Co-Operation Scheme.[14] "Mr. Meow Boon Hoe (Deputy Director, Overseas Audit/Senior GMP Auditor at Singapore Health Sciences Authority) is the 2018–2019 Chairman of PIC/S. This is a good marketing advantage from a

compliance perspective. And it's vital, given the need to export due to the lack of a local market. This is in contrast to somewhere like Thailand, which has 100 million customers in the country."

DAILY LIFE

And what about work-life balance? "Living here is very comfortable," Liu said. "We only have one season. It's clean. There are always opportunities, and teams are very international." She emphasized the range and variety of perspectives that come with the workforce diversity, a product of massive population growth from roughly four million people 10 years ago to around six million people projected for 2020. "You'll see 15 to 25 nationalities at a manufacturing site," Winnepenninckx noted.

The country's small size makes travel easy. "You can get from one side of the island to the other in an hour and 15 minutes. You don't need a car. You can take the train or a bus anywhere you need to go," Micsko said.

This condensed geography also creates challenges, however. "Space is extremely constrained," said Liu. (Interestingly, a substantial portion of the industrial space is dedicated to pharmaceuticals.) And although Singapore incinerates 100% of its waste and has no landfills, trash has become an issue; ash by-product is rapidly filling the nearby island designated for this purpose. This is just one example of the challenges facing a small island nation undergoing rapid industrial development.

AN OPEN ROAD TO THE FUTURE

Micsko is optimistic. "Singapore has a bright future. The government is looking for ways to bring in other big multinational players while investing in innovation with the local workforce and local universities." It's clear that Singapore will continue to be a key player, a formidable force in the global biopharmaceutical industry for years to come.

—Paul J. Cumbo, MLitt, MS

Singapore Affiliate: Continued Growth

Founded in 2000, the affiliate is the oldest in the Southeast Asia region. Tim Howard commented that "with respect to the APAC region, the Singapore ISPE Affiliate is one of the strongest and most active, on par with many of our affiliates and chapters in the US and EU."

The affiliate's growth in recent years has been substantial, Winnepenninckx added. "When I joined in 2012, we had maybe one or two events per year. We have gained a lot of momentum, to the point where we have around two events per month." Micsko, the current president, concurred. "Our growth is enthusiastic. I think we now have about 36 events per year. Maybe it might even be too many!"

To draw young professionals, the affiliate offers twice-monthly "Tech Tuesdays," which aim to develop and showcase local expertise rather than bringing in outside speakers. "We want to focus on our good local workforce—meaning both natives of Singapore and people from other countries who live here," Micsko said. "It's a brainstorming session. An hour in the classroom, sharing knowledge. We do a Facebook Live, which eventually we want to make more interactive. We've done six or seven of these, averaging about 25 people. We're starting to have broader representation among various industry players." In a recent brainstorming session with the Asia–Pacific Council in the Philippines, "we saw how other affiliates like Japan and the Philippines are integrating their young professionals."

The affiliate also seeks "a high synergy with other regional affiliates, like Thailand and Indonesia, with face-to-face events around six times per year," said Winnepenninckx. "We want to support the goals of the Asia–Pacific region. Ideally, we want to give back to the international community."

It seems the affiliate is on the right track. As Howard put it, "This is a highly successful, well-managed affiliate with an engaged population of volunteer members."

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EYE ON THE FUTURE

Janssen Expands Ireland Production Facility

Kyran Johnson and Jim Breen

Janssen is in the midst of a multimillion-dollar expansion project at the company's Ringaskiddy, County Cork, manufacturing facility in Ireland. The 19,100-square-meter project is expected to significantly increase Janssen's global manufacturing capacity for producing biologic medicines for multiple myeloma, rheumatoid arthritis, and Crohn's disease.

An aerial view of the site expansion

Kyran Johnson

Jim Breen

The project began in October 2017, with a goal of completing construction by the end of 2019. When completed, the Cork facility will include a new manufacturing building and expansion of the existing warehouse, laboratory, and administration buildings. Existing site infrastructure, including utilities, car parking, underground services, internal roads, yards, and pipe racks, will also be enlarged. To accommodate increased production volume, Janssen will increase onsite wastewater treatment plant capabilities. The project will create an additional 200 jobs at the site.

First opened in 2005, the Cork facility has been the production site for a selection of Janssen's biologic treatments in the immunology and oncology spaces. The expansion's goal is to help the company increase manufacturing capacity for both existing commercial products and new therapies coming through the development pipeline.

To determine the scope of the project, Janssen analyzed future needs while simultaneously assessing options for how they could be handled through internal or external manufacturing. Among the needs identified was a large-scale internal fed-batch capacity. The expansion project includes additional upstream expansion for when market demands require additional capacity and flexibility.

In addition to supplying current therapies, Janssen and other companies must develop reliable, cost-effective new treatments for disease states that are not addressed today. Janssen and other pharmaceutical manufacturers are addressing the specialized technology and supply chain models required to develop and produce innovative products. Like many in the pharmaceutical industry, Janssen welcomes this evolution and the hope it holds for patients.

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There are challenges in bringing new forms of treatments to fruition, but increasing the ability to supply specialized medicines throughout the world is also a critical opportunity. Speed is a key component in achieving these goals. Biologics present additional hurdles: They are capital-intensive, highly regulated, science-focused, and require a deep talent base.

To address these challenges, Janssen has partnered with local universities to develop industry talent, providing undergraduate and post-graduate work placements, as well as designing and delivering technical modules as part of undergraduate courses. Janssen has also forged relationships with other operating companies near the Cork facility to encourage government support for a biologics cluster in Ireland. Janssen will continue to work globally with external partners to make products, or perform intermediate steps, to ensure medicines are delivered to patients compliantly, on time, and at a fair price.

The world of pharmaceutical products continues to evolve, and with it, the factories of the future that are developing next-generation medicines need to have the ability to be reliable, compliant, and cost-effective producers of therapies for patients. Manufacturing facilities must be designed and operated for agile response to market demands and to volume changes. Janssen will continue to work globally with their partners to accommodate innovative technologies, focus on end-to-end solutions, and ensure that the focus stays on sustainable solutions for the patient.

About the Authors

Kyran Johnson is General Manager, Janssen Supply Chain, Ireland, responsible for two manufacturing sites in Cork: Janssen Sciences Ireland in Ringaskiddy and Janssen Pharmaceutical Sciences in Little Island. Kyran joined Janssen Biologics Ireland in 2005 as manufacturing director. Prior to this he held various management roles with Merck (formerly Schering-Plough [Brinny] Co.) and worked for Elan Corporation. Kyran is a board member of Janssen Sciences Ireland UC, Janssen Pharmaceutical Sciences Unlimited Company, and Business of the Community, Ireland, and Vice Chair BioPharmaChem Ireland. He is a Past Chair of the ISPE Ireland Affiliate, and has been an ISPE member since 2002.

James Breen is Vice President, Lead Biologic Expansion, Janssen Pharmaceutical. He joined Johnson & Johnson in 1997 in Shanghai, China, and progressed to a variety of vice presidential roles, such as VP Worldwide Engineering & Technical Operations, VP Network Management, VP Project Management, and VP Engineering, Global Biologics Supply Chain. Prior to J&J, Jim was employed by General Electric and Hercules, Inc., in manufacturing, project management, and engineering positions. He presently serves as an adjunct professor at Drexel University in the Engineering Department and as Chair of the ISPE Board of Directors. He has been an ISPE member since 2000.

A GROWING GLOBAL FOOTPRINT

Tiffany Coleman, LeAnna Pearson, and Caroline Rocks

This year, ISPE Young Professionals held over 60 events in 15 countries, drawing more than 2,000 attendees—an amazing testament to the growth of the YP community. This Special Section details the success of these global activities and the IYPC's exciting work over the past year.

ISPE's YP membership has grown significantly since the first YP event was hosted at the 2007 Annual Meeting by a YP group in the Boston Area Chapter. In 2010, "Young Professional" became an official ISPE member type and a recognized community. From there, YP group formation accelerated. There are now 10 YP groups across the United States and 10 in Europe representing 14 European countries. In 2015 the International YP Committee (IYPC) was formed to encourage global growth and collaboration among the ISPE YP groups and ISPE at large. ISPE YP communities are also growing in Singapore, China, India, Japan, and the Philippines. More importantly, each region held multiple YP events in past year.

REPRESENTATION

YP representatives now sit on these Communities of Practices (CoPs) and Special Interest Groups (SIGs):

- Awards Committee
- Business Development
- Disposables CoP
- EU Biotech SIG
- Facilities of the Future Program Committee
- GAMP Agile SIG
- GAMP Data Integrity SIG
- GAMP Data Integrity Retention Retrieval Recovery Retirement
- ISPE Annual Meeting
- ISPE Europe Annual Meeting
- Knowledge Network Council
- Pharmaceutical Engineering Committee
- Training Strategy Team
- Voice of the Customer
- Water and Steam Systems BG3 Task Team
- Women in Pharma®

YP Groups around the world

Belgium
Boston Area
Carolina–South Atlantic
Chesapeake Bay
D/A/CH
Delaware Valley
France
Greater Los Angeles
India
Ireland
Italy
Malaysia
Midwest
Netherlands
New Jersey
Nordic
Philippines
Rocky Mountain
San Francisco/Bay Area
San Diego
Spain
Turkey
UK

A YEAR IN NUMBERS

>60 events	200 committee members	16 COPs/SIGs with YP representatives	24 YP groups representing 19 countries	16 articles in PE magazine

Global Event Highlights

Globally, there was one YP event per week for the entire year. There were a great variety of technical events, facility tours, networking evenings (including "speed networking"), as well as career- and leadership-development seminars. YP committee collaborations to share best practices, joint YP and student events, and fun social events were also organized. It is fantastic to see all the different events that have taken place around the world this year. Flyers and photos from these events are available on the YP Community Page (https://ispe.org/membership/young-professionals). We hope that these will inspire YP groups to host events in their own areas.

Speed networking event

Philippine YPs at APAC Conference

YP Hackathon participants at the EU Annual Conference

Delaware Valley Chapter "embrace your inner lumberjack" volunteer appreciation night

Caroline Rocks at the GPMLF meeting

IYPC Strategy

It has been an incredibly busy year for the IYPC as we delivered the strategy that was presented to the Board of Directors at last year's Annual Meeting in San Diego (and published in the January-February 2018 issue of *Pharmaceutical Engineering* magazine). The committee's strategy mirrored themes in the board's 2016–2019 Strategic Plan. The table on page 35 provides a snapshot of how we delivered on our commitments.

IYPC COLLABORATION

As part of a collaboration with the Global Pharmaceutical Manufacturers' Leadership Forum (GPMLF) "Workforce of the Future" initiative, the IYPC Chair presented the "YP Perspective of Workforce of the Future" at the GPMLF meeting during the Europe Annual Conference in Rome, March 2018.

A live poll was conducted during the meeting to assess the GPMLF's perspective on YPs in their organizations. These results were combined with the gaps identified by the Workforce of the Future team, then compared to the perspective of 37 YP leaders, whose feedback had been collated in advance on whether YPs:

- Rely fully on employer organizations to develop skills after graduation
- Pursue further part-time education while working
- Have defined technical development pathways within employer organizations

During the GPMLF meeting, the IYPC also discussed knowledge gaps that YPs face when entering the pharmaceutical industry. The top gap identified by the IYPC survey was GMP training. As a result, ISPE's first YP GMP training has been added to the 2018 Annual Meeting program. This collaboration has also produced a new Workforce of the Future YP subteam. GPMLF has encouraged continued collaboration between the two groups; both the IYPC Chair and Co-Chair will present at the next GPMLF meeting in November 2018.

ISPE Strategies + IYPC Goals = Results

Strategies and goals	Results
ISPE: Rapid information delivery **IYPC:** *Improve use of YP online community page*	• Blog posts up 633% from 2017. This is a great improvement in the use of our global online community page. We encourage even more use of this in the future and have plans to upload useful content for YP groups • YP Community page was promoted in all PE Magazine YP chair editorials • Monthly rota set up for YP leaders from United States and Europe to post on the community page
ISPE: Compelling member and industry value **IYPC:** *Integrate YPs at regional and international ISPE events*	• Europe 2018 Annual Conference included second YP Hackathon, YP co-track leaders, and YP keynote speakers—a first at an ISPE international conference • 2018 Annual Meeting included YP and student brunch, YP social evening and YP GMP Training, another first • All ISPE International Conference Program Committees now have a YP representative
IYPC: Remove marketplace confusion for YP definition	• YP leader member profile surveys conducted • Based on survey results, a proposal to rename the YP reduced-rate membership tier as "Recent Graduate" and have Young Professionals as a CoP was presented to the Board. Watch for an announcement on this exciting change by end of this year.
ISPE: Local and regional relevance **IYPC:** *Establish YP groups in new regions*	New committees established in Chesapeake Bay, India, Malaysia, Philippines, Singapore, and Spain
ISPE: Operational strength **IYPC:** *Formalize YP leadership and succession planning*	IYPC "Guiding Principles" document published

BOARD OF DIRECTORS

The IYPC Chair is an ex-officio member of the ISPE International Board of Directors. This position was introduced in 2016 to bring appropriate diversity to the board and to help execute the business strategies defined in the ISPE Strategic Plan. At each meeting, the IYPC Chair gave an update of the group's activities and discussed the delivery of their strategic goals with the board.

The IYPC Chair also interviewed six board members, asking their career advice for YPs and their thoughts on the value of ISPE engagement. Their answers were published in the May-June and July-August issues of *Pharmaceutical Engineering*.

STRENGTHENING THE IYP COMMITTEE

Continued YP growth requires a solid strategy, and for this reason the IYPC worked this year to define a guideline for the future of the committee. At a face-to-face workshop, IYPC members, ISPE staff, and former board members gathered during the ISPE Quality Manufacturing Conference in June to draft the document.

The "YP Guiding Principles" include steps to maintain diversity on the IYPC across our global regions, plan for future succession of leaders, mentor new members in their progress from local to regional to international YP involvement, and create broader transparency. This document was reviewed and endorsed by ISPE Staff and Governance Committee.

YP EMPLOYER SUPPORT

Many YPs want to join ISPE but may not have support from their employers to do so. This is particularly true in organizations that do not have a senior management presence in ISPE.

The IYPC worked with industry leaders on the board of directors to define the value of ISPE to both individuals and employers. These responses were then incorporated in a brochure designed to a) help YPs seek support from their employers to be engaged with both ISPE and the wider industry and b) to promote the value of ISPE to employers and encourage management to allow their YP staff to volunteer in ISPE.

We hope this clear value proposition for both YPs and employers will help engage more organizations in ISPE and encourage members to join at an earlier career stage. Both the "YP Guiding Principles" and "Employer Value Brochure" are available on the YP Community page!

A Year in PE

It is fantastic to report that every 2018 issue of *Pharmaceutical Engineering* magazine featured contributions from YP volunteers around the world. Visit the YP Community Page to see the complete list of authors and articles: http://cop.ispe.org/p/co/ly/gid=91.

Are you interested in submitting an article to *Pharmaceutical Engineering*? Go to www.ispe.org/pharmaceutical-engineering-magazine/submit-article

Thanks for a Great 2018

OUTGOING CHAIR CAROLINE ROCKS

I have had the best year with the privilege of being IYPC Chair. I am hugely grateful to my fellow IYPC members, ISPE staff, the board, GPMLF, and YP groups globally for the work we've done together to achieve all we did this year.

LeAnna Pearson (left) and Caroline Rocks

Get involved

Attend an IYPC call or join a SIG as Young Professional representative. There are plenty of other ways to connect, too—just check out all the amazing opportunities listed in this article!

If you're interested in establishing a new YP group or joining the one in your area, contact us at ask@ispe.org with the subject line "YP."

Online community

The YP online community is where YP chapters and affiliates share details and photos of their events. It's a great place to get new ideas for your own group, too, as well as updates on the IYPC. To join, select the YP community during your registration process or update your account at www.ISPE.org/membership/young-professionals.

Globally, there was one YP event per week for the entire year

LOOK AHEAD TO 2019

Welcome New Chair LeAnna Pearson

I am excited to begin my tenure as IYPC Chair at the 2018 ISPE Annual Meeting in Philadelphia. I have been active in ISPE at both the local and national levels since I was a graduate student over a decade ago. I am also active in the Carolina–South Atlantic (CaSA) Chapter, where I serve the as Vice President and Industry Advisor for the Virginia Tech Student Chapter. I think you can see my passion for ISPE!

About Me

When I am not working on ISPE matters, I am part of a very exciting team in Raleigh, North Carolina, that is building the first genetic manufacturing facility for bluebird bio. I serve as the Manager for Quality Assurance Validation—a unique career opportunity for me. I am honored to be part of the process! When I have free time, I love to spend it outdoors, hiking, biking, or on the lakes. (See? I do have life.)

"Bril" Job, Caroline

Caroline was an amazing YP Chair who really helped drive the committee to new growth and development. I am sure that when she went to her first ISPE event in Ireland she never expected that she would be such a catalyst on an International level. So here's a big thank you, Caroline. I will strive to keep up your momentum in 2019.

What's Next?

My goal for 2019 is to build on the foundation laid by previous chairs and provide our members with value-added content. In the next issue of PE magazine, I will introduce you to my Co-Chair and announce all the exciting things that have happened.

Meet Me in Philly

By the time this article is published we'll be only days away from the 2018 ISPE Annual Meeting. I'd love to see you there—or hear from you anytime. Please contact me at lpearson@bluebirdbio.com. I look forward to meeting you.

Caroline Rocks is Senior Process Engineer AbbVie, Inc., Ireland, and a member of the ISPE Board of Directors. She has been an ISPE member since 2014.

LeAnna Pearson is Manager for Quality Assurance Validation, bluebird bio, Raleigh, North Carolina, and YP Representative to the ISPE Board of Directors. She has been an ISPE member since 2015.

Tiffany Coleman is Director of Operations, Lilu's Garden, Hudson, Colorado. She has been an ISPE member since 2009.

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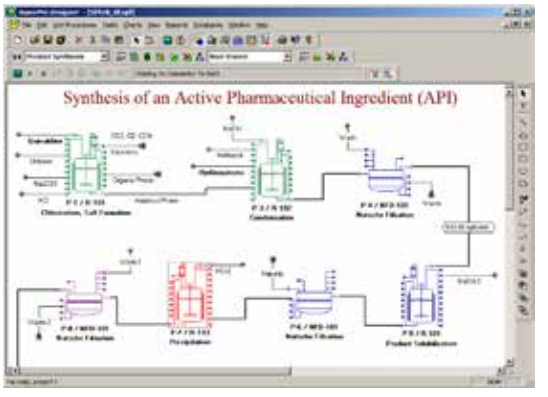

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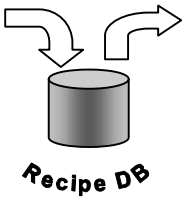

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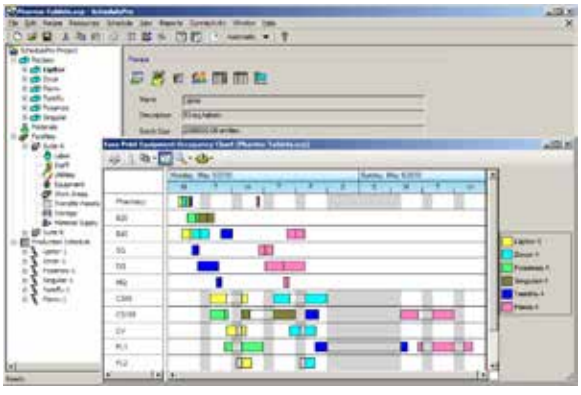

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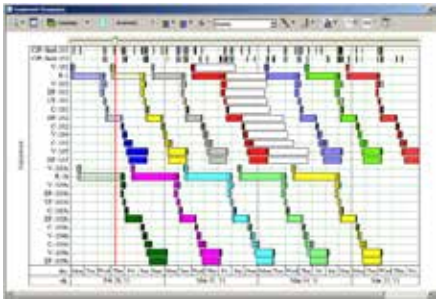
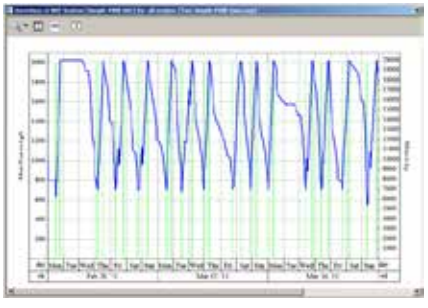


Easy production tracking, conflict resolution and rescheduling

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



Managing inventories for input, intermediate, and output materials

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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.

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MANUFACTURING AND CONTROL CHALLENGES

for Accelerated Development

Enhanced and accelerated regulatory pathways for "Breakthrough Therapies (United States) and "PRIME" medicines (European Union) have been introduced to provide faster access to exciting new therapies developed to treat unmet medical needs.[1–2] Jokura et al. give an interesting comparison of American, European, and Japanese expedited regulatory pathways.[3]

Given the importance of accelerated access for patients, regulators, and industry, ISPE has assembled the Expedited Programs for Patients team, a subteam of the PQLI® Committee. The new group has worked for more than a year to compare experiences and challenges faced by chemistry, manufacturing, and control (CMC) development teams as they work toward initial approval while continuing to supply product for clinical studies and patients.

A 2015 article by Dye et al.[4] suggests that shortening the regulatory filing period for an expedited development program by 18 to 24 months could challenge delivery of CMC information. This paper was based on hypothetical examples of accelerated development for small and large molecules, since at that time there was little experience of approvals for programs that had been assigned as breakthrough therapy status at an early development stage—i.e., after receipt of preclinical or early clinical positive information. Dye et al. summarize emerging industry CMC challenges as time, resources (amount and expertise), and materials.

Since the paper's publication, more CMC programs are part of the critical path to approval, and accelerated development programs have helped companies and regulators make new medicines available to patients.

The ISPE team, which represents both small and large molecule development, presented its preliminary findings at the ISPE Quality Manufacturing Conference on 5 June 2018. Case studies for real drug approvals presented during the conference provide some emerging considerations:

1. Early, effective, and detailed communication between sponsors and agencies throughout development facilitates more and better-informed CMC development decisions, and leads to greater regulatory flexibility built upon joint understanding of the risk-to-benefit profile.

2. Accelerated development can significantly shorten the time to market, benefitting both patients and sponsors, but does not eliminate CMC activities, lessen quality expectations, or reduce any obligation to provide adequate supply. In one assessment, for example,[5] premarket development time was considerably shorter among approved breakthrough-designated drugs (median 5.2 years) than nondesignated drugs (7.4 years), a difference of 2.2 years.

3. A compressed timeline challenges the sponsor to develop process and product understanding commensurate with the risk profile agreed with regulatory authorities.

4. There is no "one-size-fits-all" approach. Agreements are highly individualized and based on the sponsor plan to demonstrate an adequate level of process understanding to the regulator, leading to a drug product that consistently meets predetermined acceptance criteria.

5. Early development of a full lifecycle strategy (including post-approval change), and documentation of the control strategy (e.g., quality target product profile, critical quality attributes, critical process parameters, and approach to control) allows for earlier understanding of functional requirements and systematic process change control, which is almost certain to be required.

6. Where possible, there is significant benefit in leveraging prior knowledge and platform processes to support product- and process-specific understanding, process validation, and reduce redundant experimentation.

7. Strategic utilization of supply chain options provides launch flexibility:

   a. Manufacturing site selection can be critical—e.g., using a clinical manufacturing facility in a pilot plant within a commercial facility and pivotal clinical study manufacture in a commercial facility.

   b. Using expansion strategies where it is most appropriate to minimize scale-up variability and maximize process portability.

8. Minimizing process changes whenever possible allows more bridging of early clinical data.

The team intends to issue an article expanding on the points above in the next few months. Although each development is different, actual case studies appear to provide key considerations and guiding principles common to most programs, which should help sponsors.

—Christopher Potter, PhD, Technical Advisor

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ISPE Expedited Program for Patients

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Derek Blaettler, Roche/Genetech
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Huimin Yuan, Johnson and Johnson, co-chair

ISPE BOARD ELECTION RESULTS

The ISPE International Board of Directors 2018 election results are in after member voting during the summer. The new slate of officers and directors has been named. Board members govern and chart the Society's strategic direction during their terms of service.

The new board members will assume their roles at the 2018 ISPE Annual Meeting & Expo, 4–7 November in Philadelphia, Pennsylvania, US.

The 2018–2019 officers are:

- Chair: James Breen, Jr., PE, Vice President, Project Lead, Biologics Expansion, Janssen Pharmaceuticals
- Vice Chair: Frances (Fran) M. Zipp, President & CEO, Lachman Consultant Services, Inc.
- Treasurer: Thomas Hartman, Vice President of GMP Operations, Biopharm CMC, GlaxoSmithKline
- Secretary: Joanne R. Barrick, Advisor in Global Validation Support, Eli Lilly and Company

The 2017–2018 Board Chair will continue service on the board in 2018–2019 as Immediate Past Chair:

- Timothy P. Howard, CPIP, PE, Vice President Asia Operations, Commissioning Agents, Inc.

DIRECTORS

Newly Elected/Reelected/Appointed

The following are newly elected, reelected, or appointed directors. They will serve from 2018 through 2020:

- Vivianne Arencibia, President, Arencibia Quality Compliance Associates
- Gunter Baumgartner, Vice President, Global Engineering, Takeda Pharmaceuticals
- Chris Chen, Chief Executive Officer, WuXi Biologics (Shanghai) Co., Ltd.
- Christine M.V. Moore, PhD, Global Head and Executive Director, GRACS CMC–Policy, Merck & Co.
- Caroline Rocks, Senior Process Engineer, AbbVie, Inc.

Continuing

The following have completed their first year of service and will continue to serve on the board through 2019:

- Anthony (Tony) Crincoli, PE, Vice President, Global Engineering, Glenmark Pharmaceuticals
- Flemming Dahl, Head of Quality, Senior Vice President, Novo Nordisk A/S
- Kelly Keen, Vice President, Head of PMO Project Management, Celonic AG
- Alice Redmond, PhD, Vice President, European Operations, Commissioning Agents, Inc.
- Michael Rutherford, Executive Director, Computer Systems Quality and Data Integrity, Syneos Health

Ex Officio

- LeAnna Pearson, Lead Validation Engineer, bluebird bio, Young Professionals Representative (non-voting)

FOR MORE INFORMATION

Biographies of all board members are on the ISPE Board of Directors webpage: www.ispe.org/about/international-board-directors.

A NEW PLACE FOR INFORMATION

ISPE Events and More

Welcome to ISPE Briefs, a new column about happenings at ISPE—chapters and affiliates, conferences, and more.

NEW TECHNOLOGIES & MOLECULES

Ready for the Future of Biologics Manufacturing?

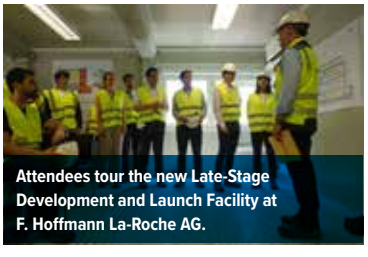
For a deep dive into what's coming in the next decade, the 2018 ISPE Biopharmaceutical Manufacturing Conference, 10–12 December, Huntington Beach, California, will help attendees explore, strategize, develop tools, and determine how to navigate the evolving technical and regulatory complexities of biopharma's exciting future, according to conference chair Andre L. Walker, Principal, Andre Walker Consulting.

"As novel therapies emerge from the clinic and provide dramatic improvement in disease treatment, the biopharmaceutical professional of today must be prepared to design, build, operate, and support the new and different facilities and processes required to meet demand," Walker said. In other words, "This won't be your parents' biopharma plant."

Speakers from Kite, Biogen, Alnylam, bluebird bio, MedImmune, Genentech, Immunogen, and more are scheduled to present. Global industry leaders and regulators will be on hand. And as part of "From Lab to GMP Production," an interactive half-day workshop led by experts in this emerging field, attendees will collaborate to design a facility and equipment layout that supports a new cell therapy treatment.

Register now at ISPE.org/Biopharma18 to learn from industry and regulatory leaders at the forefront of this transformation.

D/A/CH AFFILIATE FUTURE LEADERS' DAYS



Attendees tour the new Late-Stage Development and Launch Facility at F. Hoffmann La-Roche AG.

The ISPE D/A/CH (Germany, Austria, and Switzerland) Affiliate's Young Professionals and Students Group sponsored Future Leaders' Days on 21–22 June at F. Hoffmann-La Roche AG headquarters in Basel, Switzerland. Presentations by companies including Hoffman-La Roche, Bayer AG, Werum IT Solutions, Boehringer Ingelheim, Novartis, and CRB Group GmbH focused on engineering career paths as well as technical topics such as project management and execution, digitalization, Pharma 4.0. and biopharmaceuticals. Attendees toured the new Late Stage Development and Launch Facility in Kaiseraugst, participated in a Q&A session, networked with presenters and fellow attendees, and met with the ISPE D/A/CH Board at an evening social event.

SINGAPORE AFFILIATE CONFERENCE TOPS 1,000 ATTENDEES

Plenary panel participants (from left): Vincent Loret, Site Director, GlaxoSmithKline, Singapore; Chong Meng Chai, Head of Mammalian Manufacturing, Lonza Biologics, Singapore; Dr. Jincai Li, Vice President, Drug Substance Manufacturing (MFG1), WuXi Biologics, China; and Conference Chair Pierre Winnepenninckx, CEO and Founder, No Deviation Pte, Ltd. (moderator).

The ISPE Singapore Conference and Exhibition, 29–31 August, drew over 1,000 participants, a record attendance for the 18 years of the conference. Participants included delegations from Indonesia, Thailand, and Vietnam. Over 65 speakers shared thought leadership, best practices, and real-life experiences. The event featured the region's first Women in Pharma® session, which was held in conjunction with the conference.

International speakers included Tim Howard, ISPE Board of Directors Chair (2017–2018); Dr. Christine Moore, Global Head and Executive Director, GRACS CMC Policy, Merck, Sharp and Dohme Corporation, US; Christian Wölbeling, ISPE Pharma 4.0 and Co-Chair GAMP® MES Special Interest Groups, Senior Director Global Accounts, Werum IT Solutions, Germany; and Hazem Eleskandarani, Global Director, Commissioning & Qualification, Engineering & Property Services, Johnson & Johnson, US.

Keynote speaker Ferry Soetikno, Chief Executive Officer, Dexa Group, Indonesia, presented on "Ensuring the Supply of Quality Medications Beyond Domestic Markets." The plenary panel discussion on "Driving a Quality Culture through Leadership" generated lively debate; other popular sessions included process and technology transfer, digitization, quality culture, process and cleaning validation, and ICH Q12.

The Regulatory Affairs track brought together regional and global regulators including Boon Meow Hoe, Chairman (2018–2019), PIC/S; Vladimir Orlov, Deputy Head of Scientific, Methodology & Training Department of FSI, State Institute of Drugs and Good Practices, Russia; and regional authorities from Thailand and Singapore.

—Susan Sandler, Editorial Director

We'd like to feature your group in an upcoming column! Share the highlights of training programs, conferences, social events, or other activities with ISPE members. Article length is 250–400 words; photos should be 300 dpi or > 1 MB. Send both to Susan Sandler, Editorial Director, at ssandler@ispe.org.

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CM IN BIOTECH PROCESSES

Challenges for Implementation

Robert Dream, CPIP, PE; Christoph Herwig, PhD; and Emilie Pelletier

Continuous biotech manufacturing has the potential to achieve greater product quality at lower cost and shorter time to market. Recent advances in fully integrated control systems and a dynamic market make it more relevant than ever.

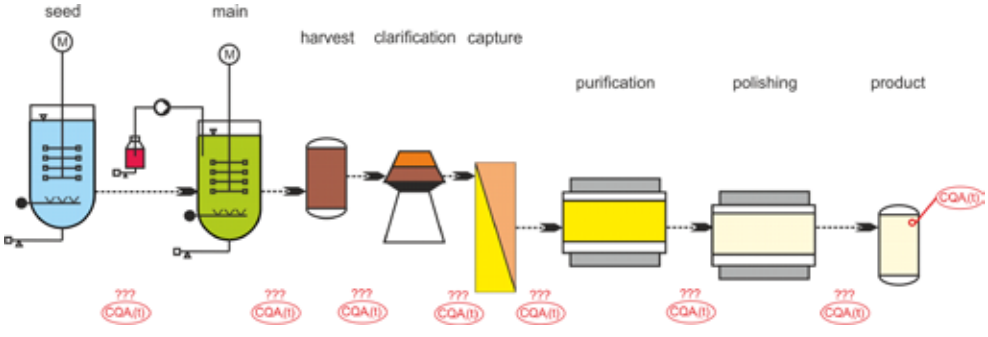
Continuous processes have become standard in many industries because they provide the best use of installed assets and produce products of consistent quality. They have been implemented in the production of pharmaceutical and food ingredients. Although continuous manufacturing (CM) in the biotech industry has been discussed for many years, recent advances in fully integrated control systems combined with the dynamic state of the market make it more relevant than ever before.

Continuous processes are operated by automated systems in which stable critical quality attributes (CQAs) are achieved by adjusting critical process parameters (CPPs) in real time. This improves process robustness, productivity, and equipment utilization. Yet even though the scientific knowledge to develop continuous processes is available, batch processes are still used almost exclusively to manufacture biopharmaceutical products. The biotechnology industry requires a shift in this mentality.

CM has many advantages: The time required for development is shorter, since multiple sets of parameters can be evaluated during a single lot. Less human intervention is required, reducing operational cost and human error. CM has a smaller footprint. By integrating single-use technology into the process line, initial capital investment may be reduced as well. Lastly, pilot-scale processes, which may also be used for clinical supply, can transition into commercial manufacturing simply by increasing the run time. This eliminates scale-up and its associated construction and validation steps and speeds up time to market. Since it is sometimes difficult to predict market demand when sizing the first commercial batch to scale process, the flexibility of continuous processes mitigates the risk of making the wrong assumption.

With all these advantages, it is no surprise that the development of CM in biopharmaceuticals has generated growing interest in the scientific community and spurred increased investment by drug manufacturers. Continuous processes have been implemented in the production of pharmaceutical and food ingredients. Continuous purification technology is commonly used for commercial production. Continuous perfusion (cell culture) processes have also been used for several years. Technology for the remaining upstream and downstream unit operations is coming to market.

Figure 1: Schematic diagram of a batch process with hold steps, enabling CQA measurements offline.



Adapted from Rajamanikam, V., P. Sagmeister, O. Spadiut, and C. Herwig. "Impurity Monitoring as Novel PAT tool for Continuous Biopharmaceutical Processes." *Continuous Bioprocessing: A Repligen E-Book*. Industry best practices compiled by Repligen. 2016.

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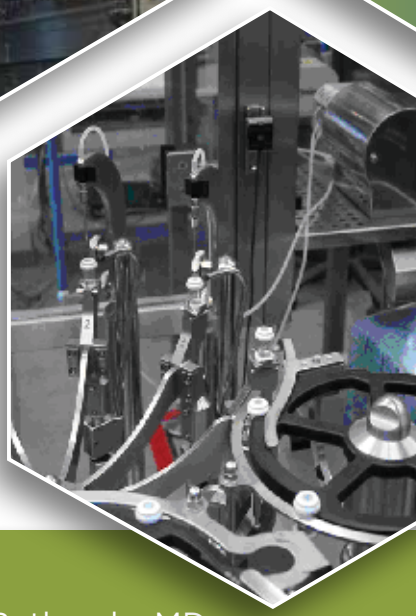

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Because many challenges remain to be overcome before its adoption, this article will present the status of CM in the commercial product lifecycle and outline work that has yet to be completed:

- R&D efforts to characterize CPPs on single-unit operations and integrate them into the process
- Integrated control strategy required for operation
- Technology available on the market
- Approaches to validation and quality
- Regulatory compliance

R&D CHALLENGES

This section lists continuous processing challenges in R&D and proposes a workflow and tools for future development work.

A continuous mode needs single-unit operations, but must also master the interplay between them. As Konstantinov and Clooney note in their white paper (emphases in original):

> A ***unit operation is continuous*** *if it is capable of processing a continuous flow input for prolonged periods of time. A continuous unit operation has minimal internal hold volume. The output can be continuous or discretized in small packets produced in a cyclic manner.*
>
> A ***process is continuous*** *if it is composed of integrated (physically connected) continuous unit operations with zero or minimal hold volume in between [and suitable controls are in place to capture process variations].*[1]

This differentiation of continuous unit operations and continuous integrated processing (Figure 1) dictates the development steps:[2]

- Understand and establish single-unit operations
- Link them to an integrated process

Continuous processing requires a different level of process understanding. As an example, classical antibody production, which uses Chinese hamster ovary (CHO) cells as a host, pools the product solution after 14 days. The time-variant dependency of CPPs and CQAs are integrated in one analytical result and the process is also registered as such. Hence, in batch processes, the outcome of the current step determines the subsequent step. When moving to continuous operation, we have to understand the time dependency between CPPs and CQAs. This calls for the enhanced use of metabolic and kinetic models and different experimental designs.

For example, classical designs of experiments (DoEs) can only capture the response of the system to time-invariant factors. For continuous operation the development strategy is reversed. We want to run with time-invariant process variables, but we need to understand the time variant dependencies on their CPPs for control. We may need dynamic model-based DoEs to develop a control strategy able to cope with process variability over time; those experimental setups should be established in the R&D environments.

Table A: Current design principle for each unit operation

Unit operation	Design principle
Media and buffer preparation	Continuous
Cell culture	Continuous
Chromatography	Staggered
Filtration	Continuous
Viral inactivation	Staggered

Continuous downstream processing starts in robust continuous upstream processing. Continuous downstream processing systems that can achieve steady-state operations may be soon available. Before we can achieve that, however, we will also need continuous upstream solutions. Since the cell lifecycle goes from exponential growth to producing, necrotic, apoptotic, dead, and lysed states, current perfusion processes, which monitor only viable cell count and viability, may not be enough to understand the dynamically changing population. Further analytical techniques, such as fluorescence-activated cell sorting and population models, must be applied.

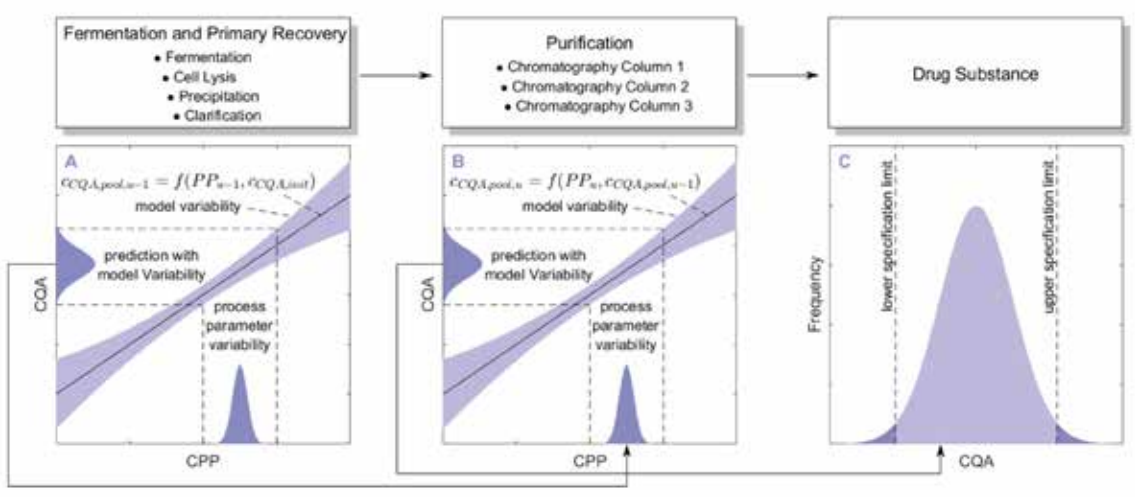
A more promising approach uses metabolically balanced cells in which the primary and secondary metabolism prevails to the metabolic burden of the recombinant product. For this, tunable promoters with genetic integration and low metabolic burden are preferred over the constitutive promoters[3] currently used in CHO cell line development.

Continuous processing requires a much earlier definition of the process control strategy. As proposed by current US Food and Drug Administration (FDA) validation guidelines, stage 1 validation includes process characterization studies (PCSs), which are the "collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality product."[4]

PCSs reveal the interplay of process parameters (PPs) on CQAs, demonstrate process robustness within multivariate normal operating ranges (NORs) and propose the control strategy, including process and analytical controls. This is currently achieved for batch processes by fusing development and manufacturing data.

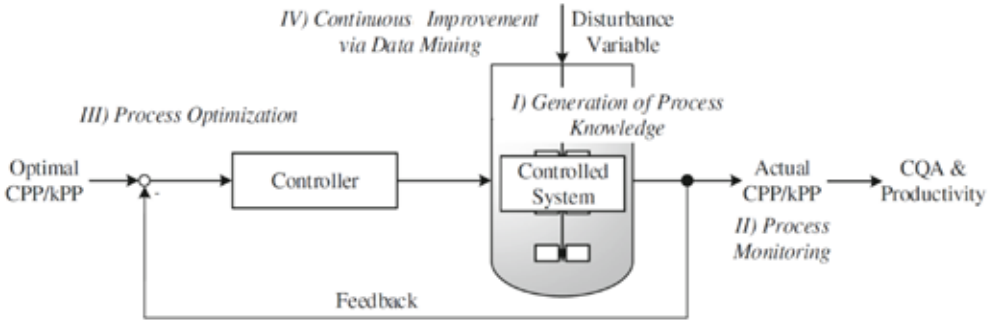
For continuous processing, time-variant dependencies between CPPs as CQAs must be transformed in a control concept, which we need as prerequisite for process design. NORs must also be defined earlier as part of a process control strategy, based on process analytical technology (PAT) models and controls. This means that PCSs should be completed during development. These may include data mining, risk assessments, characterization of process performance, screening studies, criticality assessment,[5] and integrated process modeling.[6] Scale-down model qualification may not be necessary, as the development scale may be already the production scale, since productivity is scaled by processing time. R&D labs, on the other hand, need greater data management and data science orientation skills.

Figure 2: Integrated process modeling



Source: Zahel, T., et al. "Integrated Process Modeling—A Process Validation Life Cycle Companion." *Bioengineering* 4, no. 4 (2017): 86. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5746753. Reprinted under CC BY 4.0 license (http://creativecommons.org/licenses/by/4.0).

Figure 3: Multivariate control loop



Source: Kroll, Paul, et al. "Model-Based Methods in the Biopharmaceutical Process Lifecycle." *Pharmaceutical Research* 34, no. 12 (22 November 2017): 2596–2613. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5736780. Reprinted under CC BY 4.0 license (http://creativecommons.org/licenses/by/4.0).

Using integrated modeling to accelerate continuous process development. In addition to understanding single-unit operations, the interplay between them is an important component of robust processing. Integrated process models (e.g., ASPEN, G-Proms) have been used successfully in other market segments and could be applied to batch or continuous bioprocesses to identify PPs and critical control strategies. These models should display the process and NORs of individual unit operations,[5–6] link individual unit operations, and assess error propagation in the NOR using sensitivity studies such as Monte Carlo simulations (Figure 2).[6–7]

Process control strategy prerequisites. Any robust control strategy needs:

- Analysis of output process variables—key performance indicators (KPIs) and CQAs—of unit operations
- A controller that varies CPPs to achieve a robust and continuous process

Some new at-line tools for CQA measurements use nuclear magnetic resonance spectroscopy or liquid chromatography–mass spectrometry.[7] For continuous processing, however, they must be deployed as real-time PAT tools. Various solutions may bridge this task in the near future:

- Data-driven model-based approaches using spectroscopy
- Robust on-line sampling solutions that link gold standard analytics in online mode
- Model-based approaches that link CQAs to real-time measurements, offer a clear advantageous means to measure less

Developing a multivariate controller, which allows multiple CPPs as a function of multiple CQAs, is a more difficult challenge (Figure 3). Multiple-input/multiple-output controllers[10] are available in other market segments, but are rarely applied in R&D bioprocessing labs. The trigger for this transition will be integrated real-time architecture that combines data management, real-time execution of models,

Figure 4: Tackling process variability through identification, monitoring, and control

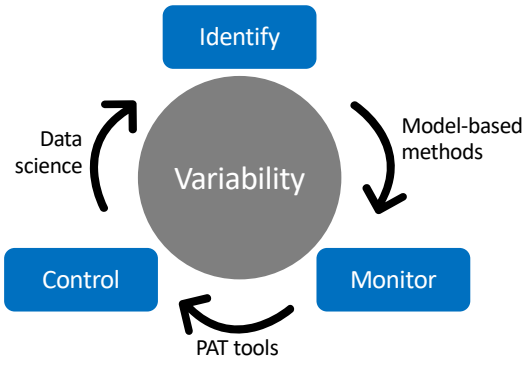
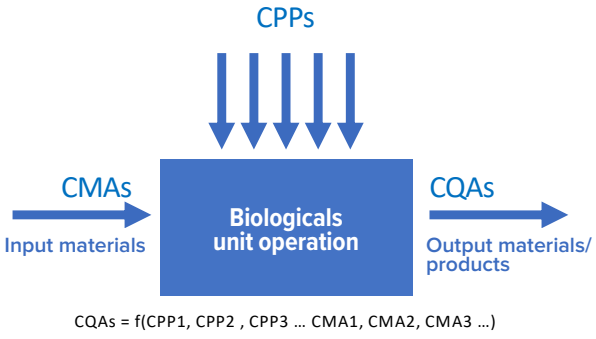


Figure 5: Relationship between CMAs, CPPs, and CQAs



advanced control algorithms, and model-generating workflows using "software as a service" tools.[8–9]

CONTROL STRATEGY CHALLENGES

Fully connected, self-optimizing production processes, the first steps toward digital manufacturing, are well under way. Automation technology that leverages more meaningful data and analytics to improve processes (often referred to as manufacturing intelligence) will provide a better view of operations, better analytics, and real-time responsive decision-making to drive continuous improvement and operational excellence (Figure 4).

Process variability associated with critical material attributes (CMAs) arises from variations in raw material quality, variation in a supplier's manufacturing process, and/or a change in suppliers. Combining ultraviolet high-pressure liquid chromatographic data with chemometrics can help determine variations in CMAs.

Key elements in drug development and product/process characterization are identifying and controlling CPPs and CMAs. These influence CQAs, which measure attributes associated with the safety and efficacy of the drug substance and drug products. We need to develop statistical methods to identify relevant CPPs and CMAs and approaches on how to control them to prevent adverse effects on drug product or drug substance (Figures 5 and 6):

1. Get process understanding linking CMA to CQAs.
2. Formulate this process understanding in a model, which allows control of the process while compensating for CMA variations.
3. Future models will use "fingerprint" methods such as spectroscopy or chromatography as PAT to deploy the model in real time.

Variability in KPIs (such as cell growth) is of utmost importance for continuous bioprocessing development because it directly affects process performance and product quality. Identifying and controlling variability in KPIs is cumbersome and requires model-based methods.

Process modeling is employed to identify variations in process development. Automated workflows generate models in a structured frame, and then implement those models to identify sources of process variability. This requires real-time data collection, transmission, and analysis to capture process variability and predict process performance.

EQUIPMENT DESIGN CHALLENGES

In recent years, equipment manufacturers have introduced significant advancements in equipment design for CM applications in the biotech industry. The development of new technologies by the single-use industry have also increased the options for the biotech industry. While robust CM options still do not exist for all critical process steps in a typical biotech process, vendors continue to develop and improve their products.

Some technology allows true continuous processing with a steady-state approach; others use a staggered approach with units placed in parallel and fed alternately. These allow continuous flow in and out of the unit operation but do not reach a steady state. Table A summarizes the principle used for each unit operation. A typical process flow diagram for a fully continuous biotech process is shown in Figure 7.

Upstream Process

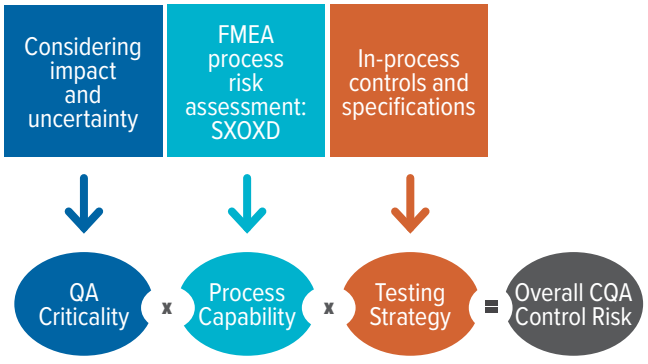
This section looks at the critical steps in a biotech process and evaluates the availability of CM equipment options currently on the market, focusing on equipment design. Cell culture is a very sophisticated process that requires stable parameters for advanced control algorithms to ensure an accurate response when a process perturbation occurs.

Current bioreactor system options are batch, fed-batch, and continuous (or perfusion). Batch, the classic option, is a closed system, and considered safer from a contamination perspective. It has the lowest product yield, however, since it requires four phases: lag (adjustment), log (logarithmic bacteria growth), stationary, and decline.

In a fed-batch system, continuous incoming substrates feed

Figure 6: CQAs and process capability are the basis for establishing a control strategy

- Criticality of attributes and process parameters are needed to establish, understand, and evaluate a risk-based control strategy
- Testing strategy for any quality attribute (QA) depends on its criticality and process capability



the reactor. By adding this fresh material, the volume of culture is greater, increasing product yield. Constantly feeding the bioreactor raises the contamination risk, however. From a design standpoint, this risk must be carefully studied to design a robust and reliable system that minimizes contamination risks.

The last option, a continuous or perfusion system, produces a higher product yield than either a batch or fed-batch system, while using the same size bioreactor. The process continually adds fresh media to the bioreactor while removing spent media and new product, keeping the bioreactor in either a lag or log growth phase. Bioreactors for continuous process applications are widely available from a variety of equipment manufacturers, with sizes ranging up to 2,000 liters; systems can also be customized for specific needs. It seems clear that the industry will move forward with this technology, but some challenges must be addressed to ensure the process remains safe.

The first challenge will be the capital investment of the installation. Batch systems have a more manual operation than perfusion systems, and are more attractive from an initial investment standpoint. An economic study should be considered to make sure the investment is worth it for the process and product (or products) that will be manufactured. The batch size and the number of batches per year will dictate whether the continuous reactor suits the process.

Implementing any continuous operation requires automated controls to react to and adjust critical parameters in real time. PAT requires good definitions of critical parameters to monitor and adjust in a timely manner according to the ongoing operation. It is especially important for continuous processes that these controls are tuned for fast response to ensure high product quality and yield.

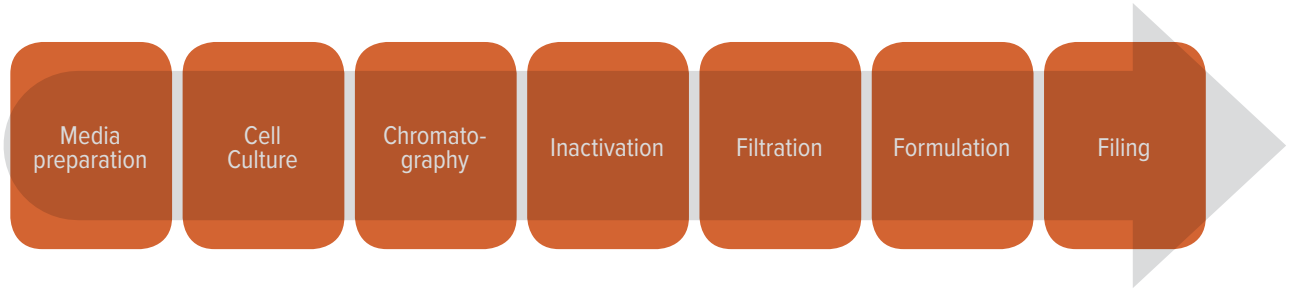
Another challenge is the risk of contamination, which is higher for continuous processes than fed-batch systems. Bioreactors are considered open systems; each time the system is opened to refill feed or harvest cells, the risk of contamination rises.[11] The main issue is detecting possible contamination in real time to reduce product losses. Installing the right instrumentation will help to detect potential contamination, but this remains a challenge for a continuous operation.

Downstream Process

Diafiltration/ultrafiltration (DF/UF) systems are probably the most common process steps in the biotechnology industry for upstream and downstream processing. This process has been widely used for many years in batch operations, but as perfusion bioreactors are increasingly used in the industry, the process bottleneck has moved downstream. Combining continuous UF/DF with tangential flow filtration (TFF) prevents buildup and clogging that might otherwise occur.[12]

Currently, only a few suppliers offer continuous TFF, even though the technology is present throughout the pharma and biotech industries. Indeed, a reverse osmosis system that generates purified water in a continuous operation is proof that the industry is not far away from getting more alternatives for their continuous UF/DF systems. As off-the-shelf options for this technology remain

Figure 7: Typical process flow



scarce, the main challenge for manufacturers who wish to implement continuous TFF is to rely on custom solution to meet a specific throughput and adapt to a specific product.

As CM takes hold in the industry, vendors have started to develop continuous UF/DF equipment options. These solutions are often single-use, scalable systems that can be used for buffer exchange for final products, desalting or buffer exchange before or after column chromatography, as well as small-molecule contaminant removal. Unlike other critical process steps, however, there are a limited number of continuous equipment options from a limited number of vendors for UF/DF. Since batch UF/DF are economical solutions, it is important to carefully evaluate whether the benefits of the continuous equipment outweigh the investment in the equipment and in the process development.

Chromatography

The chromatographic step in a biotech process can be an obstacle when converting from a traditional batch to a continuous process, often due to the long contact time required between adsorbent and adsorbate. One new technology to reach the market is continuous multicolumn chromatography, which is based on a staggered processing approach.

Studies show these systems require smaller column volumes and reduced buffer volumes compared to a standard batch process, while producing the same amount of product. Additionally, they greatly reduce the cost of chromatographic media without altering the sorbent or buffer used in the process. By switching from a single to a multicolumn chromatography system, users gain great flexibility and greater productivity. See "Transitioning to Multicolumn Chromatography" in *Pharmaceutical Engineering* (May-June 2018) for a more detailed look at the challenges and results of implementing multicolumn chromatography systems in the biotech industry.[13]

Inactivation

Currently, there is no truly continuous equipment available for the inactivation process step. The main challenge in designing equipment able to perform this step continuously is the long residence time. Commercially available systems are based on a staggered batch process in which several mixers are fed alternately, pH is adjusted, residence time met, and product unloaded. This approach allows product to be fed continuously, but outfeed is not consistent. The coiled flow inverter, a new technology currently at the proof of concept phase, uses flow design principles similar to those used in a heat exchanger. It operates at laminar flow velocities and uses radial mixing to ensure homogeneity.[14]

Buffer and Media Preparation

Currently, large batches of buffer and media are prepared off-line and fed to each unit when in operation. For a continuous process, inline dilution would help keep the storage volumes low. Batches of concentrated media and buffer sufficient to supply the continuous processing time (or a portion of it if the processing time is long) would be prepared off-line and diluted to the appropriate concentration for each unit. This type of design would be considered semicontinuous, as the bags of concentrated buffers would have to be changed when they were empty. This technology is currently available and ready to implement.

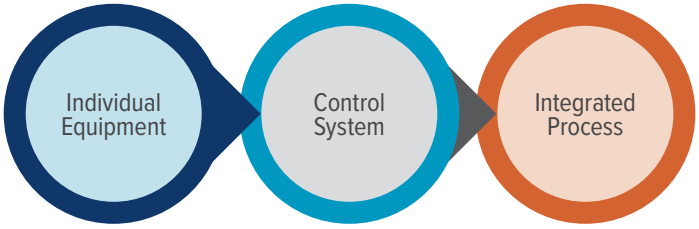
As with the upstream process steps, converting from a batch to continuous process poses challenges. End users must carefully evaluate their process and perform an economic analysis. In general, CM equipment has a higher capital investment because of the automation cost. An analysis could show that reduced facility, scale-up, and operational costs outweigh the increase. While the technology exists in the industry, it has not been fully developed for the biotech unit operations.

Bioburden

Another challenge is bioburden control. While the current batch downstream process is not sterile, bioburden is controlled. With increased run time, however, bioburden can build up in the process train. It is necessary to control the microbial load so that it does not exceed the limits that can be removed by sterile filtration. Converting to a more sterile process would eliminate this issue, but would result in a significant cost increase.

A filtered, concentrated buffer solution and closed processing are concepts that can be used in process design to mitigate this issue. Studies focusing on filter membrane saturation and chromatography

Figure 8: C&Q execution sequence



efficiency will help determine appropriate continuous batch run time. A charging, cleaning, and sterilization strategy could also be developed to increase the run time. Buffer tanks in between unit operations are an option, but do not align with continuous design philosophy. Equipment redundancy would allow the process to continue while another equipment unit is cleaned and changed over. This would also allow production to continue in the case of an equipment failure.

VALIDATION CHALLENGES

For all unit operations except perfusion, process robustness has not been formally demonstrated at a validated commercial scale. Once proof of concept has been established, development and engineering runs at a pilot scale will be necessary to validate the new technology. Studies focusing on the microbial load through time will be crucial to validate this process and make it an acceptable option.

When the technology has been developed and is ready to be implemented, a suggested methodology is:

Stage 1

Stage 1 validation and risk assessments are executed to design the control strategy as well as create user and functional requirements specifications (URS and FRS). The following information must be clearly defined in these documents:

- System boundary, including handshake points with upstream and downstream equipment, control system, and process utilities
- CQA and CPP target values measured and controlled by the equipment
- Product information and CQAs (e.g., sterility) not directly measured and controlled by the equipment
- Equipment-related risk mitigation measures defined in the risk-assessment phase

From these documents, test protocols to be executed during the commissioning and qualification (C&Q) phase (factory acceptance test; site acceptance test; installation, operational, and performance qualifications). Process-performance qualification can also be developed. A system-impact assessment that encompasses the facility and process utilities, control systems, and process equipment defines the criticality of each system in the manufacturing space. The level of testing required depends on whether the system has a direct or indirect impact on product quality. Because a continuous process functions as an integrated process, it is crucial to develop a testing strategy that will take this into account.

The main challenge in executing a C&Q strategy for a continuous process lies in the phasing and sequencing in which each system is started up and tested. The execution must match the process architecture, starting with individual components, their integration with control

systems, and finally to upstream and downstream equipment as well as utilities. The validation master plan must lay out this integrated strategy (Figure 8).

Stage 2

Stage 2 process qualification is integrated in the lifecycle concept. A risk-based process design phase provides solid proof of reproducible commercial manufacturing. A process-performance qualification strategy must choose a run time that represents a commercial batch and show how process variability is controlled and stable product is produced. A sampling plan that tests product homogeneity over time should be included.

The qualification strategy should include data integrity, since a fully automated process measures and acts on cGMP-critical data throughout the manufacturing process. This information must be secure, archived, easily accessible, and auditable.

Stage 3

In theory, the stage 3 validation phase in a CM process should be relatively easy to implement, since it is necessary to follow quality by design (QbD) principles to get to this point. An automated process with PAT provides the real-time data required to monitor CQAs and CPPs continuously. Variability within the process and product quality is detected and acted upon immediately. Overall trending and analysis on data can be implemented on multiple batches and provide the basis for continuous improvement.

REGULATORY AND QUALITY CHALLENGES

Because continuous processes are new in the biopharmaceutical industry, one of the biggest challenges related to their implementation in commercial manufacturing is the lack of operational experience and the perceived difficulty around quality management. Two main points are often part of the discussions:

- Definition of a "batch" when a process is continuous
- Managing process deviations and product out of specifications

The FDA defines a batch or lot produced via a continuous process by a unit of time instead of a quantity of product (emphasis added):

> *(2) Batch means a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.*
>
> *(10) Lot means a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or,* ***in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time*** *or quantity in a manner that assures its having uniform character and quality within specified limits.*[15]

This unit of time is defined by a variety of factors, such as:

- Commercial requirements
- Efficiency of unit operations impacted by time or quantity of product (i.e., filtration)
- Bioburden
- Leachable/extractables in single-use processes

The current quality strategy for manufacturing processes is based on segmenting operations with off-line quality checks between steps, and release management with quarantine status. For continuous processes, real-time release is more applicable as the continuous monitoring of CQAs ensure that quality is maintained throughout the manufacturing process.

The methodology for managing out-of-specification results must be determined during the design process, with various failure modes and effects analyses implemented in the QbD and subsequent quality approach. The process must react to variation at each stage and reject product when CQAs are not within specifications. These critical functions are qualified during the validation process. Additional off-line verifications can also be implemented to verify the performance of these functions. As with a batch process, deviations must be properly investigated, and appropriate corrective actions implemented to correct the root causes.

The large amount of real-time data accumulated during the manufacturing process will provide confidence in the quality decisions made, but the systems in place must allow proper access and analysis of the data.

CONCLUSION

Continuous manufacturing aligns with Pharma 4.0 objectives by increasing productivity and product quality. A well-defined process in the R&D stage, integrated PAT, and fully automated processes are key to its successful implementation.

Five main challenges must be overcome for its successful implementation in commercial biotech manufacturing:

- Develop control algorithms
- Implement PAT technology
- Design continuous equipment for all unit operations
- Develop a strategy for bioburden control
- Overcome lack of operational experience

The regulatory framework allows for continuous processes in commercial manufacturing and current validation methodology can be followed. With CM's many advantages, increased investment in development from drug manufacturers will help solve these challenges and make cGMP continuous biotech manufacturing a new reality.

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CONTINUOUS OSD IN THE FIELD

A Status Update

Lonna Gordon, EIT

Although it includes some background material, this article is based predominantly on a series of interviews with SMEs at Eli Lilly, Janssen, Hovione, C-SOPS, and Patheon from October to December 2017. The comments and observations that follow are theirs.

For close to a decade, we've heard much about the promises of continuous manufacturing (CM) for oral solid dosage (OSD). So now that four OSD drugs are being manufactured by CM in the United States (at Vertex, Janssen, and Lilly), with at least five more in the approval pipeline, it's time to take stock: Has CM delivered on its promises?

THE PROMISES

1. Simpler, faster, and cheaper development: Because the equipment is small, development should occur on full-sized equipment, with no scale-up required.

2. Lower facility capital and operating costs: Because CM processes a batch quantity over time, equipment should have a smaller footprint. This would reduce costs for the entire facility.

3. Better efficiencies: Since material is continuously in process, there should be no "work in progress" material staged and waiting to proceed to the next unit operation.

4. Improved quality and higher yields: The extensive characterization required to establish a continuous process, as well as the monitoring technology frequently used in conjunction with CM, should enable a more consistent quality outcome, eliminate the need for product testing, and enable real-time release of the final drug form.[1]

This article will examine each promise in turn, evaluating how well current continuous OSD processes stack up to the ideal.

SIMPLER, FASTER, CHEAPER

Continuous processing equipment is small, because final production volume depends on how long it runs, not how much it can hold. A 25-kilogram-per-hour (kg/hr) continuous line can theoretically complete a 600-kg batch in 24 hours. But a fluid bed designed to process 25 kg over the course of an hour is significantly smaller—small enough to fit into a laboratory. Thus, the development lab can perform tests on equipment identical to that used in the manufacturing space, and the same equipment can be used for laboratory characterization and commercial manufacturing. As a result, scale-up can be reduced or eliminated.

This significantly reduces API consumption. Even if the R&D and "pilot-scale" development steps for batch and continuous require equivalent quantities of API, the bulk of powder used in development is consumed during scale-up. Eric Jayjock, Director of Continuous Manufacturing at Patheon, estimates that scaling-up to a 300-kg batch will require 2,250 kg of material, while scaling up to a 600-kg batch will require an additional 5,580 kg of material. This

Table A: API usage during development and scale-up phases

	Estimated drug formulation used, kg	Cumulative drug formulation used, kg	API as 10% of formulation, kg	Scale-up cost, API at $5,000/kg	Scale-up cost, API at $10,000/kg
R&D	90	90	9	$45,000	$90,000
Pilot	360	450	45	$225,000	$450,000
Scale-up to 300 kg	1,800	2,250	225	$1,125,000	$2,250,000
Scale-up to 600 kg	3,600	5,850	585	$2,925,000	$5,850,000

powder is discarded after use and is not profitable in any way.[3] If the API is 10% of the formulation and worth $5,000/kg, then the total savings derived from avoiding scale-up are $2,925,000. For a new product, APIs may cost four times as much and can be difficult to obtain if extensive testing is required. Table A is based on Jayjock's cost estimate for scale-up.

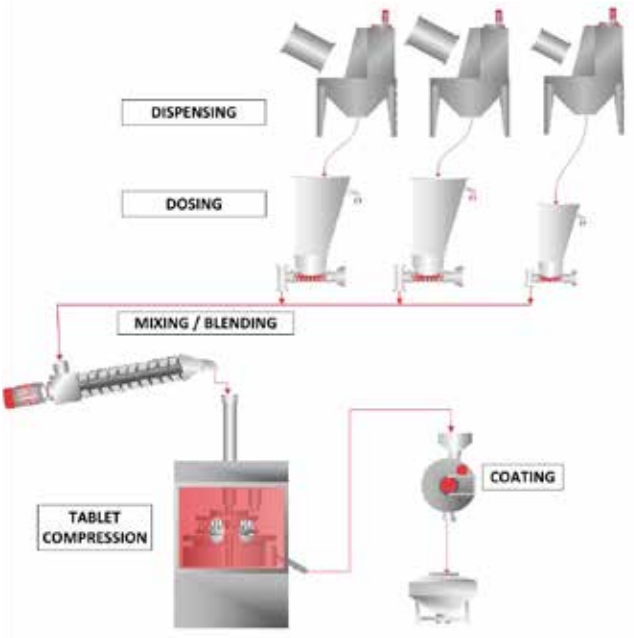
CM development is unlikely to require equivalent quantities of API. Using statistical design of experiment, scientists can test the interactions of multiple parameters rapidly and successively on a CM line. The line is started and held until it reaches steady-state operation for a given set of conditions, then a sample is taken. A parameter or set of parameters is then changed through the control system, steady-state conditions are again reached, and another sample is taken. This can be repeated until all testing is completed. Fernando J. Muzzio, Director of the Rutgers University Center for Structured Organic Particulate Systems (C-SOPS) estimates that it takes between 10 and 45 minutes to test a single data point, and characterization for most products requires between 10 and 40 such data points. This means it can take between a day and a week to complete a full-scale system characterization for a new product.

The number of unit operations necessary to manufacture a product using CM may be less than what is required for a batch process. Granulation processes are frequently developed to create an intermediate product that is robust enough to allow processing through the often-extended batch manufacturing process. Since it takes minutes rather than days to process powder through a CM line, there is not the same generation of intermediate products. David Pappa, Technical Services/Manufacturing Science Director at Lilly, stated that one of the benefits of turning to continuous manufacturing was that it provided additional robustness in allowing utilization of direct compression where that would have been difficult to achieve in a batch process (Figure 1). Lilly's CM line only does direct compression, and if they come across a drug formulation that cannot be done via direct compression on a CM line, their current strategy is to manufacture it in a traditional batch mode. This is one way CM could potentially reduce the quantity and footprint of processing equipment and associated spatial requirements even further.

Despite its smaller footprint and potentially greater efficiency, the up-front cost of purchasing a CM system is significant. Equipment for a full wet-granulation line, including material handling, can run from $12 million to $16 million (Figure 2). A few vendors have bench-scale continuous wet-granulation lines (0.5–1.5 kg/hr) designed to simulate full-scale equipment, which they say can be installed in the corner of a laboratory for as little as one-tenth the cost of a full-scale system. Scale-up for these systems is either mathematical or not required. Even if full testing is desired, however, the total volume of powder consumed in the scale-up will be less than scaling up to a batch process or testing on full-sized CM equipment from the start.

If the API to be used is so valuable that even this reduced consumption seems excessive, there is another option: C-SOPS has spent the last 10 years characterizing powders commonly used in OSD manufacturing. Muzzio says they can use this database of powder characteristics to suggest an analog—a powder that will behave similarly, but cost significantly less. The analog could then replace an expensive API during repetitive experimentation. This substitution is not limited to CM process development, but the benefit became apparent through the C-SOPS efforts to advance CM technology.

Figure 1: A continuous OSD direct compression line



With all this considered, the consensus is that CM has delivered on its promise of faster, cheaper development. That said, there is an up-front cost to adopting any new technology—especially nascent technology. The entire engineering team will have to master and understand new equipment and monitoring systems, and the learning curve can be steep. Additionally, because initial equipment offerings were developed by vendors without significant user input, adopting new technology necessarily means being the beta tester for untried systems, with associated costs in time and money.

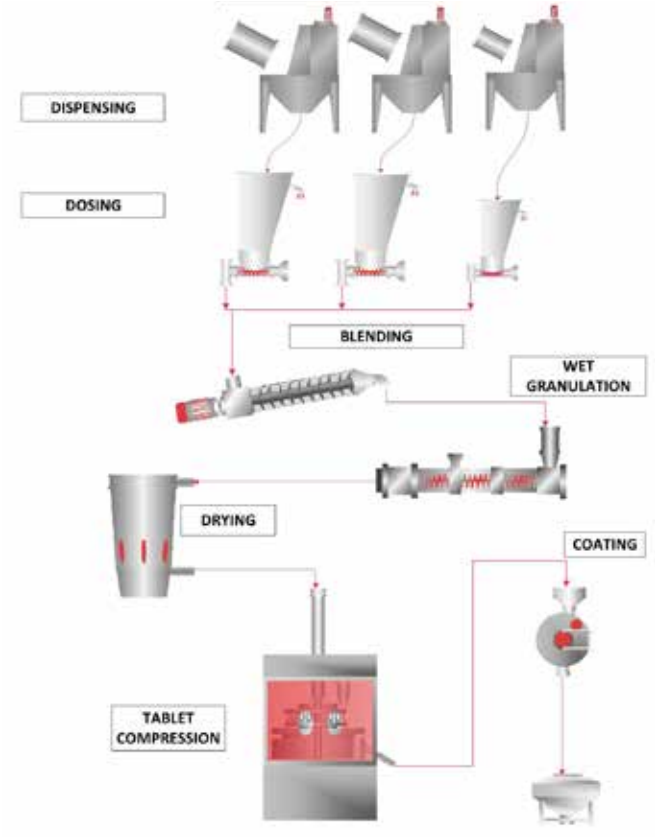
The result is both an exciting new field to explore, and a field of land mines to defuse. One particularly knotty challenge is the loss-in-weight feeders used to meter powders into the blend in precise ratios. The feeders must accurately measure the amount of powder being dispensed even while they are being refilled from bulk dispensers, and this measurement must be based on data from sensitive load cells in a manufacturing environment prone to vibration and noise.[4] This challenge has kept laboratories across the industry busy researching the ideal frequency for refilling the hoppers, the best way to isolate the feeders from environmental disturbances, and how the system should adjust if one feeder changes its feed rate.

While some information has been exchanged between various interested parties, all manufacturers and vendors ultimately work independently on the same problems. Thus, David Pappa from Lilly describes the ratio-control loop on their feeders, which uses the API feeder speed to control the speed of all excipient feeders, thus ensuring

Table B: Estimated cycle time for batch unit operations

Unit operation	Hours
Weighing	3
Blending	2
Granulation	15
Milling	2
Compression	30
QA hold (after each operation)	2

Figure 2: A continuous OSD wet-granulation line



proper content ratios. The Lilly team considers the design fundamental to the success of their line, but they are currently the only manufacturer using it. This type of extensive engineering work by vendors, manufacturers, and academic partners is not typically included in the estimated cost of development for a CM line.

An additional consideration is process analytic technology (PAT), which allows in-process monitoring with the goal of ensuring final product quality. PAT is a discipline of its own, and one with which most OSD manufacturers have little or no experience. Selecting, testing, and creating models for PAT, moreover, takes time that has not traditionally been part of process development. This means bringing workers with new expertise into the development lab.

As newer generations of CM equipment evolve, and as manufacturers develop their own expertise, these costs may drop to levels that correspond to that of batch development. But for anyone considering jumping into CM in the next 5 to 10 years, this up-front investment is a significant consideration.

LOWER FACILITY CAPITAL AND OPERATING COSTS

Because CM equipment is smaller, the facility footprint should also be correspondingly smaller, since an entire room is no longer needed per unit operation and multistory gravity-fed granulation trains are no longer necessary. Smaller rooms also mean lower air-conditioning requirements and related HVAC savings.

A 2010 MIT paper that estimated facility cost-savings for CM vs. batch operations found a 31% improvement in utilities spending, 56% reduction in material handling, 50% reduction in direct labor, and 72% reduction in QA staffing (indirect labor).[5]

Only one company, Janssen, has comparative batch and CM costs for the same product, as they performed a technology transfer from batch to CM for Prezista. While they have not released the actual figures, Lawrence de Belder, CM program manager in the Janssen supply chain, is an unflagging and enthusiastic promoter of the technology. In a 2016 presentation he demonstrated a sample calculation using fictive numbers that others could utilize to estimate their savings by using CM technology.[6]

Floor Plans

Batch size depends on run time in a CM process, but on equipment size in a batch process. This makes it difficult to do an apples-to-apples comparison. A floor plan analysis of three active CM facilities found that between 2,500 and 4,100 square feet (sq ft) were dedicated solely to direct powder-processing equipment space. (Only rooms that housed processing equipment were included in the analysis, since discretionary areas such as washrooms, staging area, corridors, and storage accounted for as much as 70% of the facility.)

A hypothetical batch facility was then configured to match a 20-kg/hr continuous-line throughput using the unit-operation durations shown in Table B. The batch facility, which was capable of four 600-kg batches in one week, would approximately match the CM OSD line production capabilities of the studied facilities over the same time period.

Several OSD batch facility floor plans were also analyzed to determine the square footage necessary to house these operations. The analysis determined that around 9,000 sq ft would be required for direct powder contact unit operations (see Table C). CM facilities would need only about one-third the processing space to be conditioned and cleaned—a significant reduction in HVAC overhead (Table D). This also translates into as much as $2 million in reduced ISO 8 environment construction costs.

Operators

QA release is required after each batch unit operation, but is required

Table C: Estimated process equipment room square footage for a batch facility capable of matching the capacity of a 20-kg/hr continuous OSD line running 24/7 over the course of a week

Parallel 600-kg batch facility	Sq ft
Weigh/disperse	1,116
Blending	1,722
High-shear granulation	1,370
Fluid-bed drying	1,662
Compression	1,818
Coating	1,580
Total processing space	**9,268**

only after process completion for a continuous process. This essentially eliminates in-process testing labor. It is not clear, however, how much direct labor is actually saved by switching to a CM process. While in theory CM staffing requirements should drop significantly because all the equipment is in two or three rooms, real-world numbers tell a slightly different story.

The average number of operators for a dry-granulation continuous process hovers between four and eight, depending on the process and employer. The average for a dry-granulation batch process, assuming that each unit has two full-time operators and all units are operating simultaneously, is six to eight.

Moreover, while daily batch process operations can be performed by any skilled operator, continuous equipment is new and complex enough that frequent support may be required from the PAT lab—an indirect labor expense that is often overlooked. This number may be expected to decrease as organizational expertise increases and systems become better known, or it may go down for another reason, says Savitha Panikar, a PAT scientist for Hovione. Some companies, she reports, have been pushing to minimize the use of spectral probes in CM line monitoring to minimize the complexity they add to regulatory filings.

Some argue that a good control strategy can ensure product quality without in-line PAT measurements. In response to a June 2017 FDA docket on continuous OSD manufacturing,[7] GSK noted that "PAT applications used during development ... may not always be required [during commercial manufacturing]."[8] In their comments on the docket Merck echoed this reluctance to presume the use of PAT at the commercial level, stating, "Different levels of control, such as PAT usage, sampling frequency, and RTD models may be appropriate for different products and processes."[9] If this presages a move toward alternative control strategies, the costly involvement of PhDs in the daily operation of continuous manufacturing lines would be reduced.

IMPROVED EFFICIENCIES

Pharmaceutical batch production equipment may have a capacity utilization as low as 30%, while in other industries using CM

Table D: Process equipment room square footage for a continuous OSD manufacturing line

20-kg/hr continuous OSD facility	Sq ft
First level processing space	1,037
Mezzanine / midlevel processing space	911
Third level processing space	1,084
Total processing space	**2,436**

utilization can be as high as 90%.[10] But while this conjures images of manufacturing lines churning out identical widgets for weeks, months, or even years on end, the reality in pharmaceutical manufacturing is not as heartwarming. This stems from a few factors.

The first reason efficiency remains low is product demand. While blockbuster drugs and OTCs could keep a CM line running 24/7, many drugs currently in the pipeline have a lower demand projection. Indeed, while talks about CM are going on at one end of the ISPE Annual Meeting, there are concurrent seminars on personalized medicine and 3D printing at the other. As companies seek profit in the long tail of medicine, the number of tablets required for the subject population drops, and the residence time required on a CM line drops as well. As a result, CM lines in OSD pharma are more likely to run multiple, similarly formulated products for shorter periods requiring a changeover in between runs more like a packaging line than a food production line.

Second, FDA regulation adds an additional level of complexity that further reduces efficiency. Pharmaceutical manufacturing processes must be validated, and each validation will cover a single batch of a given size. CM batch sizes must therefore be determined before the production run begins. If validated for a three-day batch, the line must stop producing at the three-day mark, even if it's at steady state and showing every sign of hitting quality targets.

Eric Jayjock has proposed that facilities could campaign batches without stopping in between. In these cases, the original FDA product-approval filing would include a protocol to describe how these longer campaign times would be validated. The protocol would be product-specific, as each one would have a unique risk profile. By doing this, longer (and more efficient) run times could be validated.

At the moment, however, no one is actually doing this and most express discomfort with the idea, often citing microbial concerns. Lilly has validated to the size of their batch coater, and they do not anticipate extending batch sizes. Janssen has a run time of 32 hours for Prezista, which must be followed by four shifts of cleaning, disassembly, and turnover. Vertex also runs for a few days and then spends as much or more time cleaning and reassembling.

And therein lies a third complication: Complex equipment with extensive changeover requirements means efficiencies still float below 50%. Vendors created CM equipment in anticipation of a new market, but manufacturers' limited experience has prevented them from articulating their needs with any kind of specificity. Now, with greater knowledge and understanding, reduced changeover requirements are on nearly all industry wish lists.

After shutdown, equipment must be disassembled, removed to a washroom, cleaned out of place, and reassembled. One company cleans 2,700 individual parts between batches. This makes cleaning validations both difficult and costly (and yet another up-front cost not typically included in cost-of-CM estimates). Modular parts can take some of the pain out of this, but simpler assemblies or even equipment that can be cleaned in place would make a more significant dent in the problem. Janssen has added WIP and CIP capability to some of the equipment on their later lines, and other companies are seeking to follow suit.

In contrast, batch equipment for a unit operation can be cleaned and changed over while the next unit operation proceeds to completion. In an efficient facility, the first unit operation can be cleaned, changed over, and running a second product while the tablet press is still finishing the first product. On a continuous line, all unit operations are closely connected, and there is negligible time difference between shutting down the first unit operation and shutting down the last. The entire line must be down for the duration of the cleaning process.

Right now, the requirement to spend as much time cleaning as running prevents continuous OSD from achieving the high efficiencies that CM promises. With Patheon coming online in the near future, it will be interesting to see if they bring a new paradigm to the issue of run time.

HIGHER QUALITY AND BETTER YIELD

Running a continuous process requires extensive characterization in the lab and a deep knowledge of the process that is compatible with quality by design (QbD). PAT is frequently used to track critical quality attributes and adjust critical process parameters during the process before the product can go out of spec.

The users interviewed for this article are unanimously enthusiastic on this point: Building quality management into the process has been successful. At the C-SOPS 2017 Annual Meeting, Muzzio stated that continuous processes, on average, have a quality failure rate of 1.5%, compared to 4% for batch processes.

A highly desired potential outcome of in-line monitoring is real-time release testing. If critical quality attributes can be tracked throughout the process—or tied to characteristics that can be tracked throughout the process—then the final product can be proven in-spec based on process measurements alone, without the requirement that they be tested in the lab.

There are a number of release tests that must be performed, and many can be replaced by good data from a monitored CM line. The largest exception to this is dissolution testing, which involves studying how the tablet breaks down in a warm and agitated water bath designed to simulate the human body. Because of this requirement, there is currently no product that can go straight out the door after coating. There is widespread optimism that this may soon change, however. Muzzio says they have created a dissolution model for at least one product that would allow in-line measurements to replace this release test.

While process monitoring has been a boon to the QC department, it does have a grey lining. We've already covered the complexities that PAT brings to daily operations, but there's another side effect:

lower yield. When all equipment is running and inputs are steady and predictable, a continuous process running in a steady or controlled state will produce product of consistent quality. During startup—and to some extent during shutdown as well—the continuous line is not necessarily in a controlled state, and product will be diverted to waste. At least part of this lag in reaching operational conditions at startup may be the result of near-infrared probe warmup time.[8]

On a CM line running for weeks or months, the startup and shutdown losses are negligible. But on a line that runs for only a few days this waste balloons as a percentage of the total product. While none of the interviewed manufacturers agreed to publish their yield numbers, none cited anything above 95%, and some processes were considerably lower. All were philosophical about it, however, saying it was too soon to measure; there was debugging to do and experience to be gained.

There are a few possible solutions to this issue. The first would be longer run times, but this hits a limit of utility with all but blockbuster products or those with long shelf lives. Installing smaller systems with lower throughput rates would waste less during startup and shutdown, and would also lead to longer runs for comparable batches, which would address the equipment efficiency problem. The trade-off is higher equipment occupancy for the same production quantity, which could become an issue as more and more products are developed for CM. It is also difficult to meter minute quantities of API accurately using existing feeder technology.

A third potential solution would be equipment that primes rapidly and reaches a controlled state quickly. Tablet presses are already capable of this to a large extent. If feeders and blenders could be improved to the point where low powder levels don't throw mechanisms off, yield losses could be drastically reduced.

CONCLUSION

Continuous OSD is young. Vertex received approval to manufacture as Orkambi in 2015, Janssen's Prezista was approved in 2016, Eli Lilly came onboard with Verzenio in 2017, and Vertex scored again with Symdeko in 2018. It is therefore perhaps premature to deliver a report card on its successes and challenges. The companies I spoke to seemed to think so, saying it was too early to evaluate returns on the new technology.

"Better efficiency is dependent on a number of aspects which are not necessarily valid from the first batches you start running on a CM line," said Lawrence de Belder. "It can take some time—experience, debugging, process optimization—before achieving aspirational yields."

Indeed, in reviewing the scorecard, CM falls short when it comes to delivering a simpler, more efficient process with superior yields. Manufacturers are generally happy, on the other hand, with QbD and facility, operational, and development costs.

The good news is that these shortcomings are fixable. Improved process efficiency is an ongoing goal in any facility; in CM it's shared by vendors and manufacturers, and supported by the FDA. The technology has arrived, and we have some brave early adopters. From here it should only advance, as users provide feedback to vendors who provide better equipment, in an ongoing loop of continuous improvement.

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REMOTE OBSERVATION TECHNOLOGIES

Revolutionizing the Pharmaceutical Manufacturing Space

Nick Haycocks, CEng, FLMechE, and Graham Milne, MPhys, PhD

I. INTRODUCTION

Contemporary communications technologies, particularly those relating to the internet, have the potential to revolutionize pharmaceutical manufacturing practices. The judicious use of network communication tools may benefit manufacturing operations in a number of different ways. For example, mobile communications tools adapted for cleanroom use will empower remotely-located subject matter experts to assist staff on the factory floor in both training and troubleshooting. Remote access to real-time manufacturing system data can expedite maintenance procedures and has led to analytical tools (both local and cloud-based) appearing on the market for automated, preventive maintenance solutions. Network video products will complement all these efforts; cameras embedded inside critical manufacturing processes can stream live video for use by staff located anywhere on a company's global network. Some companies are embracing all of these concepts. This opinion piece is intended to explore these applications and how they relate to the pharmaceutical industry.

2. THE BUSINESS CASE FOR PHARMACEUTICAL MANUFACTURING CONNECTIVITY

The pharmaceutical business is becoming increasingly global, with many established companies looking to expand into emerging geographical markets. In some cases, local policies and logistical considerations may require products to be manufactured within that territory. Inevitably this model predicts a proliferation in the number of manufacturing sites that larger firms will be required to operate. This may lead to smaller, localized manufacturing sites managed using an economically-appropriate workforce, which may deny them the full suite of engineering talent afforded to larger, global manufacturing sites.

By properly using network-based communication technologies, companies can better share their global expertise with these smaller operations. This approach offers business advantages in areas such as travel and productivity. First, international travel constitutes a major cost for global business. Improved communications tools can be correlated directly to a reduction in travel spending. Second, real-time network communications can expedite technical resolutions and reduce system downtime. Of course, these business arguments are not new. Nevertheless, contemporary and emerging virtual-presence solutions, particularly in the wearable technology space, have the potential to make international network-based collaboration more effective than ever.

Figure 1: The remote visualization camera system network connectivity is implemented on the business network, and completely segregated from the automation, which resides on the manufacturing network.

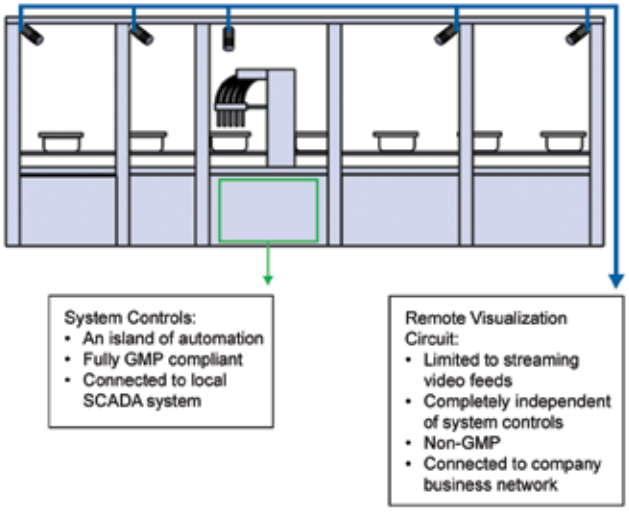
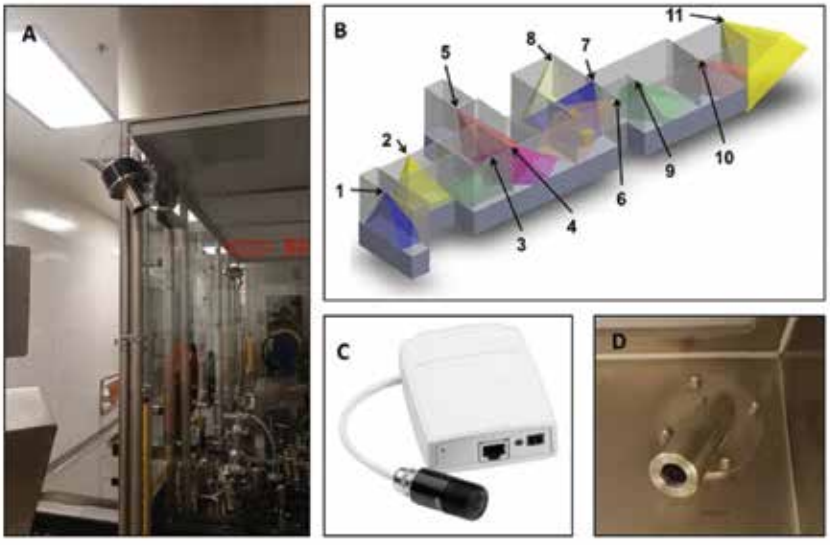
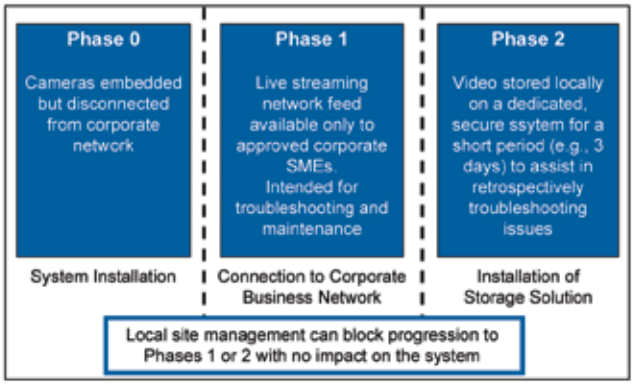


Figure 2: A) Camera mounted outside of a fill line isolator. B) drawing showing camera coverage from 11 locations. C) An Axis P1214 network camera used for this application. D) Stainless steel VPHP-compliant housing provided by system vendor inside the isolator. The caustic environment and airflow considerations inside the isolator drove to the selection of a small format camera with a low thermal footprint.



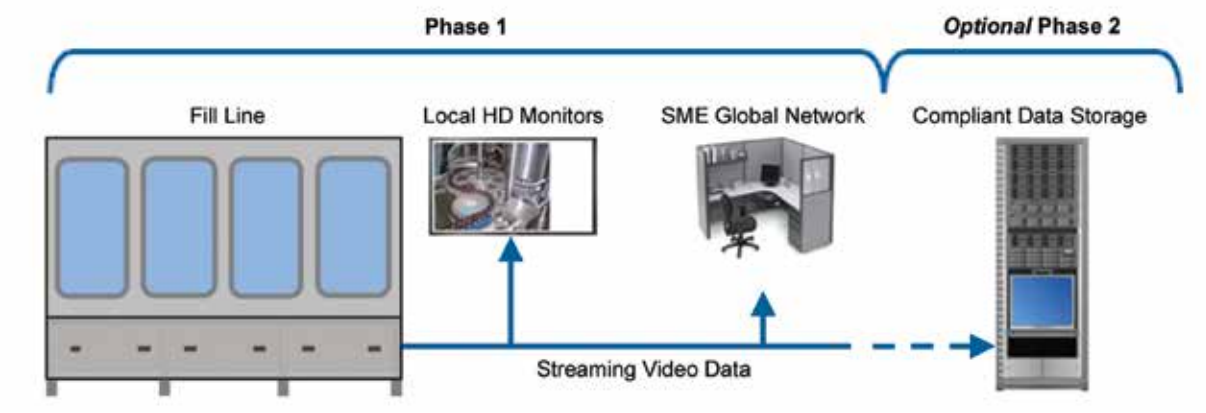
Images used with permission from Bausch+Ströbel, www.bausch-stroebel.com/en, and SKAN AG, www.skan.ch/en.

Figure 3: Camera technology, once integrated into the line, can be leveraged in a phased approach. This allows real-time usage of the system while considerations around (for example) GMP video data storage and potential regulatory concerns are addressed.



Video communication does not have to be limited to peer-to-peer communication between staff members. Companies have begun integrating network cameras into manufacturing systems. In addition to the benefits outlined, cameras integrated onto the line can serve to elucidate areas within the system that may be hard to see or access during normal operation. The primary driver is to have live, streaming video available for supporting staff during maintenance and troubleshooting procedures. As an extension, however, there is the potential for using temporarily-stored video streams to retrospectively analyze and investigate adverse events.

Figure 4: Video data storage can be devolved to a secondary phase if compliant data storage is a concern.



The compliance implications of this concept are discussed below.

As a corollary, all of these models can also be applied to the relationship between manufacturer and system vendor. Generally speaking, through an appropriate network security policy, companies could temporarily connect system vendors to machines hosted on the company's network, thereby allowing direct support from the system experts.

3. CAMERA ARCHITECTURE—SEPARATE AND DISTINCT ROOM CONTROL LOGIC

The concept of cameras embedded within a manufacturing system is nothing new—industrial cameras have been used as critical components in pharmaceutical lines for decades. Generally, these cameras, especially "smart" cameras, are qualified, validated measurement devices, fully integrated into the machine's control logic.

In this article we are proposing a wholly separate camera application. The network-enabled streaming cameras operate in complete isolation from the system architecture. Since they do not contribute to product inspection and any pass/fail decision, there is no intrinsic need for such devices to be fully validated and compliant. The proposal is that such cameras would be used only to provide operational information and not for any product quality-related decision (Figures 1 and 2).

4. COMPLIANT DATA HANDLING AND STORAGE

In addition to live streaming to relevant employees across a company's global network, embedded cameras present another opportunity with respect to data storage considerations. Long-term data storage is for the most part not pragmatic when costs are considered; however short-term data storage, perhaps over a matter of days, is eminently feasible. In a manner very similar to contemporary dashboard camera solutions for road vehicles, video could be stored for a short time in an effort to capture adverse events, particularly equipment malfunctions. This could assist enormously in subsequent root-cause investigations, especially if the video coverage of a given line is suitably comprehensive.

FDA 21 CFR Part 11[1] compliant video storage solutions are technically feasible; however, if the video is intended only for system troubleshooting and is not used for drug product lot release, we believe such a solution can be implemented without being considered an integral part of the validated production platform (Figures 3 and 4).

5. CHALLENGES IN THE PHARMACEUTICAL MANUFACTURING SPACE

The technologies discussed in this document are readily available and, in some cases have traction in other major industrial markets. The pharmaceutical industry has some unique challenges that need to be met. These may be further compounded by legal considerations associated with the jurisdiction of a particular manufacturing location.

First, pharmaceutical manufacturing generally requires the use of cleanroom manufacturing protocols. Mobile peer-to-peer communication solutions must reside permanently within the clean space. The requirements of the cleanroom place constraints on the design and materials used in the construction of an approved device. The high density of piping and supporting utilities in a typical plant generally diminishes cellular reception, forcing the need for an effective local wireless network.

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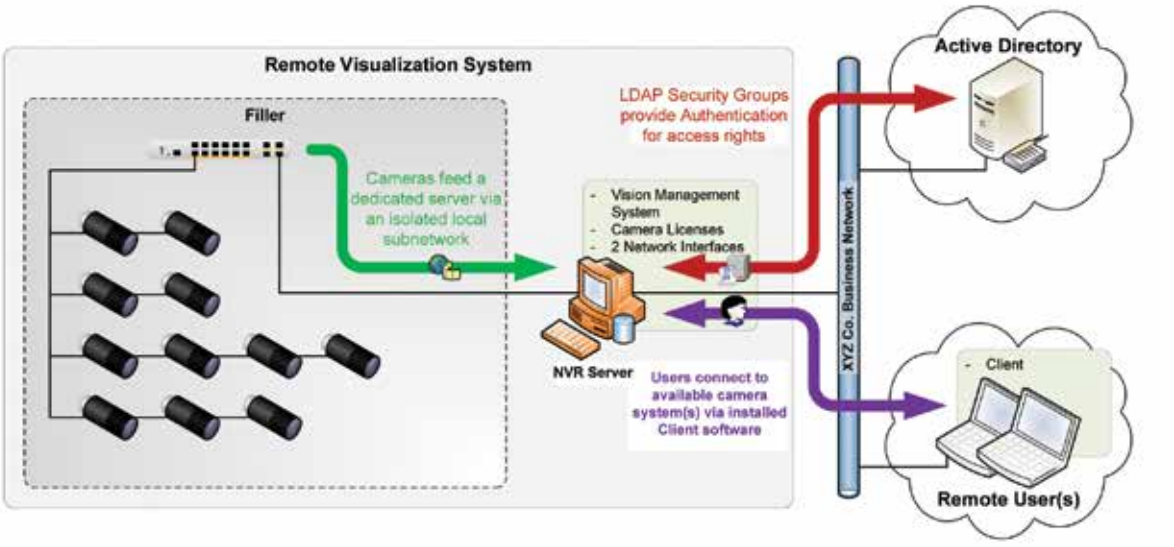
Figure 5: This image shows the overall architecture used at one company. A server, separate and distinct from the manufacturing system, is used to manage all of the camera feeds. Software on the server controls user access and also allows optional, programmable video data storage capability.



growing in importance, with several new monitoring and reporting platforms emerging in recent years from a variety of vendors. In the past, "islands of automation,'" monolithic manufacturing systems largely isolated from the internet and controlled solely through local Human Machine Interfaces (HMIs), were the standard across the industry. With the advent of the Internet of Things (IoT), we can benefit from leveraging the explosion of cloud-based industrial diagnostic tools. Connecting systems to the internet inherently introduces data security risks that must be mitigated through the diligent application of appropriate security policies and architecture.

Network cameras, if broadcast globally across a company's network, are subject to network considerations. High performance cameras represent a challenge in terms of pragmatic bandwidth consumption. In reality, network video solutions require modest video resolutions and substantial video compression in order to achieve a viable real-time viewing experience over long distances.

In some jurisdictions the use of cameras in the manufacturing space, whether mobile or embedded into production equipment, can conflict with local employment laws. Proper implementation of camera-based technologies must consider local legislation.

Regulatory considerations in this space present a challenge, especially with regard to short- or long-term video data storage, as well as potential uses of that data. Here we propose that video data can be retained in the short term to assist with qualification and maintenance of systems without complicating normal GMP use of the machine (Figure 5).

6. CONCLUSION

Emerging network-based video solutions have the potential to improve operations in the pharmaceutical manufacturing space. With that said, the industry needs guidance from regulatory authorities to ensure that these technologies are implemented in a manner that does not compromise the viability of otherwise compliant manufacturing lines. It is our hope that this article stimulates discussion and stimulates discussion with a view to the clarification of regulatory expectations.

Acknowledgments

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EQUIPMENT SURFACES

Redefining Acceptable Conditions to Eliminate Unnecessary Maintenance

Michael Mietzner, Andrew Harris, James Heimbach, and Kevin Aumiller

Although other industry publications have explored the effect of surface finish on biofilm formation, background data indicating that imperfections exceeding the American Society of Mechanical Engineers (ASME) Bioprocessing Equipment (BPE) standard are detrimental to chemical cleaning performance are lacking.[1] This paper explores the experimental design used to define appropriate remediation criteria by evaluating when cleaning capability is affected by aging and/or chemical degradation of process contact surfaces.

CURRENT APPROACH

In the pharmaceutical industry, 316L stainless steel equipment surface finishes are carefully controlled to ensure a high degree of quality in manufacturing operations. Standards such as those found in ASME BPE Part SF provide strict guidance relative to surface anomalies with the goal of enhancing cleaning capability and providing bioburden control. Imperfections in the surface finish may inhibit cleaning capability by providing voids in which process soils or microorganisms may become embedded. As such, specifications for imperfections like surface roughness, pit diameter, pit density, scratch depth, and scratch length are provided. Manufacturers adopt the acceptance criteria defined in the ASME codes and standards to aid in new equipment acceptance activities.

The surface finish specifications provided in ASME BPE are typically supplemented by other requirements for bioprocessing equipment. Standards defined in API 579/ASME FFS-1* and the National Board Inspection Codes define fitness for service as well as installation, inspection, and repair requirements for pressure vessels to ensure safe operation. Although these safety considerations are critical for the overall design program, this technical paper focuses on the importance of surface finish, including pits, scratches, and surface roughness, relative to the cleaning capability.

Relative to the anomalies (indications) defined in the ASME BPE

* A comprehensive consensus industry-recommended practice developed by the American Petroleum Institute and the American Society of Mechanical Engineers

Figure 1: Wear mechanisms

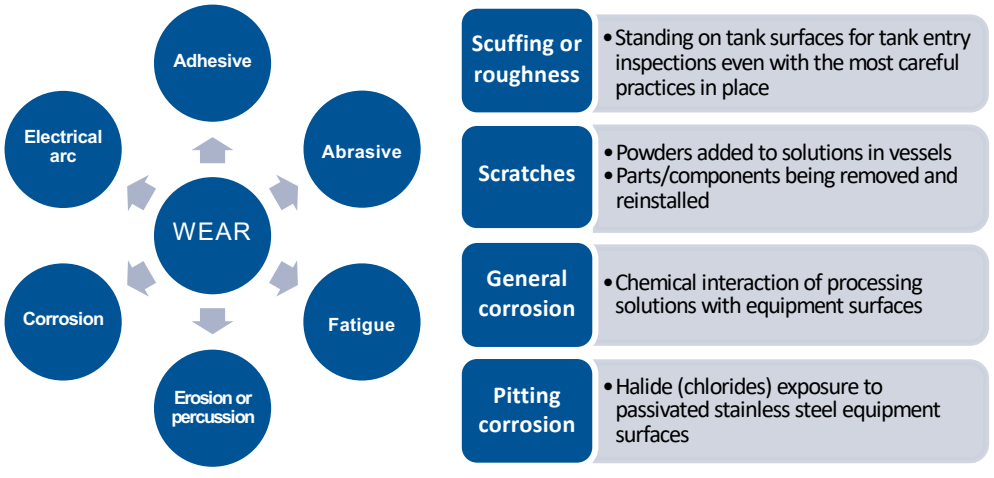


Table A: Process contact surface finish anomalies[2]

None accepted	Allowed within defined acceptance criteria
Dents	Pits (individual and clusters)
Nicks	Scratches
Surface cracks	Surface inclusions
Surface residuals	Fixture and finishing marks
Blistering	Orange peel
Porosity	Stringer indications
Weld slag (fittings, valves, vessels, components)	Weld whitening
	Weld slag (tubing)
	Cloudiness
	End grain effect
	Haze
	Variance in luster

Part SF specifications, post-fabrication quality aspects such as dents and surface cracks are deemed not acceptable at any level and are avoidable in construction. Other anomalies associated with metallurgical aspects and artifacts (e.g., pits and surface inclusions) are allowed within detailed acceptance criteria, as they are technically unavoidable.

UNAVOIDABLE WEAR ASSOCIATED WITH MANUFACTURING

Upon acceptance, equipment is typically installed, released for commissioning and validation, and then released for use. Over its life span, the equipment will be used by production facilities for a wide variety of activities that can affect surface conditions. Good manufacturing, engineering, and maintenance practices minimize but never eliminate this inevitable wear. Manufacturing activities such as raw material/utility usage have the potential to induce abrasion and corrosion. Routine equipment setup and inspection can scratch surfaces as components are removed and installed. All of these activities produce unavoidable cumulative wear in the form of scratches, pits, and changes to the surface roughness (Figure 1). Rouge effects on cleaning efficiency and surface finishes have been studied in other references and are not included in this evaluation.[3]

Current Response to Wear

Manufacturing and maintenance personnel typically perform visual inspections of process contact surfaces to ensure compliant and problem-free operation (per ASME BPE definitions, process contact refers to all equipment that comes in contact with the designated product, either directly or indirectly). These inspections can occur after every clean-in-place (CIP) activity and/or as part of routine maintenance. Inspection provides the opportunity to identify anomalies on those surfaces.

Common anomalies are small in relation to the overall equipment surface area and many are difficult to view at distance on a highly reflective, mirror-like surface. The challenges associated with detecting these anomalies can lead to several problems in a manufacturing operation, including the following:

- Discerning whether an anomaly has been recently created or was a previously accepted artifact of construction. Are you remediating a construction artifact that was once accepted based on the ASME BPE criteria?
- Disruption of manufacturing operations. Remediation response can involve particulate-generating activities (e.g., grinding) within cleanroom areas. This can create production-schedule disruptions, and typically creates more nonuniformity of the surface condition.
- Assessing safety, identity, strength, quality, and purity (SISQP) impact on the biopharmaceutical product. Identifying any anomaly during inspection may indicate surface-cleaning issues. These should be evaluated to determine whether inadequate cleaning has affected (or has the potential to affect) the product.

Remediation can range from ignoring the issue (not recommended) to immediate action. An overly conservative approach that requires immediate remediation may produce production stoppages, more tank entries, and more process contact surface wear. This is a cycle worth breaking in favor of a risk-based approach that assesses anomalies in the context of SISQP impact and provides remediation pathways based on relative cleanability data, combined with other risk factors specific to a manufacturing site.

Acceptance criteria sensitive to SISQP impact are a key piece missing from this approach, however. The challenge is to determine criteria based on inflection points of cleaning success across critical controlled anomaly dimensions. Inflection points identify the critical dimensions of anomalies at which cleaning efficacy transitions from acceptable to nonacceptable performance. These inflection points can be used to derive acceptance criteria that would not affect product SISQP, but would assure full cleanability of equipment surfaces.

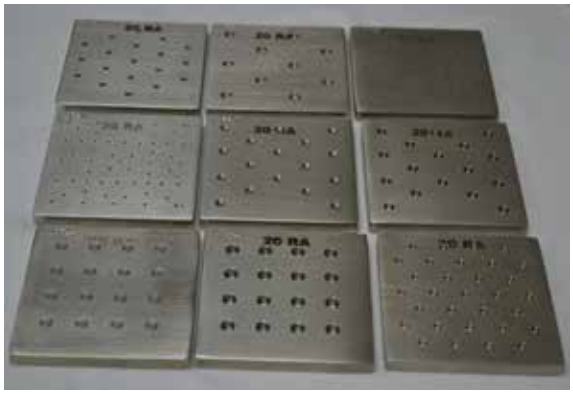
THINKING DIFFERENTLY

A surface cleanability study to identify appropriate acceptance criteria for common anomalies was conceptualized with the following framework:

- Define typical surface anomalies and dimensional ranges
- Use a cross-section of soil types to evaluate effect on cleaning
- Use a cross-section of cleaning chemistries
- Identify true inflection points in cleaning degradation

Given the range of testing desired in this study, bench-scale testing was the only viable option to explore the targeted surface anomalies. This required development of methods for surface anomaly creation, soil identification and replication, cleaning agent selection, test fixture design, and measurement system selection to elucidate differences in cleaning capability that reflect at-scale conditions suitably.

Figure 2: Surface anomalies; pitted (left), scratched (right)



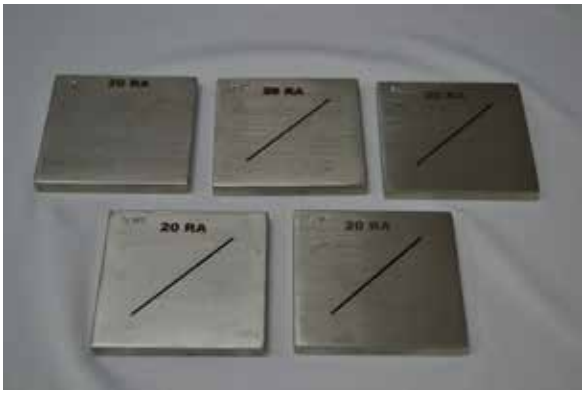


Table B: Coupon dataset

Coupon	Variables	Fixed attributes	Method
Surface roughness	20–150 microinches (µin), Ra	N/A	Sheet metal, grinding wheel
Pitting	0.2–5.0 mm depth 1.2–5.0 mm diameter 1–5 density factor (0.04–3.33 aspect ratio)	20 µin, Ra	Plate metal, milled cylindrical
Scratch	0.2–5.0 mm depth	50.8 mm length 1.0 mm width 45° angle	Plate metal, cutting wheel
Micropitting	40–2,600 micropits per coupon	N/A	Electrochemically etched

SURFACE ANOMALY CREATION

Test coupons comprised of 316L stainless steel (SS316L) were used as the basis for the study. These 2.5 inch × 2.5 inch coupons were constructed from sheet metal and plate metal.[4] The coupons were machined to achieve the desired surface anomalies, including a range of surface roughness factors, pits, scratches, and micropits, as depicted in Figure 2 and Table B.

Dimensional boundaries were based on a review of all previously measured anomalies for a 2-year period at a large-scale biopharmaceutical manufacturing facility. Pit geometry was chosen to be cylindrical to represent worst-case cleaning turbulence compared to conical pits. Precise control of diameter and depth was crucial for statistical comparison; therefore, the coupons were not exposed to additional corrosion to avoid uncontrolled variability. The density factor (i.e., number of pits per unit area) was derived from the ASME BPE specification of a cumulative total diameter for pits within an inspection area (Table A). Diagonal scratch geometry provides both horizontal and vertical orientation components.

SOIL SELECTION AND APPLICATION

While process soils were utilized for addendum studies, most of the dataset utilized a surrogate soil to provide adequate resolution of data to generate inflection points. Many process soils pose little challenge to the cleaning system and, therefore, may provide poor statistical resolution between different test conditions. This is especially true of soils that may be removed sporadically in large pieces, which creates too much variability to quantify inflection points using continuous predictors. Selecting soils that dissolve in a more predictable fashion is necessary to generate inflection points.

To reconcile the need for process scalability with the desired study outcomes, two different studies were executed with different soils.

Primary Study: BSA Surrogate Soil

A surrogate soil composed of bovine serum albumin (BSA) and fluorescein was used as the primary material for the study. BSA was chosen because it is a representative proteinaceous soil with a removal rate that can be tuned through heat treatment to a beta-sheet conformation.[5] The change in conformation creates a soil that dissolves steadily when exposed to cleaning agents, allowing relative removal rate to be adjusted up or down to minimize variability, and to gauge removal as a function of the surface attributes. Fluorescein, a molecule with the ability to fluoresce under ultraviolet (UV) light, was included as an additional detection method. The concentration of BSA and fluorescein in the mixture was optimized for suitable soiling weights and fluorescent detection, resulting in a 10% BSA and 0.011% fluorescein mixture.

Addendum Study: Process Soils

Process soil 1 was a solution from a monoclonal antibody production process mixed with fluorescein. Process soil 1 was the most challenging (worst-case) soil to clean from stainless steel within this manufacturing facility. Like the BSA surrogate, the fluorescein was added to include another detection mechanism.

Process soil 2 was a surrogate soil used to represent a known worst-case hydrophobic air–liquid interface cleaning challenge. Unlike the other soils, fluorescein was not added due to compatibility issues with the chemistry.

Figure 3: Falling film apparatus

While the range of surface anomalies was characterized with the BSA–fluorescein surrogate, the two process solutions were evaluated to ensure that the identified trends represented at-scale conditions.

With the different soils identified, a consistent soiling method had to be developed. Homogeneous distribution of soil over the coupon surface was important to ensure penetration into the various surface anomalies. The backs and edges of the test coupons were covered with contact paper and submerged in a 1,000 mL beaker containing the process soil mixture agitated at 200 RPM. After 5 minutes of exposure, the coupons were removed from the agitated solution and allowed to dry overnight with the surface imperfections facing upward. Once dry, the contact paper was removed carefully to avoid peeling the dried soil from the face of the coupons.

The dried BSA–fluorescein coupons were then heat-treated to induce the conformation of the protein. This caused the protein to denature and bound it more tightly to the coupon's surface in a predictable fashion. The temperature for heat treatment was empirically determined to optimize the concurrent dissolution of BSA and fluorescein during cleaning. When applied to coupons without surface anomalies, treatment at 90°C for 60 minutes created a condition that allowed the mixture to be completely removed in a 5-minute cleaning cycle. Results from coupons with surface anomalies could then be normalized when using the same cleaning time.

The same submersion system was used for the process soils used in the addendum studies. While the coupons were dried overnight and the contact paper was removed prior to testing as before, they were not subjected to heat treatment.

CLEANING CHEMISTRY SELECTION

Various chemical recipes using commercial alkaline detergents types CIP 100 and CIP 150 were used for the studies. An additional commercial surfactant CIP additive was also used. The first cleaning regimen of 1% CIP 100 at 60°C was chosen to perform the surrogate (BSA–fluorescein) anomaly studies to best represent standard caustic cleaning approaches throughout the industry.

The addendum studies utilized known successful cleaning regimens with the selected process soils:

- Process soil 1: 1.3% CIP 150 at 60°C; process soil 2: 5% CIP 100 + 5% CIP additive at 80°C

In addition, cleaning regimens used onsite for other soils were tested with process soil 1 to evaluate cleaning chemistry interactions with the soil and surface-anomaly combinations:

- 1% CIP 100 at 60°C
- 0.2N* NaOH at 20°C
- Purified water at 80°C

* Normality (N) is an expression of concentration as equivalents of solute per liter of solution. A 1 normal (1 N) solution of NaOH contains 1 mole per liter of hydroxide.

Figure 4: Fluorescent percentage failure for scratched coupons

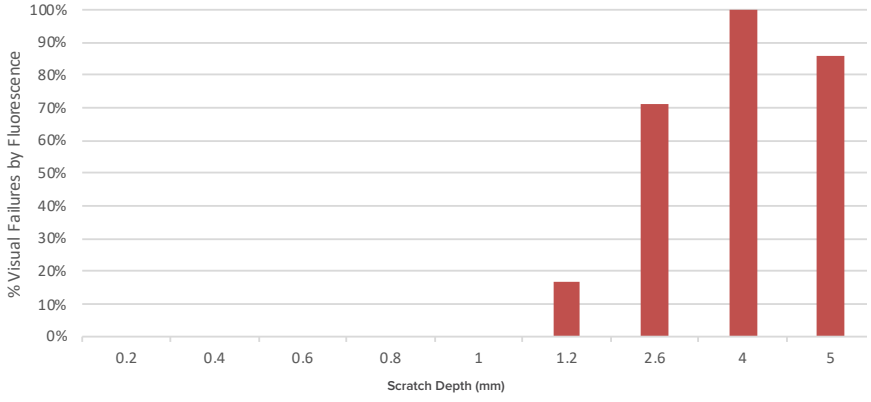


Table C: Summary of study statistics—gravimetric and TOC for BSA and addendum studies

Surface imperfection		*p* values		
		Gravimetric (BSA)	Gravimetric (addendum)	TOC
Micropits	Density factor	0.917		
Scratches	Depth	0.000[A]	0.369	0.637
	Cleaning agent		0.642	0.000
	Depth × cleaning agent		0.866	0.859
Roughness	Ra	0.135		
Pits	Density factor	Dropped	Dropped	Dropped
	Pit depth	Dropped	0.120	Dropped
	Pit aspect ratio	0.007	Dropped	Dropped
	Density factor × pit depth	Dropped	Dropped	Dropped
	Density factor × pit aspect ratio	0.000	Dropped	Dropped
	Pit depth × pit aspect ratio	0.000[B]	Dropped	Dropped
	Cleaning agent		0.014[C]	0.000[D]
	Soil		Dropped	Dropped
	R^2 adjusted	0.900	0.130	0.900

A Depth > 1.0 mm will trap residue
B Diameter > 4.0 mm with depth > 2.6 mm will trap residue
C Dominant variable
D Dominant variable, CIP 100 had the lowest TOC

$p < 0.05$
$0.15 < p < 0.05$
$p > 0.15$

BENCH-SCALE TEST FIXTURE CREATION

Figure 3 provides an example of the falling-film fixture used in this experiment. A variable-speed centrifugal pump was used to control cascade flow rate across the faces of the coupons. The flow rate was set to yield a Reynolds number of 3,000. This mimicked a turbulent falling film at 60°C, representative of field conditions within a process vessel.[6] Cleaning solution temperature was maintained using an immersion heater with proportional–integral–derivative control.

MEASUREMENT SYSTEM SELECTION

Three metrics were selected to characterize cleaning efficacy as a function of the different surface anomalies. The first was mass removal percentage. Mass measurement using an analytical balance provided a continuous dataset with a resolution of 0.3 mg that could be analyzed using regression tools. Test coupons could be measured prior to soiling, after soiling, and after cleaning to assess the relative removal of the soils from the surfaces. This gravimetric analysis was applied to all process soils in this study, as it is nonspecific.

Binary visual inspection methods were employed to complement the mass-removal percentage. This included inspection under both laboratory lighting and fluorescence to detect the fluorescein component. The presence of any residual soil was recorded as a failure, and the percentage of coupons failing visual inspection was used as an orthogonal measurement to mass-removal percentage. This provided a second independent metric to evaluate trends in the cleaning efficacy. Like the mass measurements, visual inspection could be applied universally to all soil types in this study without the need to develop specialized tools.

The final metric for the studies was total organic carbon (TOC) analysis of swab samples. This tool required a validated method that was transferred into the testing laboratory prior to use. While developed for process soil 1, TOC analysis provided a measurement of residual soil (down to < 1 µg/cm²). This continuous measurement, like gravimetric analysis, could be used in regression analyses to identify trends and significant variables that influence cleaning efficacy for the addendum study.

EXPERIMENTAL APPROACH

Cleaning time was empirically determined in screening tests to normalize the dataset against a control value. The control was defined as the time required to completely remove the various soils from an unmodified coupon with a 20 µin Ra finish using 1% CIP 100 at 60°C. Normalizing the data in this way minimized scale and soil comparability factors; this was crucial to ensuring the data were relevant to at-scale conditions. Cleaning times were found to be 5 minutes for the BSA surrogate, 2 minutes for process soil 1, and 30 minutes for process soil 2.

Soiled coupons were cleaned and then allowed to dry prior to measurement. For all studies, each set of experiments tested two coupons simultaneously. The order of coupon exposure in the testing system was randomized and performed with three replicate runs for each anomaly. The orientation of the coupons with respect to the cleaning agent flow was also randomized. One 20 µin Ra control coupon was included with each set of coupons soiled at a given time.

Figure 5: Contour plot of percent removal for pairs of factors

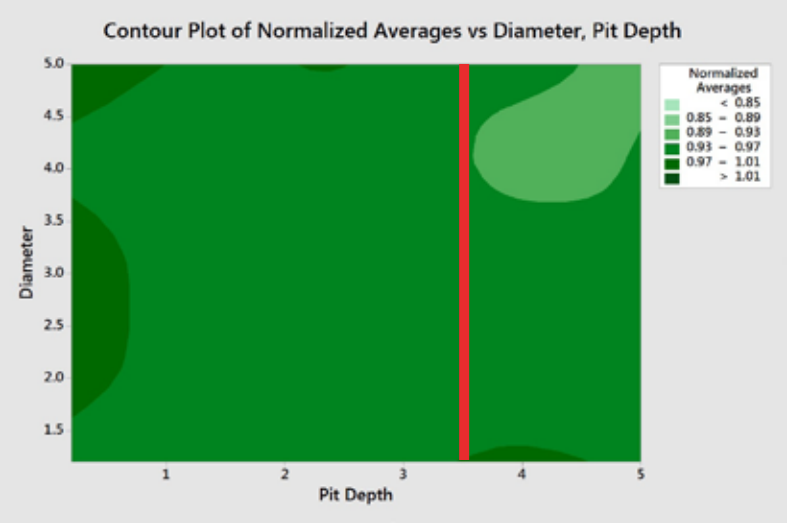
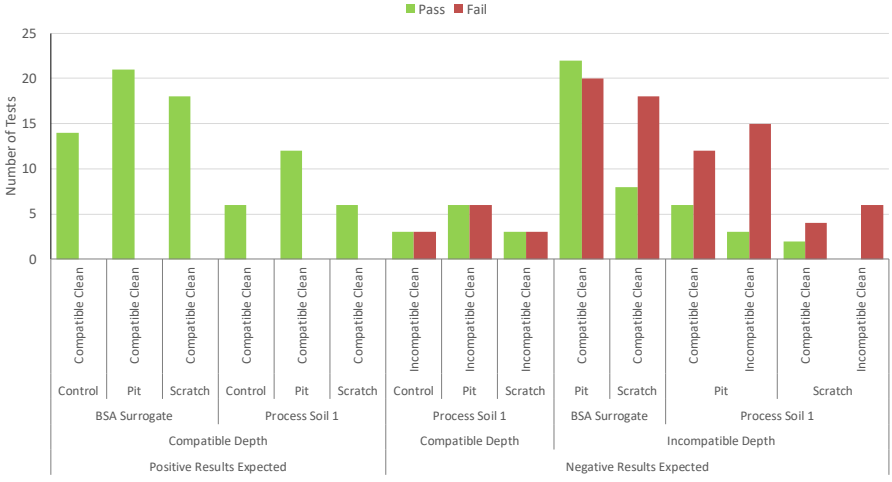


Figure 6: Gravimetric and fluorescent results



The control coupons were then pooled by soil type and averaged. Each test coupon with a surface anomaly was normalized to its respective average control.

ANALYSIS

Regression methodology was used to analyze gravimetric results for the primary BSA surrogate and the two process soils. Regression analysis was also applied to the TOC results from addendum study 1. The aggregate results are represented in the table of *p* values (see Table C). The *p* value quantifies the strength of evidence against the null hypothesis.[7] In this experimental design, the null hypothesis is that cleaning is unaffected by changes to the coupon surface characteristics. Thus, *p* values < 0.05 indicate that a particular variable likely influences the chemical cleaning capability. Conclusions on the cleaning inflection points are detailed in the following sections.

Micropitting with the primary BSA soil: Multiple regression methods were used to test the hypothesis that the normalized mass-removal percentage is a function of pit density. There was no significant ($p > 0.05$) effect of pit density on percent removal within the range tested. There were no visual failures when inspected under UV, indicating that no BSA–fluorescein soil remained on the coupons.

Scratches with the primary BSA soil: Multiple regression analyses were performed, and scratch depth was determined to be significant

Table D: Heat map for coupons with fluorescent failures

		Depth, mm				
		0.2	1.2	2.6	4.0	5.0
Diameter, mm	1.2		0%		0%	
	2.6	0%		0%		0%
	4.0		0%		50%	
	5.0	0%		100%		66%

(p = 0.000). This indicates that as the depth increases, the removal percentage decreases. The fluorescence analysis also indicated a strong correlation between the increase in depth and lower residue removal (Figure 4). As the depth increased past 1.0 mm, failures during fluorescence inspection increased dramatically.

Roughness with the primary BSA soil: Linear regression was used to test the hypothesis that the normalized mass-removal percentage is a function of surface roughness. The p value is sufficiently large (p > 0.05) to conclude that removal percentage is not a function of surface roughness within the limits tested. Additionally, there were no visual failures under UV conditions.

Pitting with the primary BSA soil: The regression analyses carried out for pits used a backward stepwise regression method for use in variable reduction (Table C). Stepwise methods are a way of systematically reducing the number of variables in a model by "rolling" nonsignificant variables into the error term, making it more sensitive to smaller effects. In this manner, it is possible to build a model that uses only statistically significant variables.

Executing the analysis in this fashion highlighted pit aspect ratio (p < 0.05), interaction of density factor and aspect ratio (p < 0.05), and interaction of pit depth and aspect ratio—the ratio of depth to diameter—(p < 0.05) as significant variables. This indicates that the primary variables of depth and diameter are the most impactful in predicting cleaning performance.

To highlight the area most affected by pitting, contour plots pit diameter and depth (Figure 5) provided indications of inflection points in residue removal efficiency as a function of the significant variables. The light green areas in the graphs indicate areas with decreased removal efficiency.

Visual effects of fluorescence using UV lighting were captured as a percentage of coupons that failed visual inspection within a two-variable matrix consisting of depth and diameter (Table D).

Coupons were assigned a pass/fail value, and were considered to fail if any fluorescent residue was detected in any pit on the surface. The results in Figure 5 and Table D help identify the inflection points that affect cleaning capability more conclusively. Conclusions from visual inspection are more discrete than those drawn from the gravimetric analysis, but they point to the same general trends. Both diameter and depth impact cleanability. At depths ≤ 1.2 mm, diameter is no longer a factor in cleanability. Basing the specification exclusively on depth provides the fastest and most accurate field measurement (pit gauge) that diameter does not share. Adopting pitting evaluation criteria on this single variable provides a conservative threshold, yet remains a feasible approach to monitor conditions.

Addendum Study Analysis

A small subset of scratch and pitting coupons straddling the inflection points were chosen for addendum studies with both process soil 1 and process soil 2. UV inspection results in Figure 6 show alignment with the inflection points for process soil 1. As the depth of pits and scratches exceeded the defined thresholds, visual failures were seen. This aligned with the predicted results derived from the primary study with the BSA surrogate. From the gravimetric analysis, scratch results did not indicate any significant variables when evaluating depth, cleaning agent, and soil. For pitting, cleaning agent was an overwhelming factor (p = 0.014), indicating the data were not normalized with soil selection. There was high gravimetric data variability for ineffective soil and cleaning agent combinations when considering both scratch and pitting datasets. As an example, recall that process soil 2 was a surrogate created to simulate a worst-case air–liquid interface condition.

A parallel study ultimately determined that process soil 2 was not representative of at-scale results, thus explaining its variability and warranting its exclusion from further analysis. TOC results also indicated that the cleaning agent was an overwhelming factor (p = 0.00) for both types of anomalies and likely confounded other factors. For example, purified water at 80°C failed typical TOC specifications on both sides of the inflection points when used to clean process soil 1. In retrospect, this was to be expected with a known ineffective soil and cleaning agent combination.

Excluding process soil 2, the BSA surrogate and addendum data were plotted against cleaning agent and soil combinations. A compatible cleaning agent was defined as one that was intended to remove the particular soil at scale. A compatible anomaly depth was defined as being below the identified inflection points determined by the BSA surrogate study. Results show a strong correlation between passing visual inspection results, compatible cleaning chemistry, and compatible pit and scratch depths predicted by the study. Conversely, more failures were seen with combinations of incompatible cleaning chemistries and pit and scratch depths. The same trends were seen with both the BSA surrogate and process soil 1, successfully bridging the two studies.

CONCLUSIONS

The goal of this study was to provide a strategy to derive the data necessary to support a risk-based visual inspection and maintenance program in operating plants. Driving simplicity and measurable criteria are essential when considering a visual inspection program. Considering all the data and observations from this case study, conclusions are summarized in Table E.

Note that combinations of anomalies were not evaluated in this study. Combining different anomalies both above and below

Table E: Study conclusions

Anomaly	Conclusions
Scratches	• The inflection point at which scratches affect cleaning is at depths > 1.0 mm • Scratch length and angle were irrelevant within the ranges tested in this study
Pits	• The inflection point where pitting impacts cleaning is at depths > 1.2 mm. • Multiple pits have no cumulative effect (density factor) and should therefore be removed as a visual inspection factor • Experience shows that pitting depth is a more repeatable, reliable, impactful, and relevant measurement than width
Micropitting	• Does not affect cleanability • May be monitored and remediated at the discretion of operations or maintenance • Tested to 2,600 micropits per inspection area
Roughness	• Surface finish is not impactful to cleanability up to 150 µin Ra • Roughness > 150 µin Ra was not tested

inflection points to identify worst-case permutations could be a useful extension of the experimental design when evaluating applicability to the site's maintenance program. In addition, it would be impossible to design a single experiment to evaluate every potential process soil between different biopharmaceutical manufacturers. The soils selected in this experiment were intended to represent common "worst-case" materials typically seen in biopharmaceutical operations. Each manufacturing site should assess the applicability to their operation and decide if repeated experiments are warranted using the methodology defined in this case study.

Recommendations

Using the study conclusions, a program can be developed to assess cleaning impact associated with surface anomalies. Below are some key considerations to help incorporate these conclusions into a visual inspection and maintenance program.

- Anomalies below the inflection limits have been shown to have no impact and are fully cleanable. This allows for a metered response when encountering anomalies below this range, which can be proactive (maintenance) instead of overly reactive.
- Anomalies at or beyond these inflection limits have been shown to have potential significance because they may not be cleanable. Investigation and tracking through the applicable quality system are appropriate, as is a more immediate remediation response.
- Anomaly response can range from monitoring the condition to delayed remediation to full immediate mechanical remediation (e.g., grind, weld, polish, electropolish).
- Additional safety factors should be considered to account for site- and application-specific conditions, capabilities, and risk factors. As an example, the percentage of the overall equipment surface area with identified anomalies, even if below the inflection limits, could be a risk factor that necessitates more immediate remediation.

Visual inspection program intervals need to be sensitive to anomaly creation due to invasiveness caused by things like vessel entry. The interval should be based on the likelihood/risk that impactful surface anomalies could be generated by routine long-term use and conditions. Technologies and approaches to limit vessel entry should also be considered if the risk is significant.

This study sought to address anomaly impact on cleaning operations within aging plants that were originally based on ASME BPE specifications. The intention is not to modify or relax any anomaly thresholds during construction of new equipment: That would require consideration of all aspects of new systems, especially corrosion resistance. New equipment must continue to meet the more conservative criteria laid out in ASME BPE.

This effort generated surface condition thresholds that can be used as a basis for a maintenance program in an aging plant.

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James Heimbach holds a BS in mechanical engineering technology from Montana State University and a master's degree in applied statistics from Rochester Institute of Technology. His tenure at Lonza spans 16 years, with additional engineering and statistical experience in aircraft and semiconductor manufacturing. He leads a group of statisticians responsible for designing/analyzing experiments, assisting with major investigations, implementing multivariate statistics, and automating myriad analytics. Jim has patents pending for work in predictive modeling related to upstream and downstream processing. He has been an ISPE member since 2018.

Kevin Aumiller earned his BS in chemical engineering from the University of Colorado. As director of CORE Services for Hyde Engineering + Consulting, he optimized cleaning validation programs at over 40 commercial manufacturing facilities across the world. Using Six Sigma and design of experiments tools, Kevin and his team executed cleaning development studies and facilitated validation of analytical methods for cleaning operations. These experimental designs have been used to justify changes for both legacy and new commercial operations using robust models aligned with QbD principles. Currently Kevin is the program leader for biodetection instrumentation at SUEZ Water Technologies in Boulder, Colorado. He has been an ISPE member since 2013.

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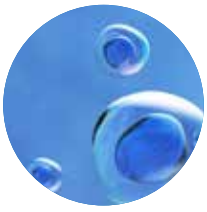

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$46 (2002)	$106 (2007)
$169 (2012)	$221 (2017)

15-YEAR INCREASE = 380%

PRESENT

$275 BILLION

Worldwide biopharmaceutical revenue to date

≥ 12%

Annual growth to date since market launch of recombinant proteins

FUTURE

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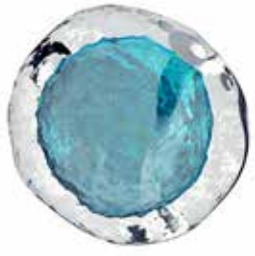
2025

Global biopharmaceutical market = $459.81 billion

Compound annual growth rate = 10.1%



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