PHARMACEUTICAL ENGINEERING®

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The Rise of Biopharm in Asia

Continuous Manufacturing:

Current Status

Multicolumn Chromatography

Novartis's Markus Krumme

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WITNESS TO THE EVOLUTION

Dr. Ferdinando Aspesi
Chair, Pharmaceutical Engineering Committee

As this is my first *Pharmaceutical Engineering* editorial, let me introduce myself. I have been in the pharmaceutical industry for the last 41 years. Over time, I became the global head of quality for three major pharmaceutical companies. I've lived and worked in six different countries, but for the last 15 years I have been a resident of the Philadelphia area.

I have witnessed the evolution of this important industry from bioextractives to recombinant DNA bioproteins, from small molecules to monoclonal antibodies. Throughout these four decades, however, the industry has never forgotten the reason for its existence: our patients.

AREAS OF INTEREST

- Despite the transition from batch to continuous manufacturing, the industry continues to struggle with process variability. The use of flow chemistry and, in the near future, continuous processing in biotechnology drug substance manufacturing, is providing better control of our manufacturing processes as well as more consistent drug product availability and quality.
- Materials characterization and consistent, reliable supply still need improvement. Technology is evolving in the areas of protein analysis and characterization, continuous freeze-drying, and freeze-drying heat-exchange efficiency.
- The industry is investing heavily in IT and data management for process modeling and artificial intelligence; both are needed for a fully automated factory of the future with built-in continuous improvement capabilities.
- Tax policies and labor costs are fueling the deployment of new technologies and products. Technology transfer and process validation continue to require high commitments of resources.
- The industry has not yet been able to convince regulatory authorities of the importance of implementing real-time release, despite a better understanding of process design and correlation with critical quality attributes.
- Despite ICH's recent efforts, including Q12, we are still in a disharmonized world. Recent mutual recognition agreements are positive signs; much work remains to lift cumbersome regulatory burdens.
- The last 20 years have seen a major technology transfer from the Western world to emerging economies. This change allows an additional 30 to 40 million people each year to spend money on medications, a trend that will drive sales growth and higher production volumes. India and China, the major recipients of these technologies, are now becoming the sources of future innovation.
- To produce students who are well educated in science and technology, it's essential that we help prepare the workforce of the future to operate in a digitized economy where mathematical models, artificial intelligence, and virtual reality will be part of their daily operations.

Our magazine provides a major opportunity to disseminate the science and technology driving these changes. I encourage all of you to contribute articles that will inform and educate our members about the challenges and opportunities facing our industry.

I look forward to working with all of you to increase the reach and influence of *Pharmaceutical Engineering*. ‹›

Dr. Ferdinando Aspesi is a Senior Partner at Bridge Associates International. He has been an ISPE member since 1992.

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Editorial Policy

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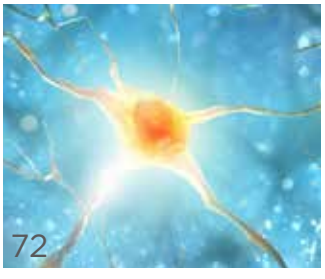

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STRATEGIC PLAN UPDATE

Tim Howard

"Local and regional relevance" is a key component of our strategic plan, and one that is critical to our success as an organization. It pledges us to "understand and shape strategy to the business, culture, and regulatory issues of local and regional markets." Here are a few ways in which we are doing just that:

Attendees gathered at the YP/student brunch and orientation during the 2017 ISPE Annual Meeting in San Diego

REGULATORY STEERING COMMITTEE

The RSC and supporting operations committees are designed to deliver on local and regional relevance. The volunteers in this network are connected through regional harmonization teams and aligned with staff and regulatory advisors to help establish a regulatory strategy that serves our members' local and regional interests.

YOUNG PROFESSIONALS

Our YPs continue to be a vital and valuable ISPE community. Many chapters and affiliates have established local or regional YP committees that sponsor regular programs for networking and education.

In the last issue of *Pharmaceutical Engineering,* I recognized some North American chapters for the longevity of their annual technical conferences and vendor shows.

In Asia, three chapters have milestone anniversaries this year:

- Japan Affiliate: 15 years
- Indonesia Affiliate: 11 years
- Philippines Affiliate: 10 years

COSPONSORED PROGRAMS

The local and regional influence of our events is enhanced when we coproduce meetings with our vibrant network of affiliates and chapters. In several recent synergistic events, our international headquarters staff have partnered with a local affiliate or chapter to convene a program.

Last year, a very successful good automated manufacturing practice (GAMP®) event was coproduced with the Great Lakes Chapter. The Irish Affiliate experienced similar success with a coproduced event. We also have plans for similar events with the Germany/Austria/Switzerland (D/A/CH) and India affiliates.

In each of the past several years, our Annual Meeting Program Committee has connected with the local chapter in the area where the meeting is held. That adds great local knowledge as well as local resources to enhance the conference experience for all attendees. The same is true for our annual Europe conference, held each spring, which has grown in attendance each of the past several years. This year's ISPE Annual Meeting & Expo returns to Philadelphia, where the Delaware Valley Chapter was a great partner in producing the 2015 meeting.

PARTNERSHIP AND COLLABORATION

We continue to pursue opportunities to partner with other organizations and nonprofit associations. Several workforce-of-the-future initiatives, for example, are being explored as possible academic partnerships to discuss growing industry concerns about the availability of trained and qualified workers.

Because the business model that works in our established markets may not be suited for other regions of the world, we also continue to seek outreach to underserved markets that could benefit from our body of knowledge. Through my connections with the South African Association of Pharmacists in Industry, we are discussing ways to provide education, training, and much-needed reference material to the African pharmaceutical industry.

Both initiatives have local and regional drivers that must be included to achieve successful outcomes. Our ongoing partnerships with other organizations improve our chances of acting on such drivers. ‹›

Timothy P. Howard, CPIP, PE, Vice President at Commissioning Agents, Inc., and President of its wholly owned subsidiary Coactive, Inc., is Chair of the ISPE International Board of Directors. He has been an ISPE member since 1993.

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ADVICE FROM THE TOP

Caroline Rocks

As part of my tenure as International Young Professionals Chair, I have the amazing opportunity to be a member of the ISPE International Board of Directors. At a recent board meeting, I sat down with six directors to ask them for advice on how to develop as a Young Professional (YP) and how to make the most of being an ISPE member.

- Alice Redmond, Vice President, European Operations, Commissioning Agents, Inc.
- Flemming Dahl, Senior Vice President, Novo Nordisk A/S
- Joanne Barrick, Advisor in Global Validation Support, Eli Lilly and Company
- Jörg Zimmermann, Vice President, Vetter Development Services
- Tom Hartman, Vice President, GMP Operations, Biopharm CMC, GlaxoSmithKline
- Kelly Keen, Project Portfolio Management, BPm, F. Hoffman-La Roche, Ltd.

The first half of our conversation is below; the other half will be published in the July-August issue of *Pharmaceutical Engineering.*

WHY SHOULD STUDENTS AND YPS BECOME ISPE MEMBERS?

Alice: It's an ideal forum for professional development that allows individuals to expand on strengths and develop in new areas. It's a fantastic way to acquire knowledge by interacting with other members. It's a great place to expand the mind technically, as well as hone communication, interaction, skills, and project-management skills.

Flemming: ISPE enables YPs and students to get a professional network early on and to access up-to-date industry knowledge.

Joanne: I wish I had understood as a student and early career professional how much help ISPE membership could have been. I had no idea how inexpensive membership was for YPs, and all the benefits available. ISPE is a great platform to connect with other YPs, who may be facing similar challenges, as well as more experienced folks who can mentor and/or open doors through additional connections. ISPE participation can also provide a much broader view of challenges and opportunities, both in the industry and in future areas of career focus. ISPE is an opportunity to learn and grow both personally and professionally.

Jörg: I see ISPE as a part of a lifelong learning experience: students and YPs can ask questions of more seasoned colleagues and expand their view to practices outside their own company. At the same time, the seasoned colleagues learn what is new and upcoming with the next generation.

Kelly: It is an amazing opportunity to understand the broader world of biopharma, engage with industry professionals, interact with many large companies, and connect with government agencies. These are opportunities that school does not offer.

Tom: I am aware of several YPs that networked their ways into good-paying industry jobs upon graduation. Don't expect opportunities to magically appear, however. The benefits of joining ISPE depend largely on your level of involvement and the commitment you make. ISPE provides an integrated platform for success, offering opportunities for networking in regulatory, quality, facilities engineering, good manufacturing practice manufacturing, process development, automation, etc. It's there for the taking.

WHAT IS THE BEST WAY TO BECOME INVOLVED?

Alice: Start going to local events and get involved in the area closest to your degree or current work. Starting like this gives confidence to expand to other areas of interest and professional development.

Flemming: Participate in an ISPE event to see if it's something for you!

Joanne: Be active and open to volunteering, as even small tasks can lead to bigger opportunities. Some examples are helping to facilitate conference sessions by carrying a microphone to those asking questions, offering to take minutes for a COP (community of practice) and selling buttons to support Women in Pharma® scholarships. These jobs do not take a lot of technical knowledge but can introduce you to a larger network. Everyone has something to offer!

Jörg: I think that this is a misconception we often have: "What I know is trivial and everybody knows it." That is not true! Coming into the industry from university, the YPs bring the latest thinking with them. My advice is to be open, be candid, ask the questions that bother you, and don't worry. Everybody started somewhere!

Kelly: Volunteer with your local chapter. Attending events and being active is key—not just joining. Attending a national event is an amazing opportunity to network and meet other YPs. Take advantage of the mentoring opportunities available, and don't be afraid to find your own mentor at the ISPE events.

Tom: Don't be shy! Everyone that attends an ISPE meeting is there to learn something, including Board members and our CEO. You know more than you realize. The industry is being transformed by YPs, who think differently in terms of social media, access to knowledge, and energy. Your eagerness, thirst for knowledge, and current contributions to the industry are more important than in-depth knowledge on one or two topics. ‹›

How did you get involved in ISPE? Join the conversation on the YP Community page: http://cop.ispe.org/yp. To join the YP Community, select it during registration or update your account on ispe.org.

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THE RISE OF BIOPHARMACEUTICAL MANUFACTURING IN ASIA

Biopharmaceuticals are booming in Asia, buoyed by enhanced regulations, an influx of venture capital, a culture of innovation, and government support. Asian pharmaceutical manufacturing has traditionally focused on generics, but things are changing.[1–2] In South Korea, biologics powerhouse Samsung BioLogics saw a 56% increase in drug sales in 2017.[3] In China, the world's second-largest market, biopharmaceuticals are expected to grow at a rate of about 13% for the next few years, outpacing the projected 9.1% annual growth rate for all pharmaceuticals.[4]

With the global biologics market projected to reach $390 billion by 2020[5] and drugs worth an estimated $64 billion coming off patent by 2020, opportunities for biosimilars are exceptional. Asia leads the way globally, with more than 300 candidates under investigation.[6] South Korea's Celltrion Group has produced Herzuma, a trastuzumab biosimilar that earned European Medicines Agency (EMA) approval in February 2018; the company is also studying CT-P13, an infliximab antibody that shows promising results in the treatment of Crohn's disease.[7]

Samsung Bioepsis, a partnership between Samsung Biologics and Biogen in South Korea, received EMA approval for two biosimilars in 2016: Benepali (etanercept) and Flixabi (infliximab). In December 2017 the company also brought a $750-million biologics facility online in Incheon, South Korea. With twelve 15,000-liter (L) bioreactors that can produce 4,500 kilograms of biologics per year[8] and manufacturing contracts that total over $3 billion, the new plant makes Samsung the world's largest biologics contract manufacturing organization (CMO).[9]

In India, Biocon received US Food and Drug Administration (FDA) approval in 2017 for Ogivri, a biosimilar to Herceptin (trastuzumab) that is the first biosimilar approved in the US for the treatment of breast and stomach cancer and the second biosimilar approved in the country for cancer treatment.[10]

REGULATORY REFORMS

While Japan and South Korea have regulatory regimes with guidelines for biosimilars as stringent as those of the EMA, recent changes to the China Food and Drug Administration (CFDA) regulations and enforcement have boosted domestic and international companies working in China.

"Along with a lot of new investment, this is the main factor responsible for the boom in biopharmaceuticals in China," said Charles Tong, Senior Vice President, Drug Research and Development at Suzhou Ribo Life Science Co., Ltd., a biotechnology company in Kunshan City, Jiangsu Province, China. "This makes drug development more closely aligned to the regulatory pathway of the [US] FDA. It was time-consuming to introduce a new product into China, which was the reason that companies used to focus on the development of generics. Regulatory reform has helped create an environment in which biotech companies can engage in innovative drug development."

Among the changes to CFDA policies are:

- Conditional marketing authorization for orphan drugs (similar to the EMA's conditional marketing authorization and the FDA's breakthrough therapy designation)
- Authorization to use foreign clinical trial data in a new drug application
- Approval for clinical trials reduced to 60 working days[11]

"The CFDA changes are favorable for drug development because they shorten the review time and make for more transparent dialogue with reviewers," continued Tong. "There is more opportunity for drug development companies to engage reviewers and have less risk and increased confidence for development."

Suzhou Ribo has benefited from these reforms. The company develops oligonucleotide drug candidates such as small interfering RNA* and antisense RNA† therapies for breast and liver cancers as well as hepatitis and HIV. In partnership with Ionis Pharma in San Diego, California,[12] Ribo has China commercial rights for two Ionis antisense RNA drug candidates, with the option on a third. Six oligonucleotide products received FDA approval in 2017.[13]

"China has joined the ICH, and there is more harmonization with global regulatory standards," said Cindy Shen, Senior Principal Technical Advisor at Shanghai Roche Pharmaceuticals. "The CFDA is now using the FDA's model for clinical trials. This will result in more competition for domestic companies from multinationals in new drug development."

* Abbreviated as siRNA, these are double-stranded RNA molecules 20–25 bases long, produced by enzymatic cleavage, that regulate the expression of genes via RNA interference.

† Abbreviated as RNA, these are noncoding single-stranded RNA used to inactivate messenger RNA synthesis and protein translation.

Chris Chen, CEO of WuXi Biologics, agrees. "The changes in the CFDA regulations are just getting started and add additional fuel on the fire that already began three to five years ago. They help the industry in many ways, making the whole process much faster. It used to take two years to get a program cleared for clinical trials, a process that takes 30 days in the US. Now they've cut that time down to three to six months, which is a huge boost for the industry."

WuXi is involved with 127 different drug programs, which Chen claims is 10% of the global portfolio of medicines in development. The company's first facility received an honorable mention as part of ISPE's 2014 Facility of the Year Awards and was the first Chinese manufacturing plant to meet current good manufacturing practice (cGMP) standards in the US, Europe, and China.

Chen also applauds CFDA's simplified regulations, which are closer to global standards and make it easier for Chinese companies focused on international markets. "Previously, if you had to get program approval from the FDA and the CFDA you had to do two sets of work," he said. "Now that the standards are more closely harmonized, you can do both at once. Regulations are a lot closer, almost harmonized. They used to be like day and night; now it's like midday."

"Chinese companies are now able to develop products to the standard acceptable to both the CFDA and the FDA," added Tong. "There are roughly the same standards for tech, data integrity, and compliance. In that regard, Chinese companies will have more competitive advantage and have capability to file to FDA with more acceptable data, giving them a greater chance to succeed."

OUTSOURCING IN CHINA

Another regulatory change permits pharmaceutical companies to outsource manufacturing to CMOs. While this is a common practice in other parts of the world, it is new in China. Easing this restriction relieves biotechnology companies from up-front infrastructure investment and allows them to focus on innovative product drug development.

This change allowed WuXi to open the world's largest biologics manufacturing facility in December 2017.[14] Its 30,000-L bioreactor capacity will provide contract services for both Chinese and international pharmaceutical companies.

"WuXi Biologics is a good example of the strong CMO capability in China," said Tong. "I see large pharmaceutical companies increasing their drug development activity by leveraging existing API (active pharmaceutical ingredient) development and manufacturing capacity in China."

Tong's company, Suzhou Ribo, collaborates with its partners through technology transfer of drug substance or drug product, then manufactures some APIs in-house. It also relies on CMOs for the manufacture of aseptic products and packaging.

INCREASED SUPPORT

"Another factor that has encouraged the industry to flourish in Asia is the unprecedented influx of private equity investment," said Chen. "We've seen companies creating high valuations in as little as three to five years."

Regional governments also encourage innovation. "This is a good time for biologics and biosimilars in China," said Shen. "One of the reasons for this is that China's health care costs are high, and the government would like to bring more affordable drugs to the public."

ASIA LEADS THE WAY GLOBALLY, WITH MORE THAN 300 CANDIDATES UNDER INVESTIGATION

Chris Chen, CEO, WuXi Biologics, Wuxi City, Miangsu Province, China

Chris Sweeney, Senior General Manager, PT Kalbio Global Medika, Jakarta, Indonesia

Cindy Shen, Senior Principal Technical Advisor, Shanghai Roche Pharmaceuticals, Shanghai, China

Charles Tong, Senior Vice President, Drug Research and Development, Suzhou Ribo Life Science Co., Ltd., Kunshan City, Jiangsu Province, China

"They've made innovation almost mandatory, and if a company doesn't innovate, you'll be out," said Chen. "This has been done through such CFDA reforms as the current rule that new drugs and biosimilars have to be differentiated from other products, which is similar to what happens in the US."

South Korea supports its biosimilars industry with tax breaks and regulatory guidance; it also allocates a generous portion of its research budget to domestic pharmaceutical companies.[6]

The expansion of health care coverage in Asia is expected to provide better access to drugs in countries such as Thailand and Indonesia, which have universal health care.[6] In China, the increase in privatized health insurance allows larger numbers to access more expensive drugs.

"Currently the market for biologics and biosimilars is small, because most people pay out of pocket," said Chen. "Private insurance is just getting started, but as it gets more sophisticated, the market size will grow."

INDONESIA

In less developed areas, domestic demand for biologics such as vaccines often drives the industry instead of drug exports. This is the case in a number of Southeast Asian countries, according to Maurice Parlane, Director at New Wayz Consulting in Auckland, New Zealand, which supports pharmaceutical companies with compliance, quality, and operational needs.

"I find it interesting to watch what's happening in places like Indonesia and Vietnam," said Parlane. He has seen Vietnam develop its biotech infrastructure quickly, noting that the Japanese influence is strong and that the ISPE affiliate is providing its support. "As a market, Indonesia is more aligned to a Western way of doing things. Big companies are spending a lot of money there."

"Biotech is in its infancy in Indonesia," said Chris Sweeney, Senior General Manager at PT Kalbio Global Medika in Jakarta. The facility earned an honorable mention in the 2017 FOYA Awards.[15] "Having said that, there are more than a dozen companies that have either opened or declared that they will open biotech facilities in the near future."

The Indonesian government has mandated that the pharmaceutical industry should build the technology for biotech products within Indonesia to reduce reliance on external sources. Several companies have taken up this challenge and have invested considerable sums in product licenses, facilities, and training, according to Sweeney.

TARGETING OVERSEAS MARKETS

CFDA rule changes have not only made it easier for Chinese companies to develop drugs for the domestic market, they help get drugs manufactured in China into overseas markets as well.

Five years ago, 20% of WuXi's clients in China had programs aimed at both the Chinese and global markets; today, that number has increased to 70%. This has encouraged other Chinese companies to partner with larger biopharmaceutical companies in other parts of the world. Some have set up offices in American cities like Boston, San Francisco, and San Diego. In addition, a few well-known domestic companies that used to focus primarily on generics are now shifting to innovative small molecule products and antibodies.

Shanghai Pharmaceuticals, for example, which wants to expand into the US and European markets through partnerships and acquisitions,[16] became one of China's largest drug makers and distributors with its purchase of Cardinal Health's Chinese arm in 2017. KBP Biosciences, a Chinese biotechnology company, built its global headquarters near Philadelphia, Pennsylvania.[17] And 3SBio, another Chinese biopharmaceutical company, purchased the Canadian contract development and manufacturing portion of Therapure Biopharma.[18]

INNOVATIONS

Adding support to the rapid development of biopharmaceutical manufacturing in Asia, GE Healthcare is building a single-use technology FlexFactory for Clover Biopharmaceuticals in Changxing, Zhejiang, China.[4] Clover plans to produce biosimilars, including an etanercept biosimilar for rheumatoid arthritis. GE has also built FlexFactories for United BioPharma in Taiwan[19] and JHL Biotech in Wuhan, China.[20]

Continuous manufacturing is another innovation tied to biopharmaceuticals, but Parlane believes it will be some time before it gains traction in Asia. "Continuous manufacturing is a good example of something that's happening a lot faster in the US than in Asia. Most of the development work is happening in the US and they're almost running away from the rest of us. There's interest in solid dose continuous manufacturing in Asia, which is an entry point," he said, pointing to Lilly's Asian solid dose program. "Someone like that is more likely to lead the charge. It's more likely to be a transfer out than an evolution in Asia. If a vendor like GE made it more accessible, you might see a biopharma company use them for capability reasons. It's not just a case of going and buying something; you have to be able to evolve the whole process."

The CEO of WuXi Biologics is more bullish about the technology's prospects. "We are a global leader in this area, particularly in biologics," Chen said. "We aim to file an IND (investigational new drug) for a continuous process this year that will see DNA entering the facility at one end and finished product coming out the other."

The company will soon complete its third facility, an integrated biologics center in Shanghai that will make traditional monoclonal antibodies, enzymes, and large-volume biologics. It will have six production lines, two for continuous processing and four for batch processing.

The landscape for biologics and biosimilars is crowded, at least in China, as generics were in years past. "The current biosimilar companies in China will face lots of challenges in the near future because of competition," predicted Shen.

Chen agrees. "There's lots of excitement, with everyone jumping in. For every product there seems to be 20 or 30 manufacturers. Eventually there will be consolidation, and the top five will survive and become more dominant players." This is reminiscent of the rise of Japanese pharmaceutical manufacturing about 20 years ago, with companies like Astellas. "China is doing exactly the same thing right now. In five years, the dominant players in China will be different from what they are now.

"The final validation of the Chinese industry will be when we get a few products approved in the US market," Chen concluded. He refers to the 10 or more PD-1 (programmed cell death protein 1) clinical trials that Chinese companies are currently running in the US. "One trend is that there will be possibly hundreds of products from China in global trials in the US. For the first time, there will be products developed in China and launched in the US or Europe. With continuous investment and the government reforms we're seeing, this won't be too long from now."

—Scott Fotheringham, PhD

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THREE THINGS THAT WILL CHANGE MEDICINE IN 2018

Vasant Narasimhan

Digital technologies and big data tools are changing every aspect of how companies operate, across myriad industries. Healthcare is no exception. We are on the verge of a digital revolution across every aspect of the sector, from the lab bench to the patient's bedside.

This presents a significant opportunity to drive the next wave of medical innovation. We can meet our patients in the digital world, to provide them with new, improved and more holistic solutions that not only lead to better outcomes, but help reduce the burden of illness. Digital solutions can democratize the research process for new medicines by helping us reach previously underserved and understudied groups of people. Digital technology will also improve how we capture and analyze data. One of the most valuable assets we have at our fingertips, data gives us a deeper understanding of patient needs. Ultimately, we can bring new and better medicines to patients who need them.

Three emerging technologies will drive the next wave of urgently-needed medical innovation:

1. **Internet of Things.** Data from smart devices can give us critical real-world context and deepen our understanding beyond conventional R&D approaches. For example, wearables and sensors can capture robust, real-time data about patients' quality of life, enabling us to understand disease progression and the impact of our treatments better.

   At Novartis, we are already using sensor technologies to quantify disease progression in multiple sclerosis patients for clinical trial research. Through the ASSESS MS system, we can track measures such as walking speed, balance, and movement of patients. Current methods for measuring physical disability in MS can produce inconsistent results, and it can be hard to track small changes in disability. By training a computer program to evaluate people with MS like an expert neurologist, ASSESS MS aims to provide consistent and reliable data that can potentially better support clinical decisions, improve the efficiency of clinical trials and make expert neurological assessments available all over the world.

2. **AI and machine learning.** These technologies are revolutionizing the way we can interrogate data, leading to a faster clinical trials process. They enable us to understand data sets more deeply, so that we can better identify new insights from our decades of clinical trial experience. All this data is complementary to information collected by conventional R&D approaches. It can help drug makers develop new medicines more quickly, smartly and cheaply than traditional models.

   For example, in partnership with Quantum Black, Novartis developed a program called Nerve Live. It combines data on clinical trial operations from multiple internal systems, applying machine learning and advanced analytics to predict and monitor trial enrolment, trial cost and trial quality. This enables us to increase automation, maximize efficiency and make data-driven decisions. Our work in this area has already delivered a 10–15% reduction in patient enrollment times in pilot trials.

3. **Emerging data platforms.** Unprecedented computing power and advances in data management systems allow us to store, organize, and optimize data for analysis and insight generation. By integrating our vast resources from current, future, and historic clinical trials into data lakes—virtual warehouses holding immense amounts of raw data in their native form—we can embrace emerging technologies and trends to drive deep insights.

   We are also exploring tech companies' powerful data processing capabilities to conduct Real Time Data Analysis on clinical trial datasets. These often run to petabytes' worth of data and can take weeks to analyze using traditional methods. Quantum computing could allow large-scale processing of highly complex clinical and biological data. If applied to develop medicine design and target selection, this could accelerate our ability to do in silico research. Blockchain also holds great promise for the healthcare industry, in addressing current challenges like interoperability of data systems and data security.

   Incorporating emerging technologies into everyday processes will be challenging. But it is clear that digital technologies and data science have incredible potential for medical innovation. We must blend the technology industry's culture with the pharmaceutical industry's expertise. A huge part of this involves encouraging the broader health-tech ecosystem, including start-ups and academic institutions, to collaborate.

We must work hard to inspire the next generation of talent to pursue this critical area. Everyone in the healthcare ecosystem should understand the full potential of digital health. The companies that will prove most successful in the future are those that see this transformation as an opportunity, rather than as an insurmountable challenge.

Let's leverage the full power of digital and data to develop medicines for the people that need them the most. ‹›

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Vasant Narasimhan is Global Head, Drug Development; Chief Executive Officer-designate, Novartis. He has been an ISPE member since 2017.

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JOB SEEKERS: OBSERVATIONS FROM A CAREER EVENT

David G. Smith

Biogen recently partnered with ISPE student chapters to host an evening of conversations about careers in the industry. During the event, I talked about job searching with some of the more than 200 attendees.

APPLICATIONS

One frustrated student told me he had applied to well over 200 job postings, with minimal response. He thought that the more he applied, the better his chance of success. If he saw a job ad and thought, "I could do that," he applied.

But here's what he didn't understand: There's no correlation between success and the number of applications you submit. Success comes from a tailored résumé that shows you are the best candidate for the position. The better you present your background with relatable and quantifiable results, the easier it will be for recruiters to see your value.

Another student was more successful. Before applying, she contacted an acquaintance—an alumnus from her school working at the company that offered the job. She scheduled a call to learn more about the position and what the hiring manager was looking for. She then tailored her résumé to match the job profile, highlighting key experiences and skills. She also asked her friend to refer her to the company's talent acquisition team. She landed both the interview and a job offer.

ARE YOU A STRONG CANDIDATE?

I talked with another group of students, all looking for similar roles, all extremely well qualified, who'd all been rejected for positions. So I did a little polling. I asked who was graduating with an engineering degree from a great program, and had a good GPA? All hands were raised. Who had completed an internship? All hands were raised. I asked a few more questions, with similar results. It quickly became clear to them that competition for good positions is stiff. Success requires commitment to preparation and dedication to the small (but important) things that make you as competitive as possible.

INDUSTRY IMMERSION

I also spoke to a group about different types of positions within the industry. Almost all the students said they were confused about the kinds of jobs they should apply for, which departments might hire people with their skills, and other dilemmas. But one student, who'd belonged to an ISPE student chapter since she was a sophomore, said that she had participated in facility tours, industry panel discussions, and networking functions hosted by her chapter. These helped her understand what positions to target in her job search. The professional network she created along the way led to a referral for her dream job, which she will begin after graduation.

Of course, studying had trumped networking for most of the group. While beefing up your résumé with the right classes and school projects is unquestionably important, waiting until graduation to grow your industry knowledge and develop a network is a sure way to find yourself struggling in a job search. Get involved early to avoid problems later.

LEADERSHIP

From the moment students began to arrive, our team was evaluating their leadership traits—or lack thereof. It's important to realize that someone is always watching during industry events. Since much of this industry involves teamwork, the way you interact with others can help you stand out—for better or worse.

What was I looking for? I wanted to see examples of inclusiveness, such as bringing others into the conversation and truly listening to what they had to say. I was looking for students who engaged easily with people they didn't know, who delivered comments and questions thoughtfully. I was also looking for unfavorable characteristics—such as staying in cliques and avoiding conversation, asking questions timidly, or interrupting others.

ACCOUNTABILITY

One of the best stories I heard was from graduate students who had created a job-seeking group. They had made a pact to meet once a week to help and hold each other accountable. They reviewed the previous week's commitment to learning about jobs in their fields of focus, the actions they took to network, companies they researched, etc. All agreed that, together, they learned more quickly, recognized gaps and challenges they had not seen in themselves, and experienced positive results. Not one of them wanted to let the group down by being unprepared. A good support system can be a critical difference in a job search. I encourage you to find or start a group of your own. You might be surprised to find what you can accomplish together.

I am grateful to the ISPE student chapters who helped us organize this event, and to the students from the 13 different schools that participated. I hope you found this recap helpful. ‹›

Have other questions? Send me a note at david.g.smith@biogen.com and I will try to answer it in a future column.

David G. Smith is Talent Acquisition Lead, PO&T North America, Biogen.

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ISPE Facilities of the Future Conference (see page 28)

Also in this section

GAMP 5: TEN YEARS ON

Ten years after its publication, the *ISPE GAMP® 5 Guide: A Risk-Based Approach to Compliant GxP Computerized Systems* is regarded as the definitive industry guidance on GxP* computerized system compliance and validation for companies and suppliers and is referenced by regulators worldwide.

This article examines whether the Guide is still current, and considers where the Good Automated Manufacturing Practice (GAMP) community should focus its guidance efforts.

GAMP 5 was developed by the ISPE GAMP Community of Practice (CoP), a worldwide group of practitioners and subject-matter experts, with significant input and review from international regulators. In 2017, the CoP leadership began a formal review of GAMP 5 to determine whether it still met its objectives and to focus its efforts on areas where there is most need and benefit.

DATA INTEGRITY

The importance of data integrity is stressed in recent guidance, citations, and public comments. GAMP 5's stated aim is to assist in achieving patient safety, product quality, and data integrity, while enabling innovation and technological advances. Patient safety is affected by the integrity of critical records, data, and decisions, as well as by aspects that affect physical attributes of the product. To underline this point, the phrase "patient safety, product quality, and data integrity" is used throughout the Guide.

The new *ISPE GAMP Records and Data Integrity Guide* (RDI), first published in 2017, takes this further. It provides principles and practical guidance for meeting current expectations involved in managing GxP-regulated records and data, ensuring that they are complete, secure, accurate, and available throughout their life cycle.

While GAMP 5 is focused primarily on compliant computerized systems and their life cycles, RDI takes a wider perspective, covering the data governance framework (including human factors), corporate data integrity programs, and the complete data life cycle, which may span several systems. It describes a holistic and flexible risk-management approach for ensuring the integrity of records and data. This is achieved by applying appropriate controls to manage identified risks within the regulated process, commensurate with the level of risk.

The two guides are complementary, yet focused on their individual objectives. They provide a framework for compliant and validated computerized systems, with GAMP 5 providing a solid foundation for record and data integrity across the regulated organization.

CoP ANALYSIS

The GAMP CoP Analysis was led by Mike Rutherford (then-GAMP Global Chair, now a director on the ISPE International Board), Chris Clark (GAMP Editorial Review Board Chair), and Siôn Wyn (ISPE Technical Consultant).

For each GAMP 5 section and appendix, the team examined the effects of technical and regulatory updates since the original publication, focusing on substantive topics and guidance rather than background, historical, or supporting information. When identifying potential gaps or enhancements, the team identified:

- Where they are addressed in existing GAMP guidance
- Where current GAMP activity is addressing the issue, with intent to publish
- Where a new GAMP activity/deliverable is likely to be required

The analysis showed that the principles and concepts of GAMP 5 have not been transformed by the changing regulatory environment. However, some themes and areas were identified for enhancement and improvement:

* International life science requirements, such as those set forth in the US FD&C Act, US PHS Act, FDA regulations, EU Directives, Japanese MHLW regulations, or other applicable national legislation or regulations under which a company operates. (ISPE Glossary)

- Increasing prevalence of third-party service providers, including cloud service providers*
- Current methods and approaches for software development, e.g., iterative and incremental methods, such as Agile†
- Increased use of tools, including the move from a document-based process toward automated tool-based processes such as requirements capture, specification, testing, installation, traceability, and configuration management†

FUTURE TOPICS

Existing GAMP Good Practice Guides (GPGs) were also reviewed. All were found to be current, except for the *GAMP Electronic Data Archiving Good Practice Guide,* published in 2007. For reasons of alignment and relevance, key topics on electronic data archiving will be included in a forthcoming *Data Integrity Good Practice Guide.*

Other topics identified for further discussion and potential publication include serialization, cybersecurity, blockchain technology, and innovative development approaches.

The GAMP Data Integrity Special Interest Group (SIG) is also working on a GPG that covers key concepts and hot topics introduced in the RDI Guide, as well as in-depth practical approaches for data integrity for manufacturing systems, laboratory systems, and data retention.

CONCLUSIONS

Based on this analysis, the primary guidance in GAMP 5 (and supporting GPGs) is deemed current and relevant, including key concepts on the life cycle and its phases, specification and verification approach, quality risk management, and governance.

Together, GAMP 5 and the RDI Guide provide a comprehensive, coherent, and effective framework for meeting current quality, regulatory, and technological challenges. Furthermore, GAMP CoP teams are already working in new key areas of innovation and opportunity, including further detailed guidance on data integrity. ‹›

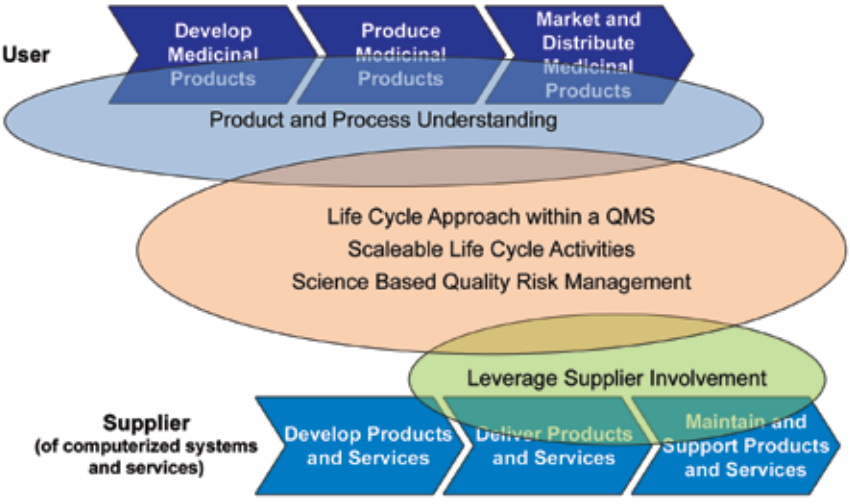
—Siôn Wyn

Siôn Wyn, Director, Conformity Ltd., is an ISPE Technical Consultant. He has been an ISPE member since 1995.

* The GAMP Cloud SIG has been actively producing articles and papers for ISPE publication, including a series of concept papers (see page 22).

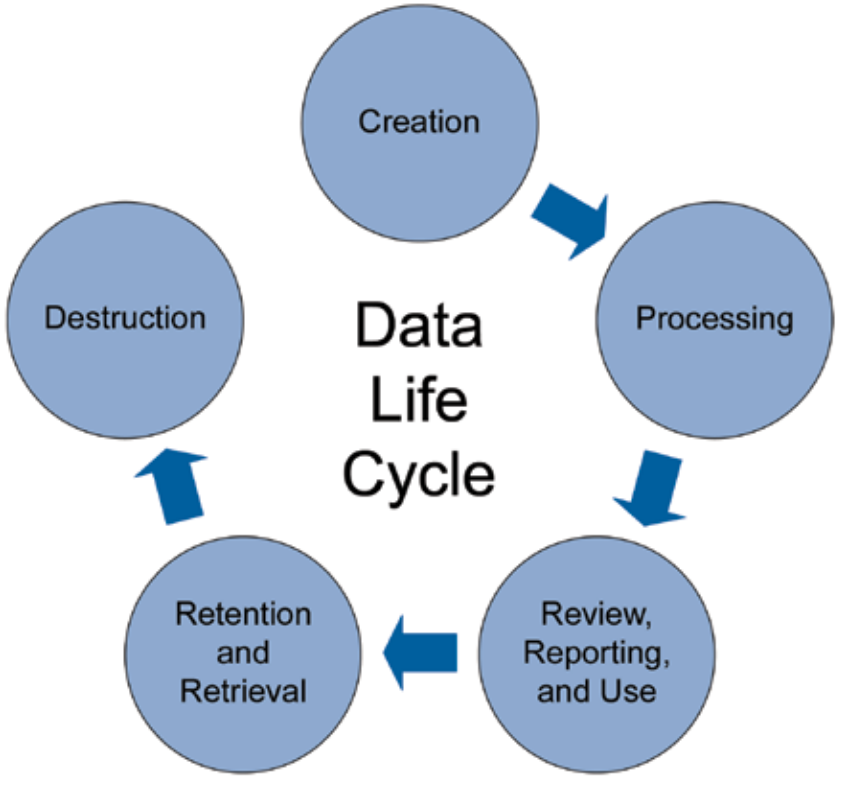
† The GAMP Agile SIG is now active and considering potential publications in both of these areas.

FIGURE 1: GAMP 5 KEY CONCEPTS



Source: ISPE GAMP 5 Guide: A Risk-Based Approach to Compliant GxP Computerized Systems, Figure 2.1

FIGURE 2: DATA LIFE CYCLE



Source: ISPE GAMP Records and Data Integrity Guide, Figure 4.1

ON THE ROAD AGAIN

Japan Affiliate's Annual Plant Tour

Akihiro Matsuki and Michael J. Lucey

Genentech, Vacaville, California

The ISPE Japan Affiliate conducted its annual pharmaceutical plant tour last October, visiting four US plants prior to attending the ISPE 2017 Annual Meeting & Expo in San Diego, California. Twenty-one professionals participated from all over Japan, including Affiliate Chairman Hirofumi Suzuki, nine members from pharmaceutical companies, 10 from engineering/construction companies, and two from equipment manufacturers. Head of Secretariat Akihiro Matsuki and Adjunct Director Michael J. Lucey led the Organizing Committee, which was made up of Affiliate Board members.

The following is a summary of each visit.

ELI LILLY

The tour's first stop was Eli Lilly's continuous manufacturing facility in Indianapolis, Indiana—ISPE's 2017 Facility of the Year Awards Overall Winner. Participants observed the continuous direct compression process and small-molecule production line. Direct compression process is the simplest form of processing for tablet manufacturing; continuous production is relatively straightforward when this process is adopted. Eli Lilly uses simulation techniques and experimental approaches, and process analytical technology (PAT) ensures quality management.

NOVARTIS

Novartis's Technical Research and Development (TRD) facility in San Carlos, California, has a production line for aminoglycoside antibiotics, with isolators for manufacturing high-potency pharmaceutical products. TRD and the commercial manufacturing facility are on the same site, facilitating good communication. Novartis was involved in all design processes, from product characteristics to production equipment.

BOEHRINGER INGELHEIM

Boehringer Ingelheim's passion for biomedicine manufacturing is clearly felt at the company's biomedicine manufacturing facility in Fremont, California. It has a production line comprising six processes: cell culture, harvesting, initial purification, final purification/formulation, filling, and warehousing. The first four processes have two lines each, with the facility designed to allow an uninterrupted view of the glassed-in production line. Single-use equipment makes for a highly flexible plant. Currently under construction is a 12-kiloliter single-use system culture tank.

GENENTECH

Genentech's Vacaville, California, biomedicine manufacturing facility Cell Culture Product 2 (CCP2) was the 2016 Facility of the Year Award winner in the Process Innovation category. A large-scale facility located 50 miles northwest of San Francisco, its unique design not only allows employees easy access to each building through the center spine, but also ensures a more flexible response to future plant reform requirements through the use of common utilities. Vacaville is impressive for its stable manufacturing, and features flexible maintenance work.

THANK YOU

The team extends special thanks to the generous hosts in the United States who opened their doors to the Japan mission, to Corey and Tanya Veverka of Total Validation Services, Inc., as well as the San Francisco/Bay Area Chapter, with which the Japan Affiliate has a long-standing relationship.

The Japan Affiliate holds an annual reunion in Tokyo for participants in past US pharmaceutical plant tours. It is an opportunity for sharing memories and networking. The most recent reunion was held in February 2018. ‹›

Akihiro Matsuki, Mitsubishi Chemical Engineering Corporation, is Head of Secretariat for the Japan Affiliate. Michael J. Lucey is Sales Development Manager at JGC Corporation, Yokohama, Japan.

ITINERARY

Monday, Oct. 23	Departed Tokyo for Indianapolis
Tuesday, Oct. 24	Eli Lilly, Indianapolis
Wednesday, Oct. 25	Novartis, San Carlos
Thursday, Oct. 26	Boehringer Ingelheim, Fremont
Friday, Oct. 27	Genentech, Vacaville
Saturday, Oct. 28	ISPE Annual Meeting registration, San Diego
Oct. 29–Nov. 1	ISPE 2017 Annual Meeting & Expo
Thursday, Nov. 2	Departed San Diego for Tokyo

A First in Fukushima

Japan Affiliate API Seminar

Akira Kunima, Fumio Kishimoto, Tsutomu Kojima

ISPE Japan Affiliate's Scientific Approach to Manufacturing and Good Manufacturing Practice Community of Practice (SAM and GMP CoP) cohosted a seminar on active pharmaceutical ingredients (API) manufacturing in Fukushima on 22 July 2017. The seminar, "Implementation of Lifecycle Approaches in API Manufacturing," was the first to be organized by a CoP in the Tohoku District. Total number of attendees was over 100, including members of the Fukushima prefecture competent agency and the area's industrial organization.

Tohoku is located in the northern part of the main island of Japan, and consists of six districts, including Fukushima. Fukushima is home to many drug, API, and medical device manufacturers. Following the 2011 nuclear power plant disaster and subsequent earthquake, industry and agriculture were hit hard. It is only recently that exporters of rice and fish have resumed trade with Europe.

This series of seminars on API lifecycle management began in Tokyo in July 2014 and continued in the Yamaguchi district in January 2015. The first wave of seminars focused on the ICH* guidelines and quality culture. The second wave, focusing on the lifecycle approach of process and cleaning validation, was held in the Shizuoka district in January 2016, and in Osaka in July 2016.

* International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

BUILDING COMMUNITY

Of Special Interest

Special interest groups (SIGs) have been an important part of ISPE for many years. SIGs are formed around a specific area of interest, policy, or technology in which members have identified a common challenge. These "microcommunities" foster interaction among a variety of technical domains and often result in creative responses to industry change. SIGs must align with a community of practice (CoP) steering committee or the Knowledge Network Council.

SIGs are excellent forums for exchanging ideas and best practices, problem-solving with other experts, and staying informed about new developments in specialized topics. Over the years, several SIGs have contributed valuable resources to ISPE: papers, articles, blog posts, Guidance Documents, and conference sessions.

One notable SIG project is the education session on current good manufacturing practices and outsourcing facilities (Section 503B of the FD&C Act*) presented by the Compounding Pharmacies SIG at the 2016 ISPE Annual Meeting & Expo. Although small in number, this SIG was nimble enough to deliver timely programming on a hot topic. The group remains focused on sharing ISPE's knowledge to improve the quality of personalized medicine and efficiency of the drug supply chain. Organized by the Sterile Products Processing CoP, the Compounding Pharmacies SIG is seeking new members from other interested CoPs.

The Serialization SIG was created in response to the DSCSA† product identifier requirement with members from the Packaging, Operations Management, Project Management, and GAMP® CoPs. This SIG spearheaded ISPE's comments on the US Food and Drug Administration's (FDA) "Grandfathering Policy for Packages and Homogenous Cases of Product Without a Product Identifier" draft guidance and the 2017 ISPE Pharmaceutical Serialization workshops. The Serialization SIG is seeking members to help develop white papers and other planned projects.

The GAMP Cloud SIG authored a series of concept papers that were published in 2016:

- "SaaS in a Regulated Environment: The Impact of Multi-Tenancy and Subcontracting"
- "Using SaaS in a Regulated Environment: A Life Cycle Approach to Risk Management"
- "Evolution of the Cloud: A Risk-Based Perspective on Leveraging PaaS within a Regulated Life Sciences Company"

The GAMP Data Integrity SIG, the most prolific of the groups, authored the blog posts "Data Quality and Data Integrity: What Is the Difference?" and "Considerations for a Corporate Data Integrity Program," as well as the 2017 best-selling *GAMP Records and Data Integrity Guide*. The group has delivered training at multiple conferences and chapter events, and has already begun to author a subsequent series of Data Integrity Good Practice Guides. ‹›

SIG membership is open to all active ISPE members in all geographic areas. If you'd like to learn more or if you're interested in joining a SIG, email us at communities@ispe.org.

—Konyika Nealy, Senior Director of Guidance Documents and Knowledge Networks

ISPE SIGs

- Compounding Pharmacies
- GAMP Agile
- GAMP Blockchain
- GAMP Cloud
- GAMP Data Integrity
- GAMP Manufacturing Executions Systems
- Serialization

* The Federal Food, Drug, and Cosmetic Act (FD&C Act), enacted in 1938, authorized the FDA to oversee the safety of food, drugs, and cosmetics. Section 503B identifies the bulk drug substances that can be used in compounding. (FDA.gov)

† Enacted in 2013, the Drug Supply Chain Security Act (DSCSA) outlines steps to build an electronic, interoperable system to identify and trace certain prescription drugs. (FDA.gov)

Risk Mitigation in the Cloud

ISPE's revised IT Infrastructure Control and Compliance Guide provides comprehensive guidance on regulatory expectations for both traditional and cloud-based IT platforms.

Have we done enough?

That's the question Stephen Ferrell, core team leader for the *ISPE GAMP® Good Practice Guide: IT Infrastructure Control and Compliance (Second Edition),* wants readers to ask themselves. IT infrastructure outsourcing, he says, has made risk mitigation particularly difficult.

"Because we are not allowed on-site audits of third-party suppliers, data and system verification rely more heavily on third-party certifications," explains Ferrell, Vice President, Product Strategy, ByteGrid. "This GPG (good practice guide) explains how a company is exposed to risk in this new environment, and what to do about it."

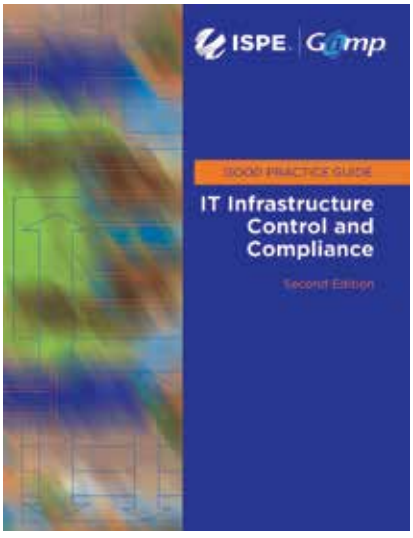
The advent of third-party suppliers and cloud services drove the revision of the GPG, which first appeared in 2005. At that time, recalls Ferrell, "people were buying their own servers and setting them up; they largely were contained within their own facility. They then subjected them to a quality assessment within their own 'four walls.' IT infrastructure was a low-risk proposition at that time because it was tangible: you could see it, you could touch it."

Stephen Ferrell

The advent of the cloud changed all that. "You lose the ability to control the infrastructure and that really drove the revision," he explained.

The revised GPG expands the scope of the first edition to include guidance on the emergence of cloud and virtualized technologies. Information has also been added to reflect significant changes in the technologies that make up IT infrastructure, including:

- Virtualization technologies that allow the sharing, combining, and maximization of resources
- Cloud computing, including cloud-based infrastructure and three cloud-based service models: infrastructure as a service, platform as a service, and software as a service
- GxP applications as a service
- Outsourcing and the increased use of third-party data centers



Ferrell acknowledges that most pharma companies have some form of cloud engagement, but for those that do not, the Guide serves as a road map, and identifies risk mitigation strategies. It tackles areas such as how to build your risk assessment, how to design your supplier qualification, how to structure your audit, and what questions you should ask.

And for those already using the cloud, the Guide will help them assess whether their risk-mitigation efforts have been sufficient. ‹›

—Anna Maria di Giorgio

ISPE GAMP Good Practice Guide: IT Infrastructure Control and Compliance (Second Edition)

Webinar

GAMP® 5 Series: IT Infrastructure Compliance and Control

Guide Team Lead

Stephen R. Ferrell, CISA, CRISC, Vice President, Product Strategy, ByteGrid, USA

Guide Team Members

- Ulrik Hjulmand-Lassen, Novo Nordisk A/S, Denmark
- Shana D. Kinney, Canon BioMedical Ltd., US
- Kevin C. Martin, Azzur Group, US
- Ashish Moholkar, Novartis, US
- René van Opstal, Van Opstal Consulting, Netherlands
- Michael F. Osburn, Cornerstone OnDemand, US
- Arthur "Randy" Perez, Novartis (retired), US
- Mike Rutherford, Eli Lilly and Company, US
- Jason Silva, ByteGrid, USA
- Eric J. Staib, PRA Health Sciences, US
- Anders Vidstrup, NNIT A/S, Denmark

FOCUSED ON EDUCATION

ISPE Korea Affiliate

Home to more than 51 million people, South Korea is one of the "Four Asian Tigers," along with Hong Kong, Singapore, and Taiwan. These countries experienced rapid expansion and high growth rates beginning in the 1960s, developing into highly advanced economies. South Korea's pharmaceutical industry is the third largest in Asia and the 13th largest in the world, with annual sales that are expected to grow from approximately $15.1 billion in 2015 to over $18 billion in 2020.

Dr. Keerang Park

The ISPE Korea Affiliate currently serves 154 members. Dr. Keerang Park, the affiliate vice president, a professor at Chungbuk Health and Science University, and CEO at CdmoGen Co., Ltd., leads the main office in Cheongju, North Chungcheong Province's largest city. "Our affiliate was founded in 2008, when we had our inaugural meeting," says Dr. Park. "We have 12 Board members at this time, and have maintained our members for about 10 years now."

Following a surge of initial growth, the membership has remained relatively stable for the past few years, with representation from industry, academia, and students, as well as a surprising number from the regulatory authority and government—whose participation and support many chapters and affiliates find hard to obtain.

More than 40% of the Korea Affiliate membership comes from the Ministry of Food and Drug Safety (MFDS), including the affiliate Chair, Dr. Chung Keel Lee. These regulators provide valuable insight and some influence into the country's pharmaceutical and biomedical plans, which Dr. Park highlights as one of the affiliate's strengths.

Dr. Park also commented on the unique status of the student membership in the Korea Affiliate. "In the beginning, the affiliate tried to promote student membership through the GMP (good manufacturing practice) training program, which is the strong expertise that we have," she said. "However, the Korean government has made many GMP education programs available to students, so our effort to promote student membership was not that successful."

Affiliate activities are focused on member education. "We try to do two educational sessions each year," says Dr. Park. "For our session this spring, we are going to invite a global lecturer from ISPE and our topic will be GAMP© 5. For our fall session, we expect to cover biopharmaceuticals, like gene therapy and cell therapy."

The affiliate has also established a Q&A forum to discuss challenges in the workplace. "Whenever anyone asks a question, our Board members, who are experts in various areas, can provide an answer in an expert way," says Dr. Park.

Additionally, the affiliate translates selected articles from *Pharmaceutical Engineering* into Korean as a benefit to members. "We don't cover everything, just several articles," says Dr. Park. "We also translate the guidelines or baselines, but we don't share those; we only use them for the educational material."

Looking forward, Dr. Park hopes to further develop the affiliate's activities and grow membership. "At the moment, we only do two educational sessions; we don't do any exhibitions or any other activities," she says. "In Korea, all of the Board members are volunteers who are actively involved in their own work, and so at this moment the two educational sessions are enough for us to prepare.

"Early on, we planned for broader activities for the ISPE affiliate, but it is very difficult to get sponsorship and volunteers," Dr. Park continues. "But we have to find a solution. Three years ago, our president changed to Dr. Ducksang Kim. He and I expect to participate in the [ISPE] Annual Meeting this year, and we're trying to find out how to expand our affiliate activities, how to promote more members, how to do more exhibitions or education sessions. But we have to plan carefully. We are considering who is going to help and who is going to sponsor—all of those things. These are the answers we need to find." ‹›

—Mike McGrath

Quick facts

Founded: 2008
Region: South Korea
Membership: 154

Board

Chair: Chung Keel Lee, PhD, MFDS

President: Ducksang Kim, PhD, Sartorius Korea Ltd.

Vice President: Keerang Park, PhD, Chungbuk Health and Science University

Treasurer: Sungchang Oh, CTCBio Inc.

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Director of Biotechnology: SangJeom Ahn, (Former) Berna Biotech Korea Corp.

Director of Bioprocessing: Chanhwa Kim, PhD, Biotechnology of Korea University

Director of Government: Chung Keel Lee, MFDS

Director of Pharmaceutical Industry: Jongkuk Kim, BioApplication Inc.

Director of Vendors: Ducksang Kim, PhD, Sartorius Korea Ltd.

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REGULATORY UPDATE

ISPE Eyes Opportunity to Advance Pharmaceutical Quality

In March 2017, ISPE submitted an extensive and detailed response[1] to the 2016 US Food and Drug Administration (FDA) draft guidance "Submission of Quality Metrics Data,"[2] the associated Federal Register Notice,[3] and webinar.[4] These comments reflected ISPE's conclusion that the program, as proposed, has low or no value, and the burden on companies would be substantial.

Consequently, ISPE recommended that the agency issue a final guidance for a limited, carefully structured pilot program. The program and associated guidance, designed in concert with industry representatives, could clarify requirements and a relative value to the burden. ISPE also recommended that the pilot be based on common mechanisms of engagement. A small but diverse group from industry, for example, could work with the FDA Quality Metrics Team to establish a structured, multiphase approach with measurable goals, milestones, and evaluation points.

As an alternative, ISPE also proposed that the FDA further review the stated goals of the quality metrics program and consider alternative approaches to its guidance, which is currently based on industry submission of harmonized data elements. ISPE indicated its willingness to work with the agency to develop such an alternative approach.

ISPE representatives had an additional series of interactions with the FDA, during which the agency requested further explanation of ISPE's recommendations for definitions related to the 2016 draft guidance for lot acceptance, product quality complaint, and invalidated out of specification (OOS) rates. ISPE also shared some preliminary thinking about the limited, carefully structured pilot.

To develop ISPE's thinking further, ISPE conducted a workshop that included representatives from several companies that participated in its Quality Metrics Pilot Program, Waves 1 and 2,[5–6] in October 2017. Using learnings from these interactions and workshop feedback, ISPE submitted further recommendations[7] to the FDA docket, including:

- Further elaboration of ISPE recommendations for definitions of lot acceptance, product quality complaint, and invalidated OOS rates
- Alternative programs meeting FDA and industry goals
- Carefully structured FDA pilot program

ADVANCING PHARMACEUTICAL QUALITY

At the participants' workshop, ISPE drafted preliminary thoughts for processes to achieve FDA goals. Suggested design elements included:

- Voluntary
- Phased
- Well-defined assessment criteria
- Inclusion of incentives/recognition

ISPE further recommended that the voluntary program could be self-propagating through engagement of early adopters/change ambassadors to show industry leadership and commitment. To encourage participation, benefits should be demonstrable and could include those recognized to support a continual improvement culture, such as reduced inspections and optimized post-approval filing processes.

Instead of submitting standardized quality metrics, ISPE also proposed that companies provide information "in advance of or in lieu of an inspection," as stated in the FDA Safety and Innovation Act,[7] which could include operational excellence elements. Further discussion on this early thinking was identified as a key next step.

This alternative program, tentatively entitled "Advancing Pharmaceutical Quality," would demonstrate value to industry, regulators, and patients by integrating tools and experience from quality culture, quality metrics, and operational excellence. It could be based on existing programs such as the US Occupational Safety and Health Administration Voluntary Protection Program and the FDA Case for Quality Program. It could also take elements from the UK Medicines and Healthcare Products Regulatory Agency preinspection information-request process. Further exploration and discussion between industry and FDA is needed to advance these ideas.

Proposed deliverables from this program include:

- Assessment and continual improvement tools
- Benchmarking forums
- Interactions with regulators, especially the FDA
- Educational tools (conferences, articles)
- Industry engagement workshops

"Advancing Pharmaceutical Quality" could provide value to industry by encouraging self-improvement as well as supplier improvement, even if it is not adopted by regulators. Parts of the program could be considered for adoption by regulators, either initially or after implementation, leading to benefits to industry through regulatory interaction and potential regulatory relief.

Proposed goals are to:

- Enable and foster industry ownership of quality beyond compliance
- Integrate quality, cultural, and operational excellence principles and learnings
- Support and incentivize continual improvement
- Promote efficient use of resources by improving operational execution
- Increase reliability of product supply (improve supply chain robustness)
- Fuel benchmarking, sharing, and learning among companies

The vision for this program would remain that elucidated by the Research Director of the FDA's Center for Drug Evaluation, Janet Woodcock: "A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight."[8]

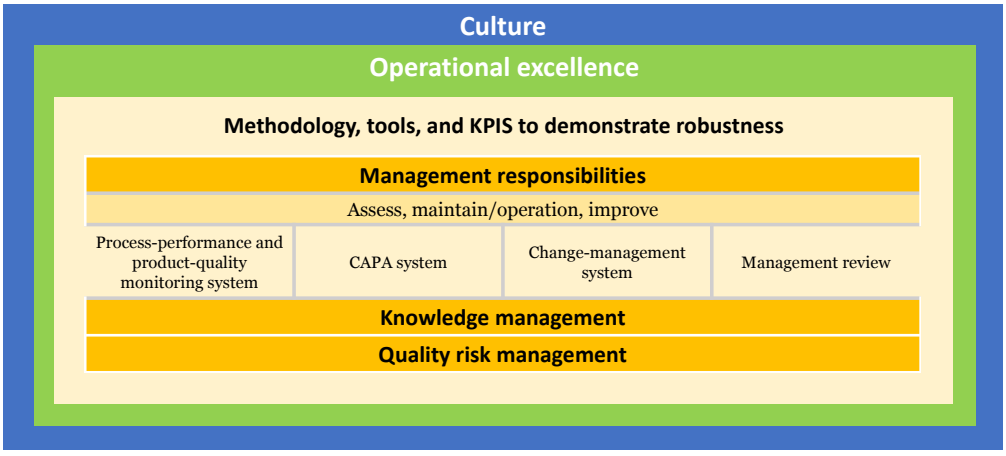
PROGRAM DESIGN

A project core team—senior representatives from companies with a range of responsibilities, including quality, operations, information technology, and regulatory—and a series of subteams are working on different elements of the program:

- Alternative program design
- Integrated approach to quality and operational excellence
- Applied quality cultural excellence
- Evaluating FDA Quality Metrics submission portal

Figure 1 is based on ICH Q10 Annex 2.[9] To deliver quality product to customers on time and in full, a

FIGURE 1: "ADVANCING PHARMACEUTICAL QUALITY" PROPOSED STRUCTURE



site in a supply chain delivering that product should have a quality system underpinned by and compliant with the site's operational excellence practices.

- As recommended in the *ISPE Operations Management Good Practice Guide,*[10] a company is likely to have a company manufacturing operations strategy that could be applied across a series of manufacturing sites. Different technologies, locations in the supply chain, and geographies, for example, would lead to differences in regulations and organizational cultures. As a result, sites may have different key performance indicators (KPIs) to balance operational efficiency and service within an acceptable cost structure.* KPI values and, more importantly, changes in KPI values could be used to assess maturity of a site by benchmarking performance and comparison with other sites within the same company or in other companies.
- As demonstrated in the ISPE Quality Metrics Pilot Program, Waves 1 and 2,[5–6] quality culture excellence is required to deliver robust and sustained quality metrics performance. Other studies, such as the University of St. Gallen's work with the FDA,[11] have shown that cultural excellence is positively associated with good business performance. In Figure 1, therefore, culture underpins all elements.

FIRST STEPS

Initial thinking is that sites would select from standardized tools relevant to the phase and maturity of their development. The team intends to identify tools and methodologies that could be used to assess site performance for management responsibilities, as well as knowledge management and quality risk management enablers. The "four pillars" included in ICH Q10—process performance and product quality monitoring, corrective action and preventive action, change management, and management review of process performance and product quality—would also be included. See the ISPE Cultural Excellence Report[12] for examples of tools to assess and improve cultural excellence.

Subteams plan to develop the tools and methodologies required, identifying those that exist in the pharmaceutical or other industries. Dialogue with regulators would incorporate their perspectives and input, since a major goal of this program is that regulators consider adoption, at least in part, and/or help evolve relevant sections to help achieve their goals.

A cross-functional subteam has also been established to evaluate the FDA quality metrics portal and share its feedback with ISPE members and companies. The subteam will share industry approaches and best practices for local collection, management, and use of metrics data, and will also provide feedback on any further FDA quality metrics guidance or announcements. All of these experiences, learnings, challenges, and opportunities will be considered for input to the Advancing Pharmaceutical Quality program.

NEXT STEPS

The project core team will meet with senior industry leaders and practitioners in early June for input and concept testing. As the program evolves, further proposals for next steps will be reviewed with ISPE leadership. ‹›

—Christopher Potter, PhD

Dr. Potter is an ISPE advisor. He has been an ISPE member since 2007.

* The ISPE Operations Management Good Practice Guide has an excellent chapter that explains how quality KPIs fit within a business measurement structure.

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KEYNOTE SPEAKERS

Lars Fruergaard Jørgensen
President and CEO, Honorary Conference Chair,
Novo Nordisk A/S

Kirsten Lund-Jurgensen, PhD
Executive Vice President and President, Pfizer Global Supply, *Pfizer Inc.*

Nick Leschly, MBA
CEO,
bluebird bio

Phil Southerland
Chief Executive Officer, Co-Founder,
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THE FUTURE IS HERE

Conference Highlights New Technology

ISPE | FACILITIES of the FUTURE

ISPE's 2018 Facilities of the Future Conference highlighted emerging technologies that are driving change in pharmaceutical manufacturing. Topics included virtual reality, robotics, artificial learning, machine learning, and 3D printing. Education sessions were divided into Industry 4.0 and continuous manufacturing (CM) tracks.

KEYNOTE PRESENTATIONS

Jim Breen, Project Lead, Biologics Expansion, Janssen Pharmaceuticals, and Conference Program Committee Chair, introduced the keynote presentations, explaining that facilities of the future and its corollary, workforce of the future (WOF), are strategic priorities for ISPE and the Global Manufacturing Leadership Forum (GPMLF).

Dr. Lawrence Yu, Deputy Director, Office of Pharmaceutical Quality (OPQ) at the US Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER), reviewed the agency's integration of facility evaluations and inspection programs.

CDER and the Office of Regulatory Affairs have entered into a "concept of operations" (ConOps) agreement to ensure consistency, efficiency, and transparency in facility evaluations, inspections, and regulatory decision-making for marketing applications across FDA. This will enhance quality and increase access to FDA decisions. It will also improve timelines for regulatory, advisory, and enforcement actions.

Yu said that the agency plans to meet the Generic Drug User Fee Amendments II commitment to communicate surveillance inspection classifications to facility owners within 90 days of an inspection's completion, setting a goal of 90% for meeting this time frame in 2018.

Kent Mansfield, President, TruTag Technologies, Inc., highlighted novel uses of nanoporous silica (pSi) in pharmaceuticals. pSi can be used in nanomedicine, drug-delivery vehicles, photoluminescent devices, product authentication, and data intelligence. High-purity silicon is etched to create a uniform porosity: 10–15 nanometer (nm) pores are typical.

For pharmaceutical use, the silicon is converted to silicon dioxide, then a manufacturing process similar to that used for semiconductors creates specific porosity patterns to program spectral codes. "That's key to how we decode and read them," said Daniels. "This process used to be highly manual. Now it's completely robotic." Other applications include on-dose variably coded pSi markers for solid dose products, injectable drug delivery with a pore morphology to manage elution, nanopore silica implants, which have few side effects and can be consumed by the body, unlike polymer implants.

"We can use these in continuous manufacturing to identify and characterize what's going through the process," said Mansfield. "There's a high potential for nanopore silica."

CONTINUOUS MANUFACTURING

Several sessions provided useful overviews of individual companies' progress in CM.

Eli Lilly and Company was named ISPE's 2017 Facility of the Year Award (FOYA) Overall Winner for its continuous direct compression manufacturing plants in Indiana and Puerto Rico (see *Pharmaceutical Engineering,* January-February 2018). **David Pappa,** Director, Technical Services/Manufacturing Science, Eli Lilly and Company, discussed the benefits of CM.

In batch mode, a single campaign could be weeks or months, he said. "In continuous manufacturing, we've streamlined and reduced that to weeks or days. And we've shown that direct compression in continuous manufacturing provides as much efficiency and is as good as traditional batch production."

CM's smaller scale also reduces development time, improves productivity, and sends product to market faster. Safety and containment are easier to manage because CM's smaller footprint requires only about 40% of the space traditionally required. Finally, CM offers greater flexibility: on-demand batch size, multiple configurations, real-time release, and online testing save time and energy. CM also allows more efficient changeover cleanings, with single-use bags for formulation and filing.

Continuous processing presents some unique challenges, including global regulatory expectations, the need for collaboration, and appropriate guidance. "This is coming," Pappa said, "but it's not finished yet. There's more road to be traveled."

Katherine Merton, Head, JLABS, New York City and Boston, spoke about Johnson & Johnson's collaborative approach to alternative laboratories and health care startups.

Five years ago, faced with too much lab space, J&J's San Diego laboratory launched JLABS, a flexible, capital-efficient environment to provide lab workspace for entrepreneurs in exchange for rent. Three hundred companies are now part of this ecosystem, with 150 current residents.

Since then, JLABs has grown to eight incubator sites, with a different focus in each location: for example, pharmaceuticals in San Diego and medical devices in Houston. Entrepreneurs in JLABs can access venture capital through an investor hub. Over $9 billion has been invested to date.

Brent Liefers, Senior Director, Operations, Singota Solutions, and **John Harmer,** Director of Sales, Vanrx Pharmasystems, presented a case study on gloveless robotic workcells. These closed, self-contained isolators remove the need for human intervention, which is the biggest problem in aseptic filling. They also reduce surfaces for decontamination and diminish aeration times. Robotic process handling and nested ready-to-use components eliminate container-to-container contact.

The workcell design minimizes integration problems, simplifies facility construction, and accelerates timelines to bring the facility online. Installation challenges include equipment coordination and facility timelines, as well as coordination with the FDA.

INDUSTRY 4.0

Brad Sepp, Director Manufacturing Sciences and Technology, Emergent BioSolutions, Inc., and **Paul Kubera,** Vice President, Process Technology, ABEC, Inc., discussed "Implementing a 4,000-Liter Single-Use Bioreactor for Large-Scale Flexible Manufacturing."

In 2012, Emergent's Bayview facility in Baltimore, Maryland, was designated by the US government as a Center for Innovation in Advanced Development and Manufacturing (CIADM) site to address national biologics preparedness priorities.

To meet CIADM goals, Emergent partnered with ABEC Inc., a bioprocess equipment provider, to create a highly flexible facility with the capability to run cell-culture, viral-vector, and microbial-manufacturing processes. The design features 50- to 4,000-liter (L) single-use bioreactors configured for rapid response and changeover. The expansion project earned Emergent an Honorable Mention in ISPE's 2017 FOYA Awards.

The facility's flexible design improves productivity and reduces costs; it also permits process transfer flexibility. During the 2015 Ebola outbreak, for example, the company manufactured a proof-of-concept vaccine candidate in less than four months. A technology transfer from GlaxoSmithKine for raxibacumab, a monoclonal antibody for inhalational anthrax, was previously licensed at 1,600 and 20,000 L in stainless steel. Emergent performed a 50-L transfer run in ABEC's custom single run technology. "The question was whether the cells would grow the same way in plastic. And the 50-L test showed that they did," said Kuba.

Rick Lu, Director, Manufacturing Technology and Innovation, AstraZeneca, and **Timo Simmen,** Director, Parenteral Technology Innovation & Standardisation, Janssen, both members of the BioPhorum Operations Group (BPOG), gave an update on the Biomanufacturing Technology Road Map.

The first edition of the *Technology Roadmap,* published July 2017,* identified enabling technologies and capabilities. The scope of the second edition BPOG *Technology Roadmap* is currently under discussion, with finalization scheduled for November 2018. Options being considered are process development, drug substance, drug product, disruptive technologies, cell and gene therapy, vaccines, and new expression systems.

Lu asked attendees to consider discussing participation with their companies. "There's plenty of time to get engaged and think about how to contribute," he said.

Nicole Monachino, Vice President, Business Operations and General Counsel, Quality Executive Partners, presented an overview of Virtuosi, a virtual reality educational platform developed in response to industry concerns about worker training. The Virtuosi system simulates a complete floor-to-ceiling lab environment and provides visualizations only possible with virtual reality, like airflow and patterns studies. The programming is highly sensitive to motion and order of operations. (Virtuosi's demonstration booth and 3D headset were a conference highlight.)

"You get to go into a virtual lab and perform tasks," Monachino explained. "You get immediate feedback. You can actually pick up a vial. It even shows you if you skip a step. When you wash your hands, it checks to make sure you're doing it correctly and rinsing enough."

Compared to traditional training, Monachino said, retention from virtual reality training is as high as 80%, and it enables critical thinking. Both reduce downtime and risk.

Jason Collins, Director, Process Architecture, IPS, discussed aseptic manufacturing, citing the need for multipurpose facilities that can adapt to new technology. Other challenges include global compliance, the need for quick adaptation to new business drives, and lack of space for phasing and expansion.

Heating, ventilation, and air-conditioning systems can be installed directly above the rooms they support. Interstitial space can provide access for maintenance, drainage from product areas does not need to be underground, and critical utilities can be directly below the systems they support. Robotics and smaller, modular, multiformat, movable units can reduce space requirements. Filling lines can be contained in the room, below the ceiling.

Flexibility can also be built in by eliminating columns on the production floor so structural elements don't interfere with equipment arrangements or maintenance access. Modular air-handling units and ductwork penetrations allow reconfiguration as needed. Open positions permit future phasing and expansion. Removable floors can allow renovation without disrupting production. Architectural solutions, combined with modular, scalable, expandable construction, can also improve facility performance.

Margaret Prendergast, Director of Bioengineer, Allevi (previously BioBots), Inc., shared her work on bioprinting, which she called "the future of medicine." Bioprinting uses a 3D printing process to create synthetic human tissue by outputting layer upon layer of living cells, growth factors, and biomaterials to fabricate biomedical parts.

Allevi's goal is to put "a 3D printer on every scientist's desktop, at a fraction of the cost," Prendergast said. The company's first product was a $10,000 extruder. Alevi now produces bioprinters, materials, bioinks, and software.

"Our customers have had great success," she noted, citing benchmarks such as printing bone and soft materials such as an artery and mouse kidney, automated methods to print cancer tumor models that are combined with bioprinted liver models for drug testing, and the first thrombosis on a chip that can test a variety of drugs.

Future goals include automated tissue printing for trachea, cartilage, bone, skin, heart, liver, lung, kidney, blood vessels, brain, nerve, and muscle tissues, mostly for drug testing.

Mike Adelstein, President and CEO, Potomac Photonics, presented his work on advanced micro manufacturing technologies, which can produce microdevices as small as 1 micrometer (µm). The diameter of a human hair, for comparison, is 75 µm. Laser micromachining is compatible with a wide range of materials and can drill holes with µm-level precision.

"We laser machined 25,000 1.9-µm holes in less than 5 minutes … in stainless steel!" Adelstein exclaimed. Microchanneling, a process that has been

* Available on the BPOG public website: https://www.biophorum.com/executive-summary

Workforce of the Future

Robots and super-profiles

Dr. Antonio Moreira, Vice Provost for Academic Affairs, University of Maryland, Baltimore County (UMBC), spoke about preparing the biopharmaceutical WOF—a workforce that he warned is already in short supply. In the next 5 to 10 years the global pharmaceutical industry will need a highly skilled workforce with competencies that include CM technologies, 3D printing, combination products, automation, big data management, CAR T-cells, and other new specialties.

To meet the demand, the GPMLF Workforce of the Future Initiative is developing curricula that will prepare students for industry. GPMLF is in partnership with several universities, since industry and academia must work together to build the WOF. Sponsored by the GPMLF and ISPE, UMBC's WOF team also works with students in middle and high schools. Dr. Moreira and his team have identified 13 "super-profiles" necessary for the pharmaceutical WOF, including bioassay scientist, automation engineer, microbiologist, and device technology expert. Each requires cross-functional skills, such as data management and analytics, in addition to technical expertise.

Jay Douglass, Chief Operating Officer, Advanced Robotics for Manufacturing Institute (ARM), noted that robots will be a large component of the WOF and discussed an initiative that is helping to drive its development.

ARM is a nonprofit consortium that facilitates robotic solutions in manufacturing. Founded by Carnegie Mellon University in 2017, it has 150 members in manufacturing, academia, technology, government, and regional economic development. Completed projects may be licensed to other ARM participants.

Douglass urged attendees to share ideas about how robotics could work in the pharmaceutical industry. "Facilitate your investment in your own future," he said.

extremely expensive in the past, can now be done at a fraction of the cost. Micro-3D printing can be used to study how cells interact in various configurations. "We're trying to get down to 10 µm or less in 3D printing," he said. Initiatives include 3D printed microfluidics chips to identify early cancer cells.

Other possible applications include brain catheters, tiny channels for radiation cancer therapy, implantable lenses, 3D printed organs, and testing for antibiotic susceptibility.

Dhruv Patel, CEO, and **Christopher Look**, CTO, Synapto LLC, showed how a portable electroencephalogram (EEG) and artificial intelligence can diagnose Alzheimer's disease earlier and at a fraction of the current cost, using a lightweight noninvasive headset that captures EEG data of both resting and active brain waves called evoked related potentials, which are created as the patient presses the space bar when he or she hears a high tone.

Data sets were gathered from 256 patients in Brazil, Greece, and the United States. Results were analyzed by machine learning and deep learning mathematical models. Cross-validation distinguished true positives from false positives. In the Greek data set, the system diagnosed Alzheimer's correctly with 82% accuracy—better than other researchers around the world.

A pilot clinical study is planned for 60–80 at-risk early-stage patients. In the future, Patel and Look hope to develop presymptomatic testing as well as analyze disease progression.

Kathryn Colonna Worrilow, PhD, Founder and CEO, LifeAire Systems, shared the story of LifeAire Systems. Through live monitoring of contaminants such as volatile organic compounds (VOCs), chemical pathogens, HVAC components, and other toxic substances in an in vitro fertilization lab, Worrilow and her team learned that airborne contaminants at parts-per-billion levels were affecting clinical outcomes. Worrilow developed a system to provide sterile air, with chemical and biological pathogens below detection levels on a single pass at reduced air-changes per hour.

The system has 22 patents to date, with others pending. LifeAire has been installed in more than 35 clinical facilities in the United States, including the Mayo Clinic; others are in China and Canada.

Dr. Juandria Williams, Branch Chief (Acting), CDER/OPQ/OPF/DIA, offered the FDA's perspective on emerging technology. The FDA developed its Emerging Technology Team (ETT) in 2015 to encourage the adoption of innovative technology.

With ETT's help, FDA has identified CM as an emerging technology with the potential to increase the efficiency, flexibility, agility, and robustness of pharmaceutical manufacturing. Since 2015, it has approved four new drugs produced by CM—one of which had previously been approved for patch process—and played a critical role in approving the first 3D-printed drug product.

Robert Blouin, PharmD, Provost, University of North Carolina (UNC) at Chapel Hill, told how he developed a culture of collaboration and innovation at the Eshelman School of Pharmacy.

Blouin came to UNC in 2003 and encouraged the university to see its opportunity to play a major role in drug discovery. By securing support from the board and forming strategic partnerships, Blouin transformed the school: The student population doubled, faculty tripled, and research space quadrupled. National Institutes of Health funding increased by 1,800%. Additional transformations followed with a series of donations totaling $133 million from Dr. Fred Eshelman, CEO and founder of PPD Inc., for whom the school is named. UNC at Chapel Hill soon became one of the top-ranked pharmacy schools in the world.

The path to success, he continued, starts with a vision and a strategic plan. Hold people accountable for their work, and realize that you may have to do unpopular things to create change. Hire the right people, or they won't be productive. Look for inquisitiveness, resilience, and adaptability. Invest in people for the long term. "If you don't have the right people, you can't compete. You just can't."

Finally, "we have to transform our culture of thinking, Blouin said, "and get people to think differently. That's our biggest challenge—and our greatest opportunity."

—Amy R. Loerch, Publications Manager

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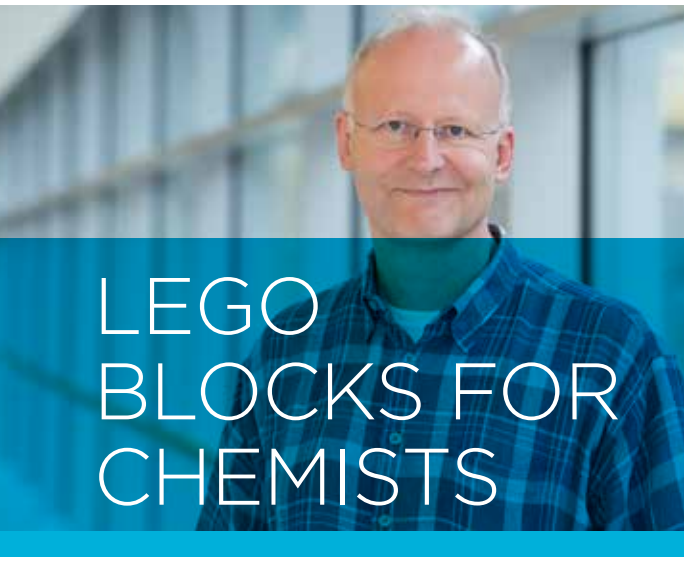

LEGO BLOCKS FOR CHEMISTS

The Advent of Continuous Manufacturing

Spurred by pressure from governments and consumers to curb rising drug prices, pharmaceutical manufacturers are increasingly willing to look beyond traditional batch processing to cut costs and increase efficiency. One of the industry's most dramatic innovations on this front is continuous manufacturing (CM). The technology, which produces drugs in an uninterrupted process, benefits patients, health care providers, and the pharmaceutical industry by reducing facility footprints, lowering capital and operating costs, enhancing reliability and flexibility, and improving quality control.

Continuous processing is not new," said Markus Krumme, head of continuous manufacturing at Novartis. "For the past 50 years, oil refineries have relied on it. The reason why the pharmaceutical industry has not implemented continuous manufacturing until recently, and still not widely, is that other industries—oil, gas, plastics—create high-volume, low-specific-value commodities. They may make thousands of tons of oil at a time, but the price of a gallon is only $1.50. Contrast that with drug making, where we produce relatively small volumes, but a kilo of a specific product costs $2,000."

In 2006, Daniel Vasella, CEO of Novartis at the time, asked his staff if it were conceivable to have a continuous process as simple as feeding raw material into one end and having a finished tablet come out the other.

"The answer is yes, but that 'simple' concept turned into a fully automated plant," said Krumme, who helped found the Novartis Continuous Manufacturing Facility in Basel, Switzerland. He likens the development of continuous processing to the evolution of flight. "The basic idea of flight was present when the Wright brothers took off for the first time. The Airbus A380 has the same concept, also has wings and an engine, but is substantially more complex."

Krumme and Novartis's head of technical operations decided to answer Vasella's question. They assembled an internal team and began talking to people outside of traditional pharmaceutical manufacturing to avoid biased views about typical industry problem-solving. "It's a bit like asking a child to draw something out of their imagination, where you quite possibly will get something really crazy, but also something interesting and new."

Novartis next turned to MIT, entering into a 10-year collaboration to design and develop a continuous plant. The team had only a few constraints: It had to be unconventional, it had to be continuous, and it had to produce a viable product. Then the company left the academics alone. Five years later MIT had developed and installed a pilot plant at the university.

"This was the proof of principle using university-grade research we were hoping for," Krumme said. "It was completely different in terms of technology from what we were using to make tablets at the time, but they nevertheless made something that looked like a tablet.

"We took what they showed us and restarted, trying to be as unbiased as possible, even though, as industrial engineers, we couldn't forget everything we'd seen. We tried to funnel the same train of thought that MIT used without transferring any of the detail of what was developed there."

This process led to the creation of the Novartis Continuous Manufacturing Facility in Basel.

FAST, FLEXIBLE, SCALABLE

Some estimates suggest that CM could shave 30%–50% off the cost of making drugs, and that production could be up to 90% faster than batch mode. CM can also reduce—and possibly eliminate—scale-up time. Unlike traditional manufacturing, it can be scaled for immediate demand and allow variable batch sizes, including smaller batches of specialty products. The company's development goal is to operate 24/7 with throughput times as short as half a day.

"The way we've built our facility is highly modular, like Lego blocks for chemists," Krumme said. "You can build a lot of different things, not by changing the structure of any one block, but just by assembling blocks in different ways."

Could this type of process alleviate the instances of drug shortages that are due, for example, to facility damage and other effects of natural disasters, such as last year's hurricane in Puerto Rico?

"I would say not yet, but it can be an attractive tool if used properly. I can conceive if we standardized the Lego blocks into chemical production, we could be flexible in what is produced, where it's produced, and how fast a

Top left: the Novartis Continuous Manufacturing Facility in Basel; top right: upstream processing; above: downstream

SOME ESTIMATES SUGGEST THAT CM COULD SHAVE 30%–50% OFF THE COST OF MAKING DRUGS, AND THAT PRODUCTION COULD BE UP TO 90% FASTER THAN BATCH MODE

new assembly could be built out of preexisting blocks. If used in the right way, we could create an agile industrial environment that would allow mitigation of drug shortages. It would be smart to go in this direction."

The idea of facilities being built out of components is reminiscent of the GE Healthcare Life Sciences FlexFactory (see page 12), the first of which was built for JHL Biotech in Wuhan, China. Prefabricated as 62 modules in Germany and shipped to China, the facility included intact cleanrooms. It will produce biosimilars for the domestic market.[1]

"While continuous processing allows smaller batches of specialty products—and could be a helpful tool for producing personalized medicines—it is not playing in the same field as a drug like Novartis's Kymriah, a biologic that is an extreme version of a specialized medicine," Krumme said. "But it does let us manipulate the run time, whether that's one hour, one day, or one week, and leads to a scalable batch size. It is, in this sense, a helpful tool for personalized medicine."

OUTCOME-BASED CONTROLS IMPROVE QUALITY CONTROL

A major benefit of CM is quality control, according to Krumme, although this may seem counterintuitive to many in the industry.

"This is perhaps the most regulated industry," he said. "From a regulatory and quality perspective, people tend to be conservative. If a doctor asks a patient whether he or she would like to take an experimental drug or one that has been tested a thousand times, 90% will choose the known drug even if it has unpleasant side effects. Regulators function with the same psychology and, when in doubt, will insist on the production path that is already known."

CM permits sequential and continuous assessment of product, which differs from intermittent, post-production testing in batch mode. This "outcome-based control" allows Novartis to assess portions of a product run and test the quality of every tablet almost as soon as it's produced. This can't be done with batch processing, during which a mistake can ruin an entire batch of drug substance.

"Continuous manufacturing allows us to manipulate the process while it's flowing, sampling what comes out after five minutes, for example, then adjusting the conditions to improve the product. We might discard the first five minutes of product if it proves defective," said Krumme.

Some regulators agree with these quality benefits and recognize the possibilities of the new technology. Dr. Lawrence Yu, for example, Deputy Director in the Office of Pharmaceutical Quality at the US Food and Drug Administration (FDA), has promoted continuous manufacturing as a more reliable and safer alternative to batch processes.[2] In 2016, for the first time, the FDA allowed a drug maker to switch from batch production to CM for an existing drug.[3]

Pfizer Inc., one of the companies that have moved into continuous processing, won an ISPE Facility of the Year Award (FOYA) in 2016 for its portable, continuous, miniature, and modular (PCMM) technology for solid oral dosage forms.[4] Eli Lilly won two 2017 FOYA category awards and was

A wider view of the upstream processing area

named the overall FOYA winner for its continuous direct compression manufacturing kits 2 and 3 in Indianapolis, Indiana, and Carolina, Puerto Rico. The company recently completed a continuous manufacturing facility in Kinsale, Ireland, to accelerate production of medicine for oncology clinical trials.[5–6]

SKILLS NEEDED

"Fortunately, we have been able to hire the base skills that we need, then develop people together with the technology," Krumme said. "We have a certain number of kits that we operate, and we grow the skills and the facilities simultaneously. While we're not constrained by a lack of skills, the training of people is substantial. We need organic chemists, pharmaceutical scientists who develop continuous-compatible processes, kit builders, and people to operate the kits, all at the same rate. We need process people who are automation-literate at a high level—both chemical engineers and pharma scientists—and are open to trying out new principles that are different than what they learned in school. And we need many more people versed in computer-based, advanced-control techniques compared to a traditional operation."

THE PACE OF ACCEPTANCE

While there is enthusiasm for the technology and increasing adoption, Krumme doesn't see it taking over the industry anytime soon. "It's not realistic to believe we can expect a revolution like the speed at which cell phones were adopted in the 1990s. We've had drugs on the market for 50 years that are still efficacious. Why would we need to change the way we make those products?"

Clearly, it is larger companies like Novartis that lead the way. But smaller companies and contract manufacturing organizations (CMOs) seem poised to embrace this technology as they seek new efficiencies, improved quality, and increased flexibility.

"We see machine equipment vendors that are investing in this type of technology," explained Krumme. "There are CMOs that are adopting continuous technologies piece by piece, and some Chinese companies are involved in small-volume continuous flow chemistry. As the originators, we are using different kinds of chemistry that are well-suited to continuous processing. If these vendors are not ready to use these innovative chemical processes, we won't be able to work with them."

Novartis would like to see aspects of the technology developed at MIT embraced throughout the industry, which is one reason that some of the intellectual property rights continue to be held by MIT.

"New drugs—from Novartis as well as others—are coming from this technology," Krumme concluded. "We're using a system of continuous-specific quality management principles and, while we're leading the pack, I suspect lots more will come." ‹›

—Scott Fotheringham, PhD

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TRANSITIONING TO MULTICOLUMN CHROMATOGRAPHY

Real-World Challenges and Results

Lindsay Arnold

Although pharmaceutical manufacturing is traditionally a change-averse industry, the benefits of continuous processing demonstrated in other industries are beginning to drive interest in its application to bioprocessing. This article reports on MedImmune's exploration of bioprocess areas that could be advantageously transitioned from batch operations to continuous processing.

Downstream processing is often the most challenging part of any bioprocess, and chromatography is a cost- and time-intensive portion of this operation due to the complex nature of the technology and the high cost of the sorbents (also commonly referred to as resins) required. As such, we evaluated continuous multicolumn chromatography (MCC) for its potential to reduce costs and deliver other benefits (lower sorbent consumption, flexible footprints, etc.) at large scale.

PROCESS INTENSIFICATION

Mature industries such as car manufacturing, steel production, and commodity chemical manufacturing have established continuous processing solutions over the past 100 years. This has helped improve capital utilization and reduce operating expenses while achieving greater process control, which enhances safety and product quality.

When applied to the production of biopharmaceuticals, continuous processing enables similar benefits. While buffers, sorbents, raw materials, viral clearance fundamentals, bioburden-control systems, contact materials, and other attributes of batch processing do not change after conversion to continuous manufacturing, overall productivity improves, with higher and more consistent yields. Greater process control enhances product quality. And since more productive continuous bioprocess systems tend to be more compact, current manufacturing footprint can be conserved or reduced.

In addition, because batch scale-up is replaced with increasing process run times, continuous processing provides a greater ability to respond to variable market demand. Adopting single-use technologies further increases efficiencies—with faster process setup and elimination of cleaning/cleaning validation steps—while reducing the risk of cross-contamination in multiproduct facilities.

STEPWISE TRANSFORMATION

Moving from batch manufacturing to a fully integrated continuous process involves significant change and investment, both of which carry an elevated level of risk. Recognizing the value of the continuous processing approach while understanding the evolution is just beginning.*

Because of this, MedImmune has approached continuous bioprocessing for unit operations by adopting a modular approach that implements continuous manufacturing where it offers the greatest benefits. This hybrid approach allows us to gain experience in the continuous processing space while continuing to maximize the value of our existing batch manufacturing infrastructure.

MULTICOLUMN CHROMATOGRAPHY

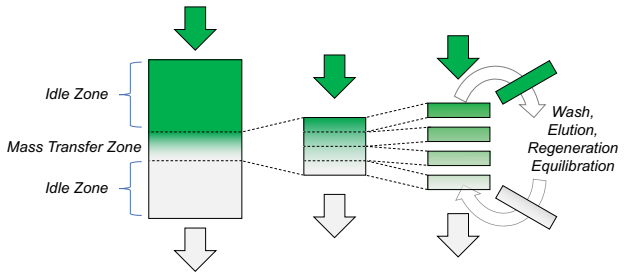
The first phase in this modular approach explored MCC as an alternative to batch chromatography for protein A capture. Chromatography is a fundamental unit operation in the purification process for which alternative solutions may offer economic and efficiency advantages.

In typical batch primary capture chromatography, less than 60%–70% of total sorbent binding capacity is used. As bioprocess fluid is fed to the column, the top sorbent becomes saturated but the bottom encounters little to no product. All activity occurs in the mass-transfer zone, which accounts for only a small portion of the column, while the remaining areas serve as idle zones.

Saturating the latter portion of the sorbent would result in costly product breakthrough, so initial product development experimentation sets a binding capacity limit of 10% product breakthrough. As this value propagates into the manufacturing setting, however, additional safety factors are added, further reducing the resin utilization. Higher binding capacities could be attained by increasing the residence time of the bioprocess fluid on the column, but this would affect processing time and total time in plant. In traditional batch mode, sorbent underutilization is the manufacturer's opportunity cost that is sacrificed to strike a balance between speed and product recovery.

* Some downstream processing steps (i.e., filtration and flow-through chromatography) are currently compatible with continuous bioprocessing, and there is extensive discussion in the pharmaceutical industry about developing fully continuous end-to-end, integrated downstream bioprocessing solutions.

FIGURE 1: PRINCIPLES OF MULTICOLUMN CHROMATOGRAPHY



With MCC (Figure 1), smaller columns with reduced bed heights are linked in series and used for the same process steps that a batch column would undergo. These smaller columns are cycled multiple times to process a comparable volume. In this case, however, the resin is allowed to load to high breakthrough, with product from the first column captured on the second (second pass) column. This preserves high yield, but also exploits a much higher binding capacity on the first column. With continuous countercurrent loading, the same residence times are achieved, but only the mass transfer zone must be accommodated by the load columns, eliminating the sorbent required for idle zones in batch chromatography.

Much less sorbent and much smaller columns, therefore, purify the same amount of product as in a batch process. Overall, greater than 40%-higher sorbent capacity can be attained. A batch column, for example, typically achieves a binding capacity of 35 grams (g) of product per liter (L) of sorbent (at 10% breakthrough). Continuous processing could achieve a binding capacity of 50 g/L or more. Greater than 95% of equilibrium binding capacity can usually be attained, a parameter that is simply unattainable in batch processing. In addition, no product is lost to breakthrough, and buffer requirements are reduced. Furthermore, due to rapid cycling, the multicolumn configuration can be designed to allow chromatographic sorbent to reach its full reusable lifetime within a campaign, allowing a single-use/disposable format. Importantly, all batch process steps are maintained, and the same sorbent chemistries and buffer solutions can be used.

BUSINESS CASE

To compare continuous and batch processes, the first step in our exploration was to calculate potential cost savings at large scale for different column sizes. This translates the benefits of the higher binding capacity and smaller columns into tangible criteria, such as time in plant and cost of goods.

For this exercise, a 2,000-L batch with a titer of 5 g/L monoclonal antibody (mAb) was processed in batch mode using a column with a height of 20 centimeters (cm) and a 60-cm diameter, or in continuous mode using either four columns with a height of 10 cm and a 30-cm diameter, or three columns with the same height but a 20-cm diameter.

For the batch process, 57 L of sorbent and six cycles requiring 6,100 L of buffer and a total column wet time of 8 hours (hr) afforded a productivity of 20 g/L sorbent/hr. For the continuous process designed with comparable processing time, eight cycles were performed, reducing the sorbent (28 L), buffer (4,000 L), and column wet time (6 hr). With the smaller column MCC design, the number of cycles and wet time were notably higher (25 and 20 hr, respectively) than the batch process. Sorbent requirement, however, was dramatically reduced to 9 L, and buffer consumption was lower still at 4,200 L.

Importantly, both continuous processes had measurably higher productivities: 60 and 55 g/L sorbent/hr for the larger and smaller columns, respectively. Cost savings were also significant: Assuming a cost of $12,000/L of sorbent, the batch process had a total cost of $648,000 compared with $336,000 and $108,000 for the two continuous operations.

In the first continuous process with 30-cm columns, buffer and sorbent consumption and column wet time are all reduced, tripling productivity as measured in g/L sorbent/hr. This scenario is advantageous when converting an existing batch process to a continuous operation. Run times for the chromatography process are already established and fit into the overall downstream operations. Any process time extension in a unit operation will affect the scheduling of operations that follow. Using a larger column allows for a wet time similar to the batch process, meeting the time constraints as defined by the existing batch process.

In the second continuous scenario, using smaller columns tripled the column wet time compared to the batch process. This approach might not, therefore, be suitable as a replacement for an existing batch operation. On the other hand, sorbent consumption is markedly lower, leading to a cost that is one-third that of the first continuous process and nearly one-sixth that of the batch process. This would be attractive when a plant is underutilized or where the costs of goods is more important, such as in a clinical production facility.

Similar calculations were then performed for chromatography at the 15,000-L scale using a bioprocess fluid with a mAb titer of 5 g/L. In this case, the batch process was conducted using a column with a height of 20 cm and a diameter of 1.8 meters (m), while the continuous process was carried out once again using four columns with a height of 10 cm and a diameter of 30 cm.

In this case, going from batch to continuous processing, consumption was reduced from 509 L to 28 L. Although the process time nearly doubled—going from 24 to 40 hr—productivity increased more than tenfold from 5 to 56 g/L sorbent/hr, and the cost was reduced by a factor of nearly 20, from $6,108,000 to $336,000.

These results demonstrate that switching from batch to continuous processes can dramatically reduce the cost of goods for biopharmaceutical chromatography processes. They also reveal several ways in which benefits can be realized with MCC technology, depending on plant constraints and the company's goals. Options exist for sorbent, buffer, and time savings, and process engineers can design continuous solutions to meet the demands of any project.

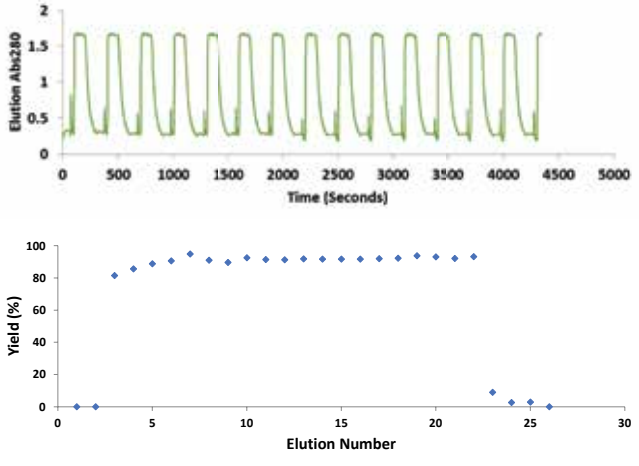
ADDITIONAL BENEFITS

The smaller quantities of sorbent and buffer required for MCC lead to other benefits as well. Lower inventory and storage requirements for smaller amounts of sorbent and buffers reduce costs and improve balance sheets. Sorbent savings are also realized for clinical programs that do not move forward.

Risks diminish as well. Because the sorbent lifetime could be consumed with a single campaign, for instance, there is no need for sorbent storage, reducing the risk of contamination over successive batches, storage, and campaigns. Smaller columns also improve safety.

FIGURE 2: CONTINUOUS MCC PLATFORM

FIGURE 3: SMALL-SCALE MCC PERFORMANCE: STEADY-STATE



Finally, MCC integrates seamlessly with upstream continuous processes. When a company is ready to move toward end-to-end continuous processing, perfusion reactions can be readily coupled with downstream chromatography operations.

DRIVERS

MedImmune's main driver for exploring continuous chromatography was the potential for sorbent savings, regardless of whether MCC is coupled with other batch operations or incorporated into a fully continuous process. The company was particularly interested in potential savings for protein A capture chromatography, because protein A is the most expensive sorbent used at MedImmune.

Once the calculations indicated that MCC was worth exploring in the lab, the next step was to select a continuous chromatography system. MCC has been around for many years, but until recently was not suitable for use in good manufacturing practice environments for biologic drug substances. The systems require extensive plumbing, which previously presented impractical setup, cleaning, and maintenance challenges.

MedImmune wanted a continuous chromatography system that could be set up and operated readily, and one that would allow an easy transition from batch to continuous processing. It needed a system flexible enough to operate processes from small to large scale, with varying numbers and sizes of columns. The company expected to investigate low-titer bioprocess fluids generated in perfusion bioreactors, higher-titer fluids from fed-batch reactions, and concentrated batch harvests with titers up to 15 g/L. To enable scale-up comparisons, a system with a higher throughput and the ability to use columns from 5 milliliters (mL) to 100 mL in size was also crucial.

The Cadence BioSMB platform (Figure 2) from Pall Life Sciences met these requirements. The system is based on a single-use, integrated valve block design with 240 diaphragm valves. One valve cassette is used per campaign. The system is available at both process-development (16 columns) and production scales (8 columns) with 1- and 3-millimeter flow paths that can operate at rates up to 70 mL/min and 5 cm columns, or 300 mL/min and columns up to 10 cm, respectively.

Finally, we used an effective modeling approach that allows easy conversion of batch processes to continuous operations. The process model enables users to quickly convert single-column breakthrough data for a batch process to the parameters appropriate for a continuous process. Notably, the same sorbent, buffer system, and product quality assays can be used.

PROTEIN A CASE STUDIES

Once the MCC system had been installed, we performed both small- and larger-scale continuous chromatography runs, then compared the results to those obtained from similar batch processes, using a clarified media containing immunoglobulin G mAb to investigate protein A capture chromatography.

The batch process used 20 mL of sorbent. Cycle time was 2.5 hr, with 650 milligrams (mg) of product processed per cycle, leading to a productivity of 13 g/L sorbent/hr.

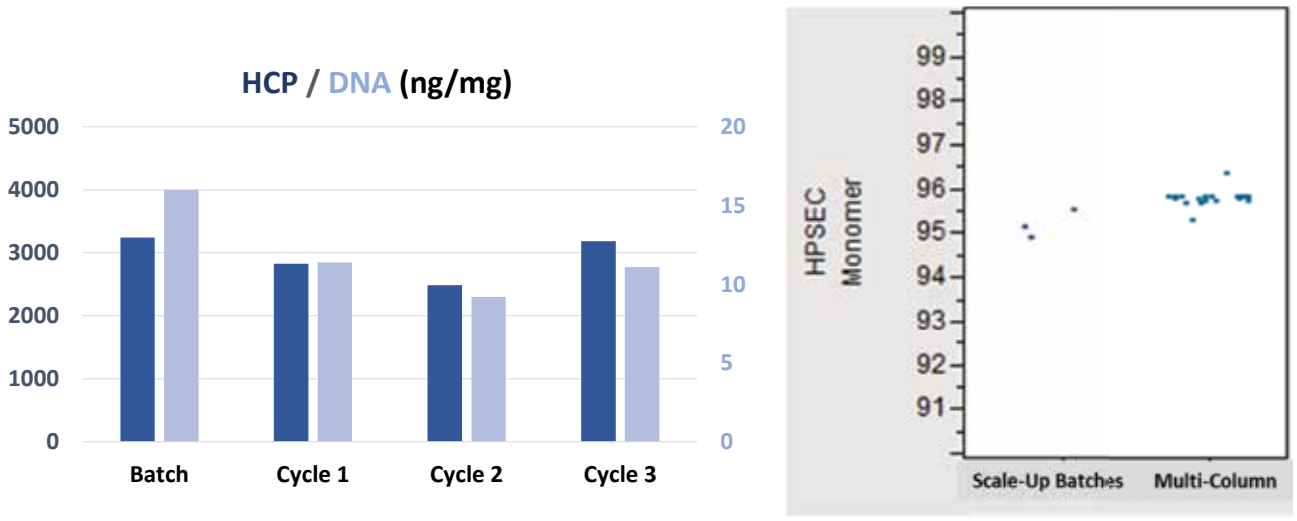
The continuous process used 25 mL of sorbent, but cycle time was reduced to 48 minutes (one-fifth that of the batch cycle). A total of 820 mg of product was processed per cycle once steady-state conditions were achieved (ramp-up occurred over the first two cycles). This yielded a productivity of 40 g /L sorbent/hr—a nearly four-fold increase.

Figures 3 and 4 show the small-scale continuous process performance. Steady-state yields were 91.0% ± 1.5%, and the total process yield was 92%. The repetitive elution peaks could allow cycle-to-cycle overlay for multivariate analysis, which could enable dynamic monitoring and provide insight into aging sorbent characteristics (Figure 3).

Host-cell protein and DNA impurities in the final product eluates were slightly higher in the batch process than in the continuous process steady-state cycles 1, 2, and 3 (Figure 4). Results are on the same magnitude, however, and can be considered similar.

The second graph in Figure 4 plots the ratio of monomer to aggregates for different runs. The scale-up batch data is historical data collected for

FIGURE 4: SMALL-SCALE MCC PERFORMANCE: IMPURITIES AND AGGREGATES



several scale-up (50–200 L) chromatographic purifications of the same mAb purified in the continuous run. Multicolumn data points for various cycles are clustered at a higher purity (the two outliers are associated with the ramp-up and ramp-down cycles). The tighter purity profile is the most important information obtained here. This study confirmed product quality comparability to batch processing.

PRODUCTIVITY AT 50-L SCALE

After evaluating the continuous MCC using 5-mL columns, we conducted a second investigation using ±100 mL of sorbent in larger columns (4.4 or 5 cm). This was an internal check to confirm that quality and yield results comparable to existing batch processes could be obtained with continuous multicolumn chromatography at mid-scale.

The MCC results were compared with batch runs at the 50–200-L scale for a variety of mAbs (platform, legacy, bispecific, fusion). No large variations or differences were seen. While product quality and yield advantages were not observed in all cases, sorbent, buffer, and time savings were achieved.

In one example, a bioprocess fluid with a mAb titer of 4.3 g/L was purified in both batch and continuous modes. In the batch process, a column with a height of 20 cm and a diameter of 14 cm required 3.1 L of sorbent (at a cost of $37,000) and 200 L of buffer. Three cycles were completed in 6 hr, resulting in a productivity of 12 g/L sorbent/hr.

For the continuous process, MedImmune wanted to use the smallest amount of sorbent possible. Four columns with a height of 5 cm and a diameter of 4.4 cm were used, requiring 300 mL of sorbent ($3,600) and 100 L of buffer. Fourteen cycles were completed in 11 hr, affording a productivity of 60 g/L sorbent/hr. Although the process took nearly twice as long, productivity was boosted by a factor of five, at one-tenth the cost and half the buffer.

CONCLUSIONS

MCC has significant potential to improve the cost and efficiency of chromatography processes in biopharmaceutical manufacturing. These potential benefits were significant enough that MedImmune conducted modeling and physical studies to explore continuous MCC in its production facilities.

In multiple protein A purifications of different mAb products at different scales (3–50 L) using a range of column sizes, product quality between batch and continuous runs was consistent. We observed increased binding capacities, reduced buffer requirements, reduced sorbent requirements, and improved productivity results, using the same batch process steps and development approach.

Based on these results, MedImmune will explore continuous MCC to improve other chromatographic separations, including the possibility of using higher-cost, higher-capacity sorbents that are impractical for batch processes. Using prepacked columns in combination with other existing single-use technologies could further facilitate continuous chromatography setup and operation in an entirely disposable approach.

The flexible throughput capabilities of continuous MCC should also be explored in diverse types of facilities for the potential to address problems ranging from the need for lower cost of goods to reduced buffer consumption due to lack of space, and many others.

Finally, the positive results obtained for MCC bring MedImmune one step closer to full continuous processing. As we gain additional experience, we will continue to target continuous unit operation implementation where the greatest benefits can be realized. ‹›

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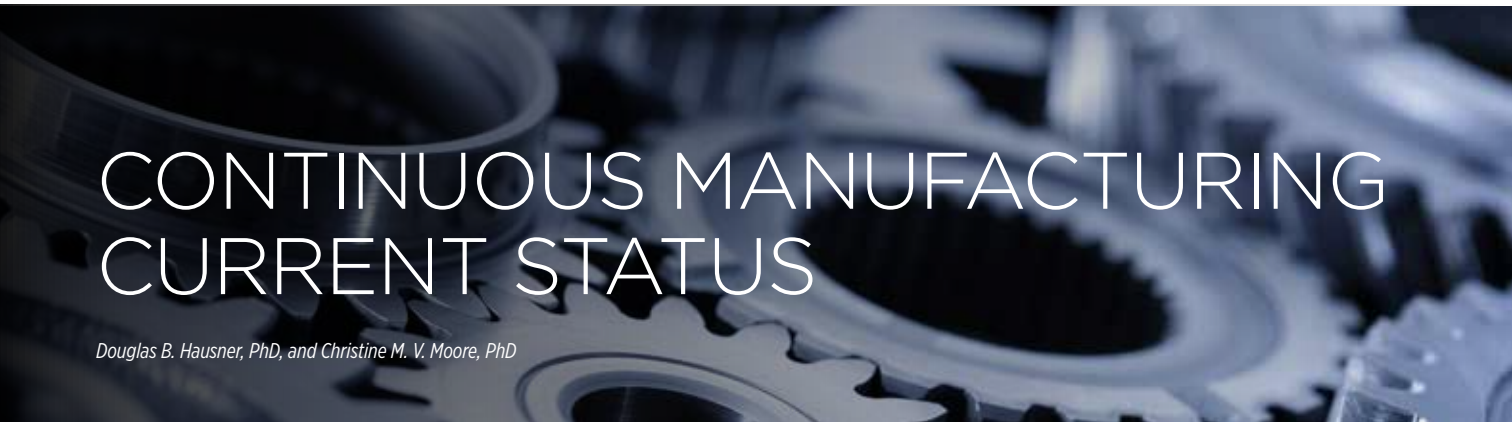

CONTINUOUS MANUFACTURING CURRENT STATUS

Douglas B. Hausner, PhD, and Christine M. V. Moore, PhD

Change in the pharmaceutical industry is notoriously slow, so it wasn't surprising that many doubted continuous manufacturing (CM) would ever be adopted. But despite the skeptics, the technology is gaining substantial ground. Since 2015, four solid oral drugs produced by continuous processes have been approved by the US Food and Drug Administration (FDA) (Table A).

Of these four approved CM products, three were new molecular entities, indicating that companies have enough confidence in this emerging technology to use it for their high-value products. Production of Janssen's Prezista, on the other hand, switched from batch to CM processing; the change was approved by the US FDA in April 2016.[1]

Europe is close behind the US, with two CM drug approvals[2, 13] and more anticipated soon, including Symdeko,[3] which is expected to be approved in the European Union before the end of the year. Health authorities in Canada, Switzerland, Australia, and New Zealand have also approved applications for CM-produced solid oral dosage forms.[4]

While recent CM approvals have focused on solid dose tablet manufacturing, momentum is growing for both active pharmaceutical ingredients (APIs) and biologics. In a sense, CM in these areas is not new: single-unit operations such as flow reactors for API and perfusion bioreactors for biologics have been used for decades. Manufacturers now find it advantageous, however, to link these single-unit operations for full end-to-end production, or even integrate drug substance and drug product manufacturing (see page 32).

API manufacturing processes typically have more steps—and therefore more complexity—compared to solid dosage manufacturing. But with CM's production efficiencies, interest in and adoption of continuous API manufacturing should increase once the first approval comes through. One Lilly continuous API good manufacturing practice facility can produce 3 kilograms a day of prexasertib monolactate monohydrate, a chemotherapy candidate for clinical trials.[5] The process links each stage in the process to quality-control systems, combining synthesis with purification and crystallization. It also enables chemistries that would be impossible or too dangerous using traditional methods.

CM upstream perfusion for biologics is already well established and used to manufacture over 20 FDA-approved products.[6] Perfusion alone is not a fair comparison, however, because it is a single-unit operation. There is significant interest in integrated multiunit continuous operation with downstream purification, and Genzyme, Merck, Bayer, and Sanofi are thought to be interested in this area.[7]

Government support for CM technology, already high, seems to be increasing, with support from the United Kingdom and European countries such as Belgium and Austria. The United States passed the 21st Century Cures Act on 31 December 2016, which promoted advanced pharmaceutical manufacturing.[8] FDA leadership, which has led much of the drive for CM, also awarded $4.9 million in grant funding to support the introduction of CM techniques for pharmaceuticals.[9] To accelerate the transition to industry, FDA Commissioner Scott Gottlieb called for funding to promote innovation on 13 February 2018.[10]

While the adoption rate for CM forms an impressive trajectory, the process of bringing the technology on board is not trivial. It requires new and different operator skills, vendors, and training to implement the technology successfully. Different flow and mixing patterns may also require different approaches to characterize and understand the process. Early adopters spent considerable time and resources to develop these capabilities before they brought products to markets. Despite these challenges, several companies now have plans for future installations, and multiple CM products are in the pipeline.

To encourage this new technology and alleviate industry concerns, several health authorities have established special working groups to shepherd development and provide advice:

- The FDA established the Emerging Technology Team in 2015 to "[support] industry's development of innovative approaches in pharmaceutical design and manufacturing. The program provides an opportunity for early dialogue during technology development and prior to the submission of a drug application. This enables [the agency] to identify and resolve potential roadblocks early in the process."[11]
- The European Medicines Agency expanded its existing Process Analytical Technology Team to include CM.
- Japan formed the Innovative Manufacturing Technology Working Group, which interfaces with industry to "discuss regulatory issues related to quality assessment and good manufacturing practice inspection to facilitate the introduction of innovative manufacturing technologies while ensuring appropriate quality. Continuous manufacturing is our primary target."[12]

Each of these groups provides an avenue for early communication and enhanced dialogue. This is important for innovative pharmaceutical companies that are introducing continuous processing to the market, since many health authorities currently have little familiarity with the technology. The enhanced communication helps inform the health authorities of new approaches and provides direction and decreases regulatory uncertainty for companies.

New technology is both a challenge and an opportunity for the pharmaceu-

TABLE A: FDA APPROVALS OF DRUGS PRODUCED BY CONTINUOUS PROCESSES

Approval	Brand	Therapeutic agent	Company	Indication
2015	Orkambi	Lumacaftor/ivacaftor	Vertex	Cystic fibrosis
2016	Prezista	Darunavir	Janssen	HIV
2017	Verzenio	Abemaciclib	Eli Lilly and Company	Advanced breast cancer
2018	Symdeko	Tezacaftor/ivacaftor; ivacaftor	Vertex	Cystic fibrosis

tical industry. CM, whatever its form, increases automation, process analytical technology, and the need for high-level process understanding and control. As it takes hold within the industry, it is imperative that we find some degree of alignment, if not standardization or harmonization, among our approaches. If we do not, adoption will remain slow as regulators seek to understand the new manufacturing technologies they encounter. In this arena, convening organizations such as ISPE can play a key role in bringing the community together to share knowledge and best practices, and disseminate the information globally.

Overall, 2018 is likely to be an interesting year for CM. Further continuous solid dose filings as well as the first API will likely see approval this year. Over time, we expect to go from an average approval rate of one per year to perhaps half a dozen in the same time frame. For those who have been working in this area, this will be truly rewarding. For everyone else, it should serve as a call to hop on the bandwagon of CM, a technology that is here to stay.

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SUPPLY CHAINS: DRAMATIC CHANGES AHEAD

Andrew D. Skibo

Biopharmaceutical supply chains are undergoing dramatic changes that will affect the design and operation of the facilities of the future. Predominant among these is the shift away from primary care to specialty products and personalized medicine, and from large-scale production of low-value small molecules to low-volume, high-value biologics.

This transition to personalized medicine bears no resemblance to the manufacturing platforms that exist today for monoclonal antibodies (mAbs) or vaccines. These are step changes in size, scale, or demand. In some cases, we might rely on the same manufacturing technology, but need 10 times as much of it. In others, we might need an entirely different platform.

Managing both the risks and costs associated with these significant changes requires nimble, creative thinking. And this, in turn, requires an influx of intelligent, skilled, and innovative employees.

FACILITY OF THE FUTURE OR DINOSAUR?

Since about 95% of current pharmaceutical revenues are derived from small-molecule products, ours is a small-molecule industry with biologics tacked on. About half of the research and development pipeline is devoted to biologics, however, and this could increase to 70%–80% by 2020.

Seeing this, some C-suite executives question the relevance of stainless steel plants, believing that those built in the 1980s and 1990s are outdated dinosaurs incapable of dealing with newer biologic products. Despite this, we continue to build plants similar to those built in the 1990s, in part because the bulk protein demand for biologics continues to increase, especially for those that expand into primary-care-sized markets. Since it takes six years to bring a large plant online, our current planning conversations extend to 2024–2026. For large-scale stainless steel, 2023 is tomorrow.

As an industry, we will have invested an additional $10–$15 billion in stainless steel plants by the early 2020s, and the products we make in them will have 10–15-year life spans. At least three-quarters of the pipeline currently in Phase I or II consists of traditional mAbs that will not be licensed for three or four years. Much of this will land in large-scale plants; this technology will be with us for the better part of the next two decades.

Over the last 15 years, the pharmaceutical industry has undergone a rough transition. Patent expiries, a drop in R&D productivity, and reimbursement challenges have all put pressure on earnings. In response, we adopted supply chain efficiency initiatives from nonpharmaceutical industries, particularly automotive manufacturing. Manufacturing costs are a larger portion of the costs of goods in those industries, so they were early leaders in cost-reduction and supply chain efficiency.

One way that we made pharmaceutical supply chains more cost-effective was to increase utilization. Automotive and chemical manufacturing, for example, must run at a utilization approaching 95% to be profitable. Twenty years ago, in contrast, it was common for pharmaceutical companies to operate at 55% utilization. That number has since increased to 85%.

One supply chain change in API production has been the shift from internal manufacturing to outsourcing. Because these products can have many synthesis steps, it's good to have redundancy in sourcing—but that can be hard to see. A supply chain for a product may look dual-sourced, but if a single step in those dual routes relies on a single producer, you have a sole-source supply chain. Issues like these have the potential to increase product supply and quality problems.

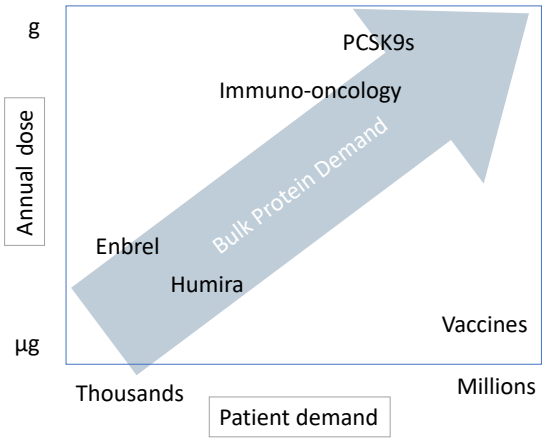
Externalized API production can also be subject to local market stresses. Fifteen years ago, much of our production was in Europe and North America. Now, companies have significant portions of their drug substance supply—in some cases more than 60%—in emerging markets. If API production is no longer internal, we can't just assume that the contract manufacturing organizations (CMOs) on which we depend have the same level of commitment to quality metrics and standards that we do.

It's possible to get there, though, and it has been done. Success depends on the companies that supply us having the desire to share our quality values. If CMOs combine commitment to a quality culture with rigorous analytics and quality metrics, then success in product supply can be more narrowly defined as product knowledge transfer.

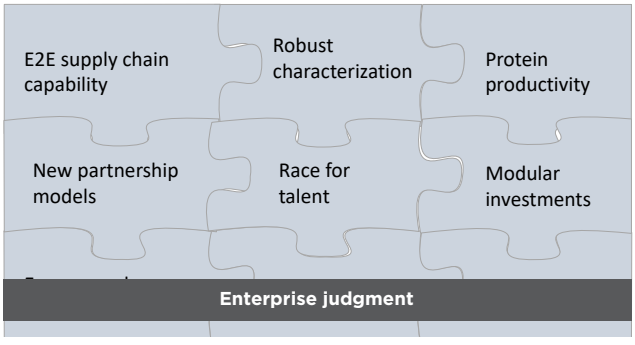
A country's culture can also affect a company's ability to respond. A good example of this occurred when the Iron Curtain fell and Eastern Europe became an accessible market. At that time, Poland's manufacturing plant standards were primitive by Western standards, but the desire to become best in class was there. All we had to do was show them the standards and get out of their way. Polish plants have since had a history of world-class production.

In other emerging markets, quality wasn't as prominent an issue; securing the greatest profit from a plant was. In those cases, we found that cultural mindsets can be difficult to change. But even in some of those locations, we've seen progress. In China, for example, the government has made it quite clear that quality matters in pharmaceuticals. Policies are enforced. As a result, we achieve the same level of quality in our AstraZeneca China plants as we do anywhere else in the world.

AS THE SCIENTIFIC AND CLINICAL CAPABILITY OF BIOLOGICS EXPANDS, WE ARE MOVING INTO PRIMARY-CARE-SIZED MARKETS THAT DRIVE UP BULK PROTEIN DEMAND



WHAT IS NEEDED?



INDUSTRY SHIFTS

One driver of the dramatic change we're seeing is the shift from predominantly primary care to specialty products. What does this imply?

- Primary-care drugs usually have multiple assets in class; specialty-care drugs are often sole assets in class.
- Specialty-care drug shortages can have an immediate and significant effect on patient health.
- Primary-care products are relatively high volume, lower value. Specialty-care products are relatively low volume, higher value. The distribution network size and risk profile are different.
- Primary-care products are more commonly mature products; their supply chain focuses on the balance of cost vs. resilience.
- Specialty-care products are newer, with unpredictable demand curves. These supply chains focus on resiliency and agility, especially in launch and early market years.

Statins are a good example of a primary-care product. There are half a dozen major brand-name products and multiple generic versions. If one company were to have a problem producing its statin, a physician could write a prescription for another with little or no effect on patient health. Risk management in this market can—and should be—different from risk management for a specialty-care market.

Specialty-care products target small, narrowly defined patient populations with severe, often life-threatening diseases. Approved products are often sole asset in class—meaning no other treatment option is available—and their complex risk/benefit profiles require deep scientific, clinical, and business expertise. Effects on patient health in the event of a supply shortage are often unavoidable, immediate, and potentially severe.

A specialty product supply chain must be managed differently. AstraZeneca's Synagis,* for example, has a much smaller patient population than a typical primary-care product and is a sole asset in its class. It's also a seasonal product that must be available when needed. If that market is shorted, you can calculate the potential morbidity and mortality with almost mathematical certainty. That is not the kind of math that I personally ever want to have to do.

As a result, these types of products must also be managed with a different risk model than typical primary-care products. We operate this supply chain with as close to minimal risk as possible. We maintain a minimum of one season's worth of inventory, and dual-source production at every step, both internally and with a CMO that we've relied on for over 15 years. This same risk profile can apply to immuno-oncology drugs, which are sole assets in class for certain indications that have patient survival profiles measured in months. If one of these drugs experiences a supply shortage, there is no time to rebuild inventory before the shortage affects patient health.

The supply chain for a new product introduction (NPI) must be more agile and flexible than that of a mature product, since potential demand is uncertain and approval times can accelerate dramatically. NPIs are more difficult to outsource because of these uncertainties. The greatest risk they present to industry is the potential inability to supply enough drug quickly. The result of not supplying sufficient product upon launch could be devastating and would almost certainly affect patient health. These problems will be exacerbated as biologics move into primary-care-sized markets for certain indications (e.g., first-line oncology, Alzheimer's disease).

MARKETPLACE DISRUPTION

We now have the tools in hand to make the transition to specialty products. The issue is to understand how to manage the supply chain for novel biologic products in general and specialty-care products specifically, and recognize the differences between them. That is disruptive, because companies have structured their supply chains to work very efficiently in one traditional marketplace. Now they have to be good in two very different marketplaces.

It will be disruptive because after spending the past 15 years outsourcing almost all API production we now must decide whether that is appropriate for those portions of our network focused upon NPIs. Our executive committees and boards, which have many other demands for investment, including pipeline development, will have to analyze the costs associated with these changes.

* A vaccine used to prevent respiratory syncytial virus infections, especially in premature infants

WHICH PLANT WOULD YOU BUILD FOR 10,000 KG/YEAR OUTPUT?

Drivers are frequently large protein demand and very low cost of goods manufactured, high value put focus on reliability of delivery

	Option 1	Option 2	Option 3	Option 4	Option 5	Option 6
	Batch	Batch with continuous	N-1 with batch	N-1 with continuous	Perfusion with batch	Perfusion with continuous
Upstream mode	Batch	Batch	N-1 perfusion	N-1 perfusion	Continuous	Continuous
Downstream mode	Batch	Continuous	Batch	Continuous	Batch	Continuous
Base titer (g/L) vvd	8	8	10	10	0.95/1.5	0.95/1.5
Scale	12.5 kL SS	12.5 kL SS	12.5 kL SS	12.5 kL SS	2 kL SUB	2 kL SUB

It will be disruptive for firms that are being pressured to manage inventory. Having an additional $1 billion tied up in inventory is the same, in economic terms, as building a new plant for that amount. I can envision models that could double a company's current inventory, which represents a huge outflow of cash. More than $13 billion is currently dedicated to new biotechnology facilities, in planning or in flight, that will be required to support NPI production. Companies are also plowing a tremendous amount of cash back into R&D.

The transition will be disruptive if we decide that supply chain risks mean that certain parts of our network can't be run at 85% utilization and need to run at 60% instead. In certain areas of our network this could take us back to the utilization rates of 15 years ago.

Speed to market will feel disruptive. We're building plants for products that are only in Phase I trials. We're accustomed to placing a purchase order for an API we'll need in 18–24 months. Now we need five to six years to plan for a product that doesn't even have an assigned product number.

DECISIONS, DECISIONS

It is common for CMOs to achieve mammalian cell culture titers in the range of 2.5–4.5 grams per liter (g/L). We can achieve titers of 6–8 g/L, and some R&D development products can reach 10 g/L. AstraZeneca developed small-scale biologics drug substance capacity specifically designed for high-titer, low-volume production where it's appropriate. This eliminates the need to run our large-scale facilities for inefficient short runs of multiple products.

Must a facility of the future mean bricks and stainless steel? Or can it mean doubling the throughput of assets you already have? The maxim "sweat the asset," drawn from other industries, is one we take seriously. What does this mean in real life?

Our Frederick, Maryland, facility is a typical 4 × 15,000-L large-scale mAb plant. In two years it has improved titers, cut cycle times, and reduced turnaround times to improve operating yield by 80%. The network essentially added a new plant without having to build one. And if you want a measure of what that achievement is worth in capital savings, a "Frederick"-type plant would cost on the order of $800 million to build and license.

What does that mean for planning new pipeline products? Let's assume, without getting into specifics, a key product demand of 3,500 kilograms at the bioreactor stage. At a titer of 2.5 g/L, a cycle time of 5.5 days, and a turnaround time of 3.0 days, that requires 168 lots or 3.0 "Fredericks." At a titer of 7.0 g/L, a cycle time of 3.75 days and a turnaround time of 1.0 days, that requires 60 lots, or 0.7 "Fredericks." By sweating your asset, you gain the equivalent of more than two new plants. To me, that is as much a "facility of the future" as new platform technology.

Accelerated regulatory approvals can be achieved in as little as three years, not the seven the industry has seen on average. We need to make decisions about a plant earlier than we traditionally would like to, but it still takes five to six years to build. As a result, we must anticipate volumes as well as the type of process platform that will be needed years ahead of any certainty regarding product approvals and demand.

We ask the R&D team to land new products on those existing platforms. As an example, we have limited perfusion capacity in our internal network. We ask that development avoid perfusion if possible, but there will be products for which there is no other option. Then we will have to respond, either via outsourced capacity or by modifying internal plants.

Another decision involves the adoption of single-use technology (SUT), whose key operating and capital cost advantage is that it replaces fixed stainless bioreactors (and other vessels) with disposable plastic-bag units that can be discarded post-use. We use SUT throughout our network, but not at the large-scale bioreactor stage. It is people-intensive, has different standard operating procedures, and may not be useful for all products. It is not simply interchangeable with fixed stainless steel. It is also available only up to 3,500-L scale, which narrows its potential use.

Deciding whether to use batch processing or continuous manufacturing (CM), another disruptive technology, depends on the type of drug being manufactured. In the small-molecule space, CM is the way to gain efficiency. For biologics, the situation is more challenging, because there is no definitive test that can determine final drug product efficacy. Guaranteeing that the manufacturing process is within the ranges and specifications used to make that product for clinical trials is currently our only measure of product efficacy. In other words, "the process is the product."

When a process deviation occurs, ring fencing those lots of product that might be affected is of critical interest. In a typical biologics batch process, we are dealing with multiple discrete lots, and can usually set the ring fence boundaries to limit the lots at risk—often to one lot. With continuous processing (oil refining is a classic example), what is the production boundary of the affected material? The ring fence? One day? One week? One month? We will solve this problem, but the challenges of converting to a continuous process are not limited to developing the manufacturing technology itself.

CONTROL NETWORKS

For blood fractionation, the control network is designed to keep blood sourced from patients with certain diseases out of the supply chain. Once we are certain that none of the blood or plasma came from a problematic source, then that pooled batch no longer needs to be tracked.

Personalized medicine, however, would benefit from having all parts of its supply chain under one roof—from the first extraction from the patient, to the lab where the drug is made, through the cold chain, and then to reinjecting the finished product into the same patient. In practice, this will be very difficult to do. For patient-specific products, managing this control network is the issue to be solved.

Personalized medicine facilities use many small bioreactors, each producing a separate patient-specific product. From a supply chain and a regulatory affairs perspective, this complexity, while necessary, is daunting. Everything that touches the product, every bioreactor it goes into, every test it undergoes in the process must be tagged with the patient's name and controlled to ensure that the final product goes back to the patient from whom the original serum was drawn. If we can't demonstrate, without fail, that nothing adverse happened anywhere in that chain, then the product will be rejected and cannot be administered. These patient-specific supply chains will also be very time sensitive.

MANAGING RISK AND COST

As we embrace the facility of the future, we must understand that we're managing risk—and it can be difficult to perceive hidden or consequential risk. We are not the automotive industry; our risk profile and tolerance are a lot different from General Motors's or Toyota's. It's surely a lot different from someone who manufactures sneakers.

Keeping track of interconnecting nodes in the supply chain is like playing nine-dimensional chess. We must imagine moving a piece to see how it will affect the movement of product many steps later. We must evaluate scenarios in which something unforeseen could affect other parts of the supply chain, then answer three questions:

- What is the risk that a failure will occur?
- What is the impact, the severity of the failure?
- Is the patient outcome acceptable?

If a hypothetical scenario has only a 1% risk of failure but the result would be catastrophic, then that risk must be examined in great detail. At the same time, we can't allow ourselves to be paralyzed by risk because we must ultimately produce the product.

DIVERSE SKILLS NEEDED

The thing I love about biologics is that technology touches every aspect of production. Regardless of your level of management, you are never out of touch with that technology. It is a mentally engaging business; solving these complex problems requires teams of all ages and levels of experience. We need people with broad intellectual curiosity, and we need plenty of them. With expansions in large-scale biologics drug substance facilities already underway, we estimate the industry will need as many as 30,000 highly skilled employees. More than two-thirds of these will have college degrees; 25%–35% of them will have advanced degrees and/or comparable years of experience.

These complexities will have a profound effect on the education of new employees. The learning curve isn't limited to the technology, but includes the molecular biology of cell culture in a bioreactor and the engineering of new equipment. Consider enterprise-wide cold chain systemic control, from plant to patient. This is a level of supply chain detail that has never been done on a global scale. Diverse disciplines are involved, including mechanical engineering, software programming, automation, controls, chemical engineering, and biochemical engineering, to name a few.

The need to design and operate the facilities of the future is limitless. So are the opportunities for innovation and discovery. ‹›

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HEAT RECOVERY REGULATIONS AND HVAC ENERGY CONSUMPTION

Jim Heemer, PE, CEM, CEA, LEED-AP, and Hugh Reynolds

Regulatory codes that require exhaust-air heat recovery on heating, ventilation, and air-conditioning (HVAC) systems have a significant impact on construction, maintenance, and energy costs. Ideally, they should reduce energy consumption and diminish a facility's carbon footprint. These are good intentions, but what if the regulations have the opposite effect?

This article compares the performance of standard systems and alternative approaches and shows that code-compliant air-handling systems can increase energy consumption.

BACKGROUND

This article was derived from the authors' experiences with three projects: two in Ireland that required compliance with European Union (EU) exhaust-heat-recovery regulations and one in Switzerland with nearly identical mandates.

The current EU exhaust-air energy-recovery requirement is outlined in the Ecodesign Directive 2009, Regulation 1253/2014,[1] which mandates exhaust-air-heat-recovery systems for air-handling units (AHUs) with 10% or more outdoor air (OA). Heat-recovery effectiveness (efficiency) specifications range from 68% to 73%, depending on heat-recovery type.

The regulation provides exceptions for a limited number of applications, such as:

- High occupant risk if fresh OA could be contaminated by toxic exhaust (e.g., explosive, toxic, corrosive, or flammable environments)
- Systems for emergency use only (smoke purge, etc.)
- Areas with high internal heat loads (such as electrical and computer rooms where heat recovery adds no benefit)

In Ireland, AHUs that serve pharmaceutical cleanrooms fall within the scope of the regulation because these spaces are designed to accommodate routine and frequent human occupancy. Mechanical utility spaces also fall within the regulation for the same reason.

Switzerland has its own standard: SIA 548 282/2.[2] Section 5.10.3 says that any AHU with more than 10% OA requires exhaust heat recovery that is 70% effective on sensible load. There is no option to avoid the requirement by using another means of heat recovery.

In the United States, the ASHRAE 90.1[3] standard provides the minimum requirements for energy-efficient design of most commercial buildings. The standard varies by climate zone and by version,* but typically requires exhaust-air heat recovery that is 50% effective for systems with 10% or more OA. Unlike the EU and Swiss regulations, the US standard also factors heat recovered from other sources to minimize exhaust heat recovery requirements.

Each regulation allows the designer to determine the type of heat recovery used to transfer heat between the exhaust air stream and the fresh outdoor airstream, such as:

- Enthalpy wheel—rotation transfers both heat and moisture between two side-by-side airstreams
- Heat pipe—a sealed pipe with refrigerant that transfers heat between side-by-side airstreams
- Air-to-air heat exchanger—typically a plate-and-frame heat exchanger that transfers heat between two side-by-side airstreams
- Run-around loop—a system that pumps heat-transfer fluid between two heat exchangers, one in the outdoor airstream and the other in the exhaust

Heat-recovery equipment, its associated ductwork, and the additional building volume required for side-by-side airstreams add considerable cost to facility design. While run-around loop systems need not be side by side, meeting the heat-transfer effectiveness dictated by US, EU, and Swiss regulations requires both outdoor and exhaust air coils with significant depth, with associated air-side coil pressure drop and fan energy.

The projects considered in this analysis use the lower-cost run-around loop; the end result, however, will be affected only by capital cost. The air-handling systems presented here are always in cooling mode at lower OA rates, so heat recovery is not beneficial, regardless of the type used.

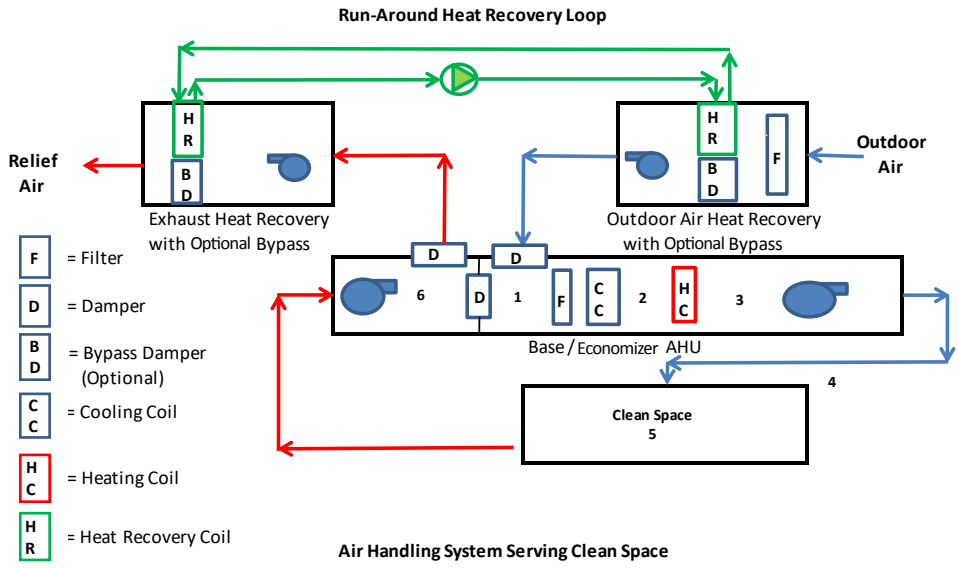
ANALYSIS

OA rates for pharmaceutical manufacturing clean and utility spaces typically range between 5% and 15%. Cleanroom air change rates are high and drive small temperature differentials between supply air and room set points. Mixing return air with OA at 5%–15% at design winter conditions is more likely to lead to a cooling load rather than a heating load, making heat recovery on these systems ineffective. Air-handling systems with low air-change rates—such as those for mechanical utility spaces—do not benefit from exhaust-air heat recovery either. These areas have equipment that emits enough heat to eliminate the need for heating throughout the year.

To provide a wide range of climate zones for this analysis, four European locations were considered: 1) Wynau, Switzerland, 2) Dublin, Ireland, 3) Helsinki, Finland, and 4) Athens, Greece. All were reviewed against the schematic shown in Figure 1.

* There is a new version every three years, and different cities require compliance to different versions.

FIGURE 1: SYSTEM CONFIGURATION



This paper reviews four system options, all of which use a fixed volume of supply air:

- Standard air-handling system with no heat recovery
- Run-around loop heat recovery with an air-side bypass, which reduces energy consumption by allowing the air to bypass heat-recovery equipment when not needed
- Run-around loop heat recovery without an air-side bypass
- Standard air-handling system with an air-side economizer for free cooling

Standard system

The standard system is based on a primary air handler that mixes required OA and return air and conditions the airstream to meet room loads. In summer, when outdoor humidity is high, the system operates in dehumidification mode, passing the airstream through a cooling coil to drop the temperature to condense moisture out of the airstream. When both OA temperature and humidity are high, the system overcools the airstream, then passes it through a reheat coil to maintain both humidity and temperature within specified limits. Reheating is usually not needed in cold weather.

Run-around loop

An air-handling system with a run-around loop has a glycol coil loop and two heat exchangers, one in the outdoor airstream and the other in the exhaust. The glycol is pumped to precool the outdoor airstream in summer, and to add heat in winter. As mentioned above, heating is normally needed only in summer to provide reheat after the cooling coil. Heat recovery only helps to reduce summer cooling load. To meet regulations, however, the system requires deep coils to provide the required heat-exchanger capacity. This increases fan and pump energy consumption, which offsets energy savings of preconditioning the OA.

Regulations also require the ability to turn off heat recovery. This can be done in two ways:

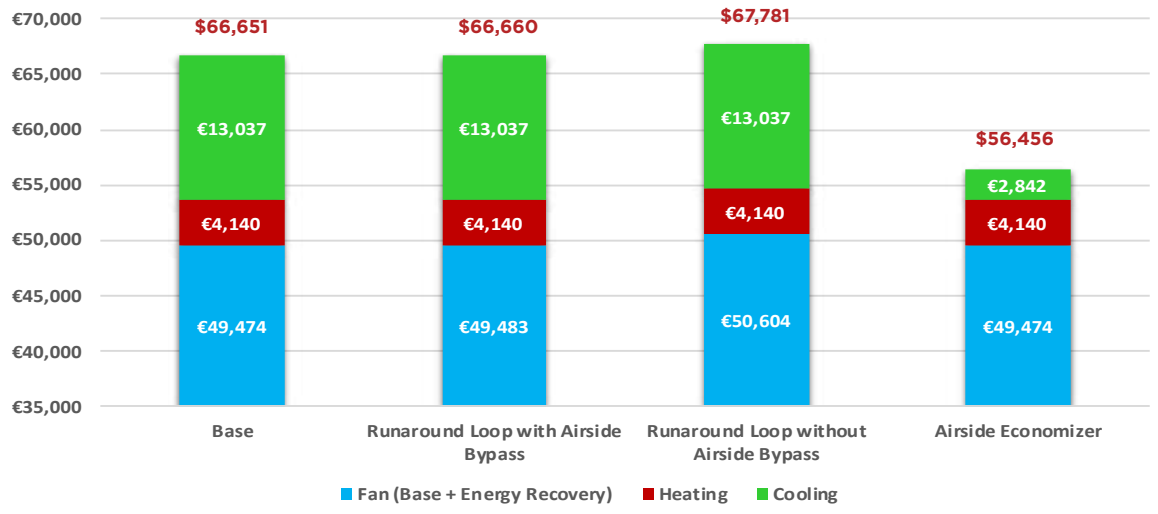
- Shutting down the pump: This incurs the lowest capital cost, but it increases fan energy consumption by requiring that the fan push air through the coils 24/7.
- Bypass around the coils: This has a higher capital cost and requires more space, but reduces fan energy consumption when the system is off and the air can bypass the heat-recovery coils.

TABLE A: DUBLIN—10% OA; TYPICAL TEMPERATURES AT VARIOUS POINTS WITHIN THE SYSTEM

Figure 1 Location	Temperatures ˚C		Description	
	Clean Space	Utility Space		
1	21.2	22.9	Summer: no heat recovery	
	19.2	19.9	winter: no heat recovery	
2	12.3	12.3	Summer: cooling	
	16.8	15.6	Winter: cooling	
3	16.8	13.4–15.6	Utility:	13.4°C summer
				15.6°C winter
4	18.2	14.5–16.5	Utility:	14.5°C summer
				16.5°C winter
5	20.0	22.0		
6	20.8	22.7		

Outdoor air: summer 25˚C; winter –5˚C

FIGURE 2: ANNUAL ENERGY COST, DUBLIN, 10% OA, ISO 8 SPACE



Air-side economizer

An air-side economizer is not a heat-recovery device: It is a heat-relief device. Since year-round cooling is normally required for low-percentage OA handling systems, an air-side economizer takes advantage of lower OA temperatures/energy levels when conditions allow. When the OA temperature is below the return air temperature and outdoor air humidity is low, the economizer modulates the outdoor and exhaust/relief airflows to meet the space set point temperature while minimizing the cooling load.

Since this is not heat-recovery equipment, however, it does not meet the heat-recovery requirements outlined by regulations. It is, however, a much better alternative to lower energy consumption.

For one project in Ireland, the owner wanted to install air-side economizers to reduce energy consumption. The project team learned, however, that if OA were to exceed 10% of total airflow, exhaust-heat recovery would be required. This would substantially increase costs, making the economizers an unattractive option.

CONFIGURATION

Air handler configurations with various components are shown in Figure 1. Table A indicates air temperatures at various locations within the system and variations by season for Dublin.

Heat recovery: Twelve row coils at 14 fins per inch were required to meet the 68% heat-recovery effectiveness mandated by the EU Ecodesign directive. A 30% propylene glycol system was modeled with a flow rate high enough to prevent frosting on the exhaust-heat-recovery coil. Both the power required to drive air through these deep coils and the high glycol flow rate increased energy consumption.

Cleanroom space: The suite was assumed to have a total volume of 2,303 cubic meters (m^3), with 25 air changes per hour (ACH) for an ISO 8 space. (This rate is from a previous project where the design was affected by these regulations. ISPE guidelines recommend a minimum of 20 ACH for a classified space.) The main suite is 2,200 m^3, with the remainder of the space split among three airlocks/gowning rooms. Total airflow for the system is 16,000 liters per second. Fan efficiencies were assumed at a high 75% to ensure that fan heat was low. The supply fan has a static pressure of 1,250 pascals (Pa), and the return fan has a static pressure of 747 Pa. Heat-recovery fans were sized for 528 Pa combined. Internal lighting loading was assumed at 10 watts (W) per square meter (m^2) and 5 W/m^2 for general loading. Internal loading was intentionally kept low to show the ineffectiveness of exhaust-air heat recovery, even in systems with low heat loads. The space was analyzed with no outside walls, which is typical for cleanroom locations.

Utility: The utility space was assumed to have the same area, volume, fan efficiencies, and internal heat loads as the clean space. Airflow was set to just meet system needs. Supply fan was analyzed with a static pressure of 1,000 Pa, and the return fan at 650 Pa. Heat-recovery fans were 528 Pa combined. The area served was assumed to be square, with 50% of each side along an outside wall, and with 20% of the wall comprised of windows. Insulation and window solar-heat-gain coefficients were assumed to be 80% of ASHRAE 90.1 version 2013 (3)–compliant values to ensure that the values were not understated. The air-change rate ranged from 5.3 to 6 ACH, depending on location.

Utility generation and cost: The base analysis assumes that hot water is heated with a natural-gas-fired boiler, with a steam-to-hot-water converter at 77% efficiency, which includes distribution losses on design cooling days, with adjustments made for variations in combustion air temperature throughout

TABLE B: SYSTEM-TO-SYSTEM CARBON FOOTPRINT COMPARISON

System	Athens, Greece		Dublin, Ireland		Helsinki, Finland		Wynau, Switzerland	
	ISO 8	Utility	ISO 8	Utility	ISO 8	Utility	ISO 8	Utility
	When OA% is below							
Base has a lower carbon footprint than the run-around loop with bypass	< 20%	< 51%	<20%	< 45%	< 12%	< 17%	< 17%	< 32%
Base has lower carbon footprint than run-around loop without bypass	< 46%	< 83%	< 27%	< 78%	< 19%	< 26%	< 24%	< 43%
Economizer has lower carbon footprint than run-around loop with bypass	< 43%	<70%	< 30%	< 68%	< 21%	<30%	< 26%	< 44%

ISO 8 space is based on 25 ACH; utility space airflow is based on load at 5.3–6 ACH, depending on location

the year. Energy cost includes both natural gas (to generate steam) and electricity to operate the pump. A more efficient condensing boiler could have been modeled, but it would be unusual for an owner to install condensing boilers to cover the heating load when they already have steam boilers. In the end, more efficient hot water heating would lead to even less value in exhaust-heat-recovery systems since less energy would be saved compared to the steam boiler system.

Chilled water was generated by an electricity-driven plant. Chilled water cost includes chiller, pump, tower fan power, and tower water makeup. Energy consumed to generate chilled water was based on an electric utility cost spreadsheet with a sliding coefficient of performance based on outdoor wet-bulb, load, and cost of tower water make-up. Energy rates were based on Eurostat energy statistics[4] for each country. The calculations were run using bin data spreadsheets. These were cross-checked against a Trane Trace700[5] modeling program and were found to have similar results.

Figure 2 shows the effect of various utility demands for Dublin at 10% OA for the ISO 8 space. All data below €35,000 is base unit supply and return fan power, and is equal for all options. The difference in fan energy cost is associated with heat recovery; heat recovery with no bypass had the highest fan power. The chart shows that the heating energy cost for all four options—reheating air after dehumidification in summer—are the same at €4,140.

The biggest difference in energy cost is the lower cooling load using an air-side economizer; this takes advantage of the cooler OA available most of the year. The difference is significant and is the main contributor to energy cost savings, which correlates closely with energy consumption and carbon footprint.

None of the four locations showed a winter heating load for either the clean space or utility space air-handling system at 10% OA. Recovering heat in the exhaust stream doesn't appear to be useful for reducing energy consumption due to internal heat loads and/or high air-change rates.

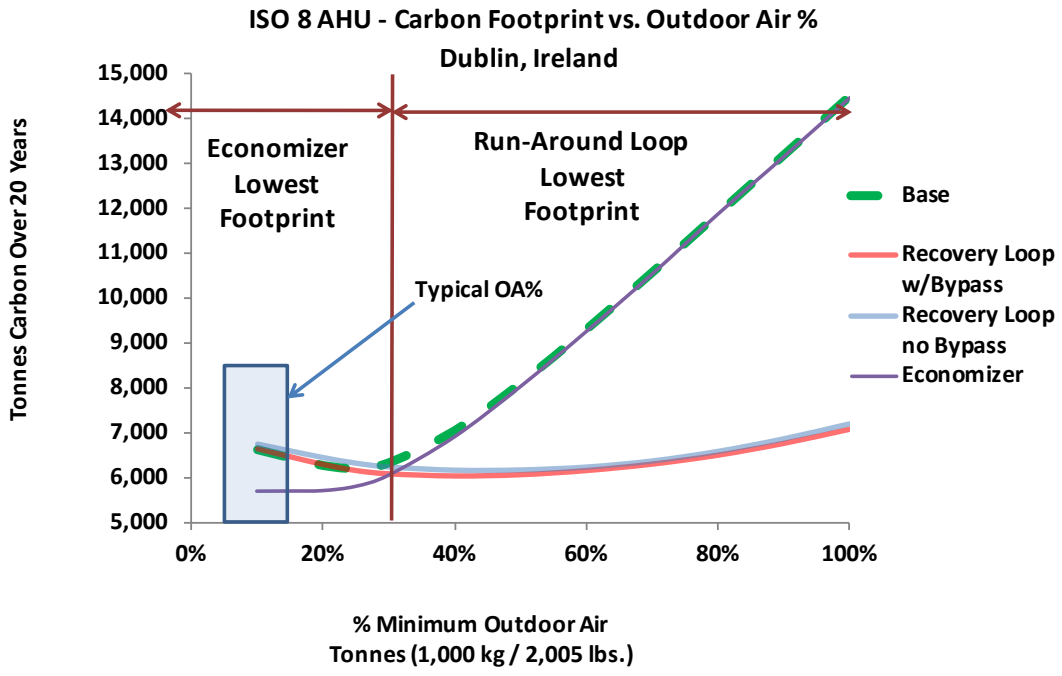
Figure 3 shows the carbon footprint over a 20-year life cycle for the Dublin ISO 8 clean space air-handling systems. Note that the economizer unit has the lowest carbon footprint when minimum OA is below 30%. In addition, there is little difference between the units with exhaust heat recovery and the base approach below 30% OA. This is attributed to internal heat generation within the facility so that mixed air does not require additional heat to satisfy space conditions.

RESULTS

The cost of operating with heat recovery—with or without air-side bypass—is higher than the base unit without heat recovery at lower OA rates. This is partly because heat recovery is not usually needed, and when heat recovery does operate in peak summer design periods, it provides minimal free cooling, since OA is at 25°C and exhaust air is at 20.8°C for clean space unit and 22.7°C for the utility unit. The cost to run the heat-recovery pump and fans is greater than the electricity and tower water savings from a slightly lower chilled-water load.

The largest savings are derived from the free cooling provided by the air-side economizer, a method not recognized by Swiss or EU energy code regulations. ASHRAE 90.1 requires an economizer for most climate zones in addition to heat recovery above 10% OA.

FIGURE 3: ISO 8 AHU, CARBON FOOTPRINT VS. OA%, DUBLIN



AN AIR-SIDE ECONOMIZER DOES NOT MEET THE HEAT-RECOVERY REQUIREMENTS OUTLINED BY REGULATIONS. IT IS, HOWEVER, A MUCH BETTER ALTERNATIVE TO LOWER ENERGY CONSUMPTION

Figure 4 shows the carbon footprint over a 20-year life cycle for systems serving a utility space. Note that the base and air-side economizer have a lower carbon footprint, even at a higher OA rate relative to the ISO 8 cleanroom analysis. This is due in large part to right-sizing the AHU to just meet load, minimizing the reheat impact and increasing free cooling by lowering air delivery temperatures to meet load at the lower airflow rate.

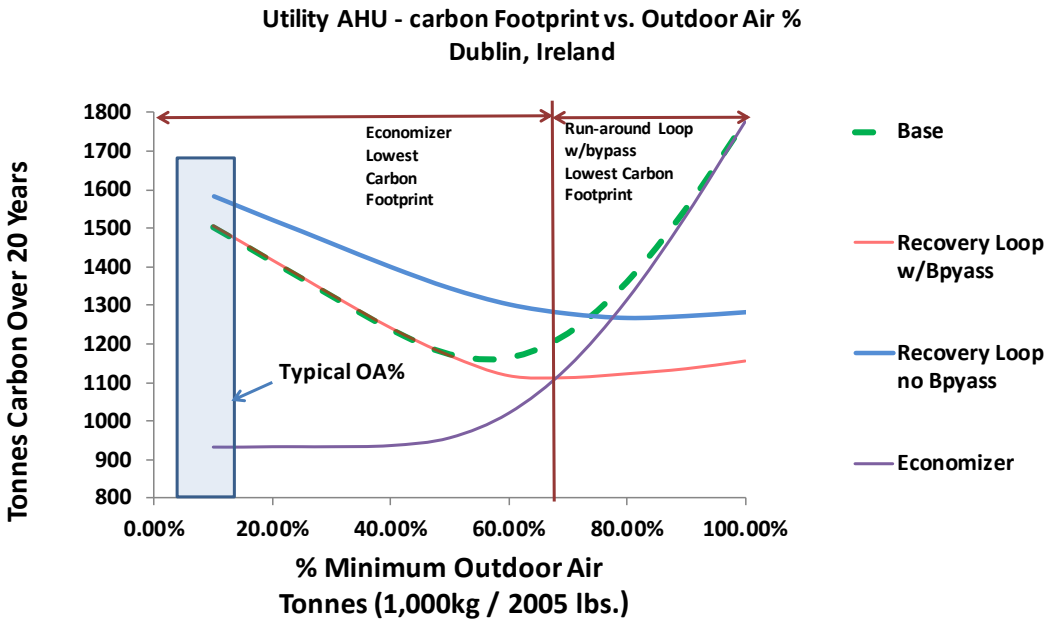
Table B lists the percent of OA below which the base and air-side economizer systems have a lower carbon footprint than the heat-recovery loop, with or without bypass. For the 25 ACH ISO 8 space considered, adding exhaust heat recovery increases energy consumption when OA is below 12%–20%, depending on location. For the utility space, adding exhaust heat recovery increases energy consumption when OA is below 17%–51%, depending on location.

If an air-side economizer is added to the base AHU, it reduces energy consumption when OA is below 21%–43% for the ISO 8 space and 30%–70% for the utility space, depending on location. This is a better value than the code-compliant unit with exhaust heat recovery and air-side bypass.

CONCLUSION

Current energy codes in both Europe and the US are intended to reduce energy consumption and reduce carbon footprint. Depending on the code considered, facilities are either required to have or find it hard to avoid installing exhaust-heat recovery on air-handling systems with 10% or more OA. For clean spaces and supporting mechanical utility spaces, however—those with moderate-to-high heat loads and/or high air-change rates and low OA percentages—the analysis presented here shows that the codes do

FIGURE 4: UTILITY AHU, CARBON FOOTPRINT VS. OA%, DUBLIN



not appear to reduce energy consumption and carbon footprint as intended.

The capital cost of installing code-compliant energy-recovery systems can be significant and includes:

- Additional building footprint and volume
- Increased engineering
- Added equipment
- More complex systems and controls
- Associated test and balance work

These systems also require additional care in design, installation, and commissioning, plus annual maintenance costs such as equipment maintenance, filter replacement, and instrumentation calibration. The added equipment and system complexity may increase the risk of potential system failure. These costs were not factored into the analysis.

As these codes are applied to many HVAC systems used in the pharmaceutical industry, they drive higher energy consumption and greater carbon footprint than would be necessary if an air-side economizer were recognized as an alternative energy-conservation measure for low-to-moderate OA rates, as identified in Table B.

EU regulation 1253/2014 will be reviewed in 2019, and ASHRAE 90.1 comes up for review every three years. These reviews may provide opportunities for the pharmaceutical and other high-tech industries to influence requirements and interpretation of these documents by gathering additional data and ensuring that regulations provide the lower energy consumption and carbon footprint intended. ‹›

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LAPSES IN GLOBAL GMP COMPLIANCE AND ENFORCEMENT

Impact on FPPs

Sia Chong Hock, Loo Shang Jun, and Chan Lai Wah

Due to space constraints, the authors are unable to discuss all topics or regulatory bodies. This review highlights areas of increasing concern.

The quality of finished pharmaceutical products (FPPs) plays a critical role in their safety profiles and therapeutic efficacy. Globalized trade and pharmaceutical company mergers are internationalizing production, and national regulations are disrupted by these developments. For this reason, major pharmaceutical exporters have adopted similar good manufacturing practice (GMP) standards. Quality defects may arise, however, due to lapses in GMP compliance by manufacturers and less-than-effective inspections by regulatory authorities.

These issues could be alleviated within the industry by implementing quality by design (QbD), improving data integrity management, and reducing pharmaceutical manufacturing errors by adding mistake-proofing controls. Where necessary, regulatory authorities should conduct unannounced inspections and increase the robustness of their processes.

This article reviews and analyzes the current national/international GMP regulatory framework, including standards from international organizations such as the Pharmaceutical Inspection Cooperation Scheme (PIC/S), World Health Organization (WHO), and Association of Southeast Asian Nations (ASEAN).

GMP REGULATORY FRAMEWORK

Manufacturing and quality control (QC) operations in the pharmaceutical industry are controlled via a GMP framework determined by regulatory authorities (RAs) and international organizations (IOs). (See the sidebar on pages 58–59.)

Most RAs and IOs have a basic GMP standard for FPPs. This standard is complemented by annexes, appendices, and/or supplementary guidelines for specific categories of products and dosage forms such as active pharmaceutical ingredients (APIs), biologicals and blood products, and related manufacturing activities that include sampling, process validation, and computerized systems validation. The GMP regulatory framework adopted by most IOs and RAs, including their main GMP protocols and supplementary guidelines, are essentially similar.

PIC/S is a major player in the international harmonization of GMP standards. As of 1 August 2016, it comprises 49 RAs, called "participating authorities," including the US Food and Drug Administration (FDA), UK Medicines and Healthcare Products Regulatory Agency (MHRA), Australia's Therapeutic Goods Administration, and Health Canada.* Participating authority GMP standards are harmonized to the PIC/S framework, including the PIC/S GMP guide for medicinal products. Most countries in the world's top 10 pharmaceutical exporters and importers have RAs that are PIC/S members (Table A and Figure 1). In January 2018, the RAs of Mexico, Turkey, and Iran were added to the PIC/S roster, bringing the total to 52.

Differences in GMP standards

Table B compares GMP standards for sterile and nonsterile FPPs among major RAs and IOs. While many key GMP components (left-hand column) are similar, the most significant difference is the pharmacopoeial reference standard used. Specifications and test limits established during production and QC may also vary. In addition, all jurisdictions except India's Central Drugs Standard Control Organization (CDSCO) recommend integrating quality risk management (QRM) into the existing GMP framework. Harmonization of these standards helps reduce inspection duplication and improve cost savings. It also facilitates access to the international market.

GMP IMPLEMENTATION

GMP standards represent the minimum compliance necessary for a manufacturer to obtain marketing authorization from the RA. Although most GMP regulatory framework and standards are adequate, issues with manufacturing processes, product quality, and safety continue to occur worldwide.[22–23] These incidents are due primarily to lapses in GMP compliance by manufacturers and inadequate GMP enforcement by RAs; they have produced nonconforming FPPs, recall operations, hospitalizations, and patient deaths.

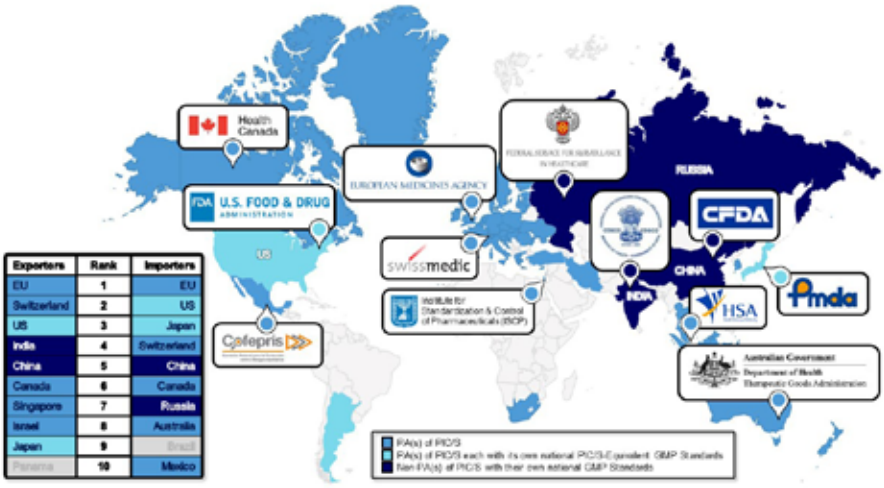
While different manufacturers can employ different control mechanisms, experience shows that some manufacturing and QC processes are not sufficient to ensure production of good quality medicines.

Data integrity

Data integrity is a global problem. It refers to the completeness, consistency, and accuracy of data throughout the data life cycle. Data must not be im-

* The European Medicines Agency (EMA) is an associated partner organization of PIC/S, not a participating authority. EMA works closely with the RAs of EU member states and the European Economic Area (EEA).[21] RAs of EU member states and the EEA are PIC/S participating authorities.

FIGURE 1



Exporters	Rank	Importers
EU	1	EU
Switzerland	2	US
US	3	Japan
India	4	Switzerland
China	5	China
Canada	6	Canada
Singapore	7	Russia
Israel	8	Australia
Japan	9	Brazil
Panama	10	Mexico

Membership status reflects that of PIC/S. Several PIC/S Participating Authorities—including Argentina, Japan, and the United States—use GMP guides that are different from (but equivalent to) the PIC/S GMP Guide.

properly modified; it should be attributable, legible, contemporaneous (i.e., contemporaneously recorded), original, and accurate, as well as complete, consistent, enduring, and available (ALCOA+).[24] Data documentation is a fundamental GMP requirement.

In 2013, a subsidiary of Indian generic pharmaceutical manufacturer Ranbaxy Laboratories Limited was fined $500 million for falsified stability testing data and incomplete QC test records at its manufacturing facilities—the largest financial penalty paid by a generic pharmaceutical company.[25]

In that same year, Front Range Laboratories, a third-party testing laboratory for more than 100 pharmacies, was cited by the US FDA for improper use of analytical methods, sending inaccurate results to five pharmacies. Two other unnamed third-party laboratories in the United States were also found to have reported inaccurate test results in the same year.[28] Massive recall operations for parenteral products were conducted due to the lack of sterility assurance.

More recently, in 2015, US FDA inspectors cited Hebei Yuxing Bio-Engineering in China for incomplete laboratory test records, undocumented experimental results, and unexplained deletion of raw chromatographic data.[26] An FDA review indicated that in the first 10 months of 2015, the agency issued 16 warning letters, 12 of which involved data integrity, up from 10 in 2014 and six in 2013.[27]

The MHRA has also identified data integrity issues as a key reason for the rise of major and critical deficiencies. In "GMP Inspection Deficiencies 2013," MHRA noted that "of 630 GMP inspections carried out in 2013, 216 resulted in major or critical deficiencies."[29] In 2015, these deficiencies rose further, to 339.[51] The WHO has also taken a leading role in promoting data integrity.

Contract manufacturing

Driven by cost savings, technical expertise, and increased efficiency, FPP contract manufacturing for developed markets has grown significantly. Beneath the promising outlook, however, lie considerable GMP concerns.

Since 2013, Wockhardt, a contract manufacturing organization (CMO) in India, has been under regulatory pressure for data integrity violations and GMP deficiencies.[30] In 2013, the MHRA withdrew GMP certificates from two of its manufacturing sites in India and recalled 45 types of oral preparations. More recently, the FDA warned Emcure, another large CMO in India, about its significant violations of GMP regulations. This affected many of the large multinational pharmaceutical manufacturers that utilize the services of these CMOs; many FPPs were recalled as a result.[31]

Deviations

Deviations such as out-of-specification can occur during manufacturing. Thorough and timely investigations are critically important in formulating corrective and preventive actions. A review by the MHRA from 2009 to 2013, however, revealed that the failure to investigate deviations remained the most common deficiency.[29]

POLITICAL AND LEGAL LANDSCAPE

Manpower, resources, and infrastructure

Insufficient manpower is a root cause for GMP compliance lapses. It often forces workers to compromise on product quality to meet production targets and can lead to inaccurate or incomplete documentation and other data integrity issues.[32] Well-trained and -qualified employees, conversely, are an

TABLE A: TOP 10 EXPORTERS/IMPORTERS OF PHARMACEUTICALS AND THEIR SHARE OF WORLD EXPORTS/IMPORTS[5]

	$ Value, billions	Exports, %
European Union	340	63.9
Switzerland	65	12.2
United States	52	9.8
India	14	2.6
China	14	2.6
Canada	8	1.4
Singapore	8	1.4
Israel	7	1.2
Japan	4	0.7
Panama	4	0.7
Total	**516**	**96.5**

	$ Value, billions	Imports, %
European Union	260	47.5
United States	90	16.4
Japan	24	4.4
Switzerland	23	4.2
China	20	3.7
Canada	13	2.3
Russia	9	1.7
Australia	8	1.4
Brazil	7	1.3
Mexico	5	1.0
Total	**459**	**83.9**

essential component of GMP, ensuring apt performance of assigned tasks. In the China Food and Drug Administration (CFDA) Annual Report of Drug Inspection 2015, staff training was cited as the most frequent deficiency.[33]

In India, a report revealed that the Indian pharmaceutical industry will face a shortage of workers until 2022, due to inadequate education and training for specific job roles. This also deters graduates from choosing careers in this sector.[34] Collectively, these factors propagate a chain reaction.

Large countries like India have regulators for individual states and a central regulator in the capital. This can create bureaucratic issues, especially since the central regulator CDSCO and the state RAs have different functions.

In the United States, both the FDA and state authorities face constraints in enforcing GMP compliance. Because compounded medicines do not have to be approved by the FDA, for example, the agency faced significant challenges in stopping three compounding pharmacies (ApothéCure, NuVision Pharmacy, and Downing Labs) that repeatedly refused inspections and recall operations.[35] Despite multiple warnings, they continued to violate GMP regulations and sell potentially unsafe medicines until 2015.

In many jurisdictions, RAs have insufficient capacity to inspect and monitor the ever-increasing number of manufacturers. China has about 2,700 GMP inspectors, and a majority of them are overloaded with work.[36]

A 2009–2010 study by the Mashelkar Committee revealed similar findings in India. In 2014, the country's Drug Controller General revealed that its 1,500 drug inspectors represented only 7.5% of the total number required.[37] Indian state authorities must also contend with inadequate infrastructure, resources, and assistance from CDSCO, impeding coordination between state authorities and implementation of legislation.[38]

An ineffective QMS, in contrast, can compromise the organization's inspection capacity.[36] In addition to a manpower crunch, lax management has hindered the establishment of a high-caliber inspection team in the CFDA. The "China Regulatory and Market Access Pharmaceutical Report," published in 2014, noted that only 1,800 of the country's inspectors were under 50 years old, and only about 800 (28.5%) had participated in more than one GMP inspection in the past 10 years. The 2015 CFDA Annual Report of Drug Inspection revealed that fewer than half the number of pharmaceutical manufacturers were inspected for GMP certification in 2015 (221) than in 2014 (584).[33]

The US FDA has also faced challenges in implementing QMS. One case in 2012 involved a multistate outbreak of fungal meningitis, which killed 64 people. Although there were clear signs indicating that the New England Compounding Center had violated GMP regulations, the US FDA and the Massachusetts Board of Pharmacy failed to take definitive action against the pharmacy. The US FDA later attempted to address the problem by allowing pharmacies to make a limited 30-day supply of medicines in advance of a prescription.[39] This new arrangement, however, presented stability issues due to chemical degradation and microbial proliferation.

HARMONIZATION AND COLLABORATION

Expansion in international trade presents a growing need to develop appropriate, consistent, and globally applicable quality standards for medicines within the existing regulatory framework. International efforts have been devoted to harmonizing regulatory requirements, GMP inspection procedures, and pharmacopoeial standards.

QMS

A comprehensively designed and effectively implemented quality management system (QMS) is key to regulatory capacity. QMS encompasses everything necessary to implement an organization's quality policy and meet quality objectives.[1]

PIC/S

PIC/S aims to harmonize inspection procedures worldwide by developing common GMP standards and providing inspector training. It also works to facilitate cooperation and networking between RAs through joint visit

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programs, guided inspections, and expert circles.[†40] PIC/S also facilitates legally binding arrangements, such as the mutual recognition agreement (MRA) between Singapore and Australia on medicinal product GMP inspection, and the ASEAN sectoral MRA on GMP inspection for manufacturers of medicinal products. In addition, PIC/S collaborates with professional associations in joint training events and has signed cooperation agreements with European and international organizations.[21]

The influence of PIC/S is also growing in the Asia-Pacific region. Out of the nine RAs that became PIC/S participating authorities over the past four years, seven of them were from this region. At least six other Asia-Pacific RAs, including China and India, have also expressed an interest in joining PIC/S.[41]

ICMRA

According to the International Coalition of Medicines Regulatory Authorities (ICMRA) website, ICMRA is "a voluntary, executive level, strategic coordinating, advocacy, and leadership entity of regulatory authorities." The coalition was established in May 2012 "to address current and emerging human medicine regulatory and safety challenges globally, strategically, and in an ongoing transparent, authoritative and institutional manner." The ECA Foundation notes that the ICMRA "aims to provide direction for areas and activities common to many authorities' missions, identify areas for potential synergies, and wherever possible, leverage on existing initiatives (e.g., PIC/S, ICH, APEC) and resources." Unlike PIC/S, ICMRA covers a broader scope that includes GMP.[42]

PDG

Manufacturers that supply products worldwide must confirm their FPPs meet pharmacopoeial specifications in different countries. Harmonizing these standards will simplify quality assurance (QA) processes and eliminate redundant testing. The Pharmacopeial Discussion Group (PDG) comprises representatives from the European, Japanese, and US Pharmacopeias.[43] It aims to harmonize pharmacopoeial standards, including pharmaceutical preparation monographs and selected general chapters. Currently, the PDG meets twice a year and holds monthly status and technical teleconferences to advance its work.[43]

The WHO has been an invited observer of the PDG since 2001.[43] Various general test methods harmonized by the PDG have since been adapted to the WHO's International Pharmacopoeia, and are included in the sixth edition, published in 2016.

PQM

Established in 2009, the Promoting Quality of Medicines (PQM) program helps manufacturers meet economic and technical challenges in producing FPPs that meet WHO's Prequalification of Medicines Program GMP standards. The PQM is funded by the United States Agency for International Development (USAID) and implemented by the US Pharmacopeia. To date, USP-USAID collaborative efforts have benefited communities in more than 35 countries.[44]

The PQM also works with RAs to establish accredited QC-monitoring programs and enhance the capacity of various national quality control laboratories to meet international standards.[52] PQM also co-organizes trainings on GMP and QC test procedures with the WHO and RAs.[45]

PROPOSED SOLUTIONS

QbD

QbD builds quality into the product and manufacturing process.[46] It is a science- and risk-based approach to pharmaceutical development that begins with predefined objectives. This is unlike the traditional GMP framework, in which product quality is achieved predominantly by end product testing.

QbD enhances the manufacturer's ability to identify the root causes of manufacturing failures, reducing GMP deficiencies that arise out of failure to investigate anomalies. It also eases RAs' GMP enforcement efforts by refining regulatory-review criteria. This is crucial, especially when RAs have limited regulatory capacity, as fewer inspections are required.[46] Other techniques such as near-infrared and Raman spectroscopy can also be adopted for online measurement of critical quality attributes.

Resource and cost constraints, however, often present challenges to manufacturers and RAs. Emerging economies are challenged by lack of training and equipment cost. Western companies are automating production as the cost of labor rises, while emerging economies still rely on manual processing, which carries a greater risk of human failure.

Data integrity and mistake-proofing

ALCOA+ principles alone cannot eliminate data integrity issues. A holistic approach, involving both technical and human controls, is required to address these issues. Manufacturing personnel, manual processes, and the technologies involved must be improved.

People by nature are prone to variability in techniques and judgment. The great majority of reported defective medicinal products have resulted

—continued on page 62

[†] PIC/S expert circles facilitate discussions and information exchange among inspectors specialized in specific GMP subject areas. Expert circles meet regularly to develop draft guidance and recommendations, and offer training in their respective fields.

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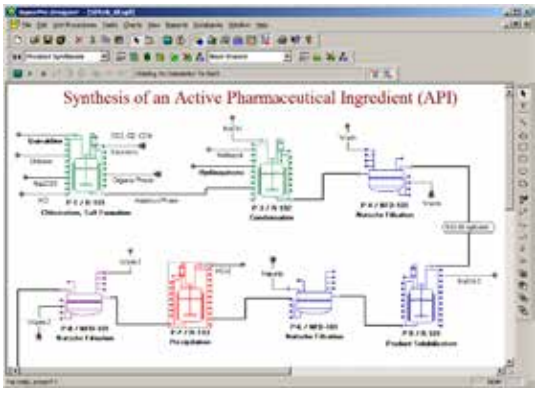

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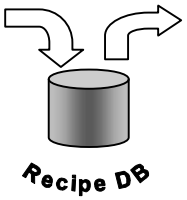

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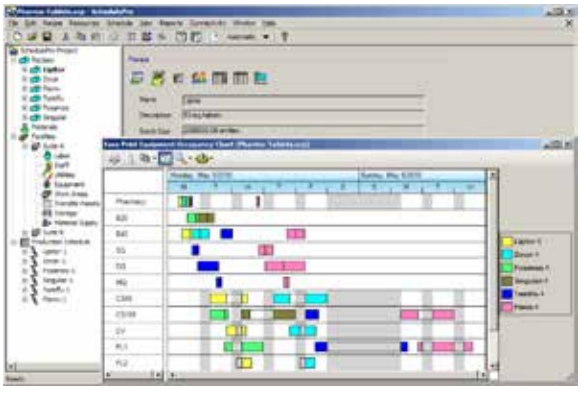

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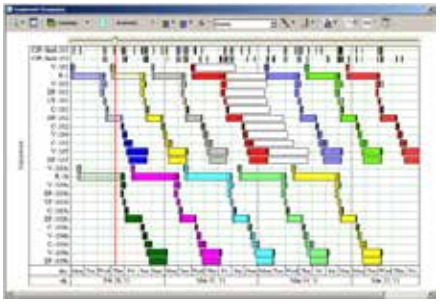

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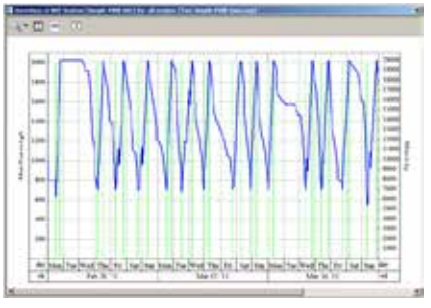

Managing inventories for input, intermediate, and output materials

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

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

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Global GMP Regulatory Framework for FPPs

International organizations

ASEAN

- Association of Southeast Asian Nations[10–12]
- Some member states conduct overseas inspections.
- A sectoral mutual recognition arrangement (MRA) on GMP Inspection for Manufacturers of Medicinal Products, signed in 2009, contains 19 articles on FPPs. Its scope currently excludes APIs, biologicals, radiopharmaceuticals, investigational medicinal products and traditional/herbal medicinal products.
- All member states must operate a PIC/S-equivalent GMP inspection framework; they must also recognize and accept the inspection reports and GMP certificates issued by ASEAN's four listed inspection services (LIS):
  - Singapore: Health Sciences Authority
  - Malaysia: National Pharmaceutical Regulatory Agency
  - Indonesia: National Agency of Drug and Food Control
  - Thailand: Food and Drug Administration
- To qualify for listing, the ASEAN GMP inspectorate must demonstrate equivalency to the PIC/S framework. Any ASEAN inspectorate that is a PIC/S member will be automatically accepted for listing without any further technical assessment.
- A joint sectoral committee (JSC) was established in 2012 to oversee MRA implementation and functioning. An ASEAN GMP inspectorate that intends to be an ASEAN LIS can submit an official application to the JSC.
- Future developments: Scope may be extended to include APIs and biologicals. ASEAN is collaborating with PIC/S, ISPE, and other stakeholders to improve its inspectorates and inspectors' competency.

PIC/s

- Pharmaceutical Inspection Co-operation Scheme[1, 6–8]
- Not all participating authorities conduct overseas inspections.
- An informal cooperative arrangement; not legally binding.
- Strives to facilitate mutual recognition of GMP inspection results among PAs through voluntary exchange of nonbinding information.
- Adopts a science-based quality risk management tool for planning frequency and scope of GMP inspection.
- Each participating authority undergoes periodic reassessment to ensure that its systems, procedures, and inspection system remain equivalent to the PIC/S framework.
- Current (13th) version of GMP guide was published in 2017. Part I covers GMP requirements for the manufacture of medicinal products in finished dosage forms, and has 20 annexes, which provide details on specific categories of products and areas of manufacturing activity. Part II covers GMP for APIs.

WHO

- World Health Organization[9]
- Conducts overseas inspections.
- GMP guide has a set of basic principles on main requirements for pharmaceutical products; other supplementary guidelines cover specific dosage forms and related aspects of manufacturing.
- Revised in 2014, the GMP guide functions as a standard to justify GMP status for the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Trade. It also serves as training material for inspectors in RAs, and for production, QA, and QC personnel in the industry. This general guide may be adapted to meet needs of various jurisdictions.
- Used primarily in developing countries, it is also embedded in GMP standards of developed countries with more detailed QA systems. It does not, however, cover safety aspects for personnel engaged in manufacturing or in environmental protection.

Regulatory Authorities

CDSCO

- Central Drugs Standard Control Organization: national regulatory authority of India[17–18]
- Conducts overseas inspections.
- Current GMP standard was published in 2005 by the Ministry of Health and Family Welfare of India. Part I covers GMP standards for premises and materials. It consists of a main document on general standards and six subsections on standards for APIs and specific FPPs. Part II covers GMP standards for plant and equipment.
- The Indian regulatory system is divided into central and state levels. At the national level, CDSCO is responsible for implementing standards for drugs, coordinating activities for state authorities, and providing expert advice to bring about uniformity in GMP enforcement. The state authorities issue licenses and GMP regulations.
- State authorities and CDSCO conduct joint inspections.
- All manufacturers must have a license and comply with quality control requirements.

CFDA

- China Food and Drug Administration: national regulatory authority of the People's Republic of China[14–16]
- Conducts overseas inspections.
- Current edition of GMP standards was published in 2010 by the China Ministry of Health.[14] Main document on basic GMP standards and eight annexes, covering GMP standards for sterile products, biologicals, blood products, APIs, traditional Chinese medicines, traditional Chinese herbs for decoction, medicinal oxygen, and radiopharmaceuticals.
- Annex for Validation and Verification and the Annex for Computerized System were published in 2015.
- Regulatory system is divided into three levels: national, provincial, and city. At the national level, the CFDA formulates regulations and inspects manufacturers of higher-risk pharmaceutical products. At the provincial and city levels, authorities enforce CFDA regulations and inspect manufacturers of lower-risk pharmaceutical products.
- All FPP manufacturers must undergo GMP inspection and certification before manufacturer authorization certificate and product license can be issued.
- Publicly available database of GMP-certified manufacturers includes the scope of CFDA inspections and manufacturers' history of GMP compliance.

SID & GP

- State Institute of Drugs and Good Practices: national regulatory authority of Russia[19–20]
- Conducts overseas inspections.
- Current GMP standard was published in 2013 by Russia's Ministry of Industry and Trade (MinPromTorg). It is divided into two parts with 18 appendices. Part I covers key requirements for production and quality control. Part II covers basic requirements for APIs. Appendices provide details on specific areas of manufacturing activity.
- Commissioned by MinPromTorg as the expert organization engaged in the license control of pharmaceutical manufacturers in Russia.
- Authorized to inspect foreign manufacturers of drug products outside of Russia beginning in 2016.
- Inspectors check for compliance with Russian GMP standard and issue certificates of manufacturers' compliance with GMP, enabling foreign manufacturers to supply their drug products to the Russian market.

US FDA

- US Food and Drug Administration: national regulatory authority of the United States[13]
- Conducts overseas inspections.
- Current GMP regulations:
  - Are promulgated by the US Code of Federal Regulations.
  - Emphasize that manufacturers are required to comply with the US FDA framework and regulations
  - Cover drugs, biological products, and medical devices.
  - Focus on operations monitoring and regulation of manufacturing processes and technologies. This enables quick corrective actions against faulty manufacturing processes to avoid production of defective FPPs.
  - Encourage manufacturers to adopt a scientific approach to GMP by emphasizing risk-control point analysis and decision-making.

TABLE B: GMP STANDARDS FOR FPPS, EXCLUDING BIOLOGICALS, BLOOD PRODUCTS, AND RADIOPHARMACEUTICALS

	PIC/S	WHO	US FDA	CFDA	CDSCO	SID and GP
Personnel						
Qualifications	Similar					
Experience	Similar					
Training	Similar					
Premises						
Pest control	Similar					
Clean air/room classification*	Grades A–D	Grades A–D	Classes 100–100,000 and ISO Grades 5–8	Grades A–D	Grades A–D	Grades A–D
Microbial monitoring limits*	Grades A–D	Grades A–D	Classes 100–100 000 and ISO Grades 5–8	Grades A–D	Grades A–D	Grades A–D
Air pressure differential*	10–15 Pascal	10–15 Pascal	10–15 Pascal	Not specified	≥ 15 Pascal	10–15 Pascal
Monitoring frequency						
Particulate count*	Routinely	Routinely	Every production shift	Daily	Every 6 months	Routinely
Air change rate*	Not specified	Not specified	Every production shift	Not specified	Every 6 months	Not specified
Air pressure differential*	Not specified	Not specified	Every production shift	Not specified	Daily	Routinely
Temperature and humidity*	Based on product and nature of operations	Based on product and nature of operations	Every production shift	Based on product and nature of operations	Daily	Based on product and nature of operations
HEPA filter integrity testing*	Not specified	Every 6–12 months	Twice a year	Routinely; frequency not specified	Every year	Routinely; frequency not specified
Production						
Qualification and validation	Similar					
Quality control						
Reference/retention samples	Similar					
Stability testing	Similar					
Pharmacopeia standards	European or other pharmacopoeias	International Pharmacopoeia	United States Pharmacopeia	Chinese Pharmacopoeia	Indian Pharmaco-poeia	Russian Federation State Pharmacopoeia
Other						
Self-inspection	Similar					
Quality risk management	Similar				QRM con-cepts not mentioned	Similar
Documentation and data integrity	Similar					

**GMP components or subcomponents applicable only to sterile products manufacture.*

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from human error, not technology failures. Lack of awareness among employees and ineffective training often result in employees who fail to understand the relevance of data integrity. As systems and processes are not inherently compliant, people must create compliance using tools, systems, and technology. "Human factors engineering" is the science of designing systems to fit human capabilities and limitations in perception, cognition, and physical performance.[48]

Technical controls, such as tamper-proof equipment and validated computerized information technology (IT) systems, strengthen data integrity. Because they are repeatable, they can be designed, tested, operated, and maintained so that data integrity is ensured and well-documented. Without qualified data stewards, however, IT systems alone cannot ensure data integrity either.[47]

"Poka yoke,"[i] or mistake-proofing, refers to techniques that make it impossible to make mistakes, helping people and processes work right the first time. It substantially improves quality by either preventing defects at the start or eliminating defects in the process as early as possible.[49] Although poka yoke is seldom employed in pharmaceutical manufacturing, it could possibly eliminate both human and mechanical errors, thereby reducing GMP deficiencies. Poka yoke techniques should merit more attention.

Leadership and organizational cultures also have a positive effect on data integrity. Administrative safeguards like policies, procedures, and management processes should also be focused on preserving data integrity.[47] Manufacturers should participate in data integrity training and review processes to stay abreast of ever-modernizing technologies.

Inspections

PIC/S leads the world in the harmonization and maintenance of GMP inspection and quality system standards. Each of its participating authorities is also reassessed periodically to ensure that its procedures and inspection systems conform to the PIC/S framework. Membership is growing, especially in ASEAN member nations and other Asian countries. This positive development may help increase the overall competence of inspectors and improve the robustness of regulatory inspection systems globally.

During routine announced inspections, however, it is always possible that manufacturers may exhibit the Hawthorne effect: i.e., alter their behavior due to their awareness of being observed.[50] Unannounced inspections have the advantage of catching manufacturers off guard, allowing inspectors to witness operations as they are on a daily basis.

In some countries, GMP standards may not be legally binding. Despite stipulated policy guidelines, for example, many RAs are unable to conduct unannounced inspections at foreign sites as they must verify the availability of appropriate personnel in the plant beforehand. Inspectors may even be denied access for inspection, and especially so at foreign sites.

CONCLUSION

Even with generally equivalent and adequate GMP standards for FPPs across major jurisdictions, issues with manufacturing processes, product quality, and safety are still prevalent worldwide due to lapses in GMP compliance by manufacturers and lapses in GMP enforcement by RAs. These lapses, such as failure to investigate deviations and data integrity deficiencies, are further aggravated by the growth of global FPP contract manufacturing.

Although various measures have been adopted to cope with these lapses, stricter measures must be implemented. It is pertinent to note, however, that more stringent regulations may add cost and other burdens to manufacturers and regulators who already face resource constraints.

As the FPP market continues to expand, RA enforcement of GMP compliance by manufacturers will become more challenging. Despite the abundance of cross-cutting supranational and national regulatory structures and legal systems, regulators have been making conscientious efforts to harmonize regulatory requirements. As pharmaceutical manufacturing evolves from an art to a science- and engineering-based activity, manufacturers and RAs should harness their knowledge to improve GMP compliance and regulatory frameworks.

Although the manufacturer-regulator relationship may sometimes be contentious, it is crucial for both parties to work together to ensure quality FPPs worldwide for the ultimate benefit of consumers. ISPE provides a forum in which manufacturers and regulators can work together to develop new technologies and ways of working to benefit consumers.

[i] From the Japanese *yokeru,* "to avoid," and *poka*, "inadvertent errors"

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EVALUATING IN-LINE VOLUME REDUCTION DURING mAb PRODUCTION

Ole Elvang Jensen and Alexandra Guerra, PhD

In-line concentration solves problems found in mAb production, including insufficient storage capacity and process tank volumes, extended processing times, and large hold-up loop volumes for ultrafiltration concentration. It optimizes the ion-exchange step following capture, reduces costs and processing times for virus filtration and polishing, and significantly improves the ultrafiltration/diafiltration yield, all without large hardware investments.

Biopharmaceutical manufacturers are under pressure to reduce costs and increase the robustness and flexibility of their manufacturing operations. Optimization of downstream purification steps is required to achieve these goals. In-line concentration of dilute solutions prior to various downstream unit operations can result in both cost and time efficiencies.

The use of single-pass tangential flow filtration (SPTFF) technology to cope with commonly found monoclonal antibody (mAb) production challenges has been previously reported.[1–3] SPTFF systems employ flow ratio control, which insures a fixed ratio between feed and retentate flows.

This study investigated the performance and scale-up possibilities for in-line concentration on a mAb production platform using a patented SPTFF technology approach designed by Pall Life Sciences for a simplified control scheme with a fixed retentate resistor (Figure 1). The study was built on behalf of Novo Nordisk.

MATERIALS AND METHODS

Setup

This study was conducted using an in-line concentration module with a 30-kilodalton (kDa) Delta-regenerated cellulose membrane. This holder-less preassembled device, based on new SPTFF technology, is equipped with a built-in fixed retentate resistor that supplies a set backpressure to the retentate side, achieving a target volumetric concentration factor (VCF) of 2x–5x or higher.[4] All that is needed to operate the system is a feed-pressure source (i.e., pump or pressurized vessel) and a feed pressure-measurement device. The staged flow path is a series-and-parallel arrangement of T-series cassettes in a 3-2-1-1 configuration, referred to as "four in series."

The effective total area of the membrane was 0.065 square meters (m^2). The system was equipped with a Quattroflow 150S pump and three Pendotech PrePS-N-000 pressure sensors.

Methods

Three experiments were performed:

- Volume reduction after the capture column (P1)
- Volume reduction before virus filtration (P2)
- Final ultrafiltration (UF) concentration after ultrafiltration/diafiltration (UF/DF) (P3)

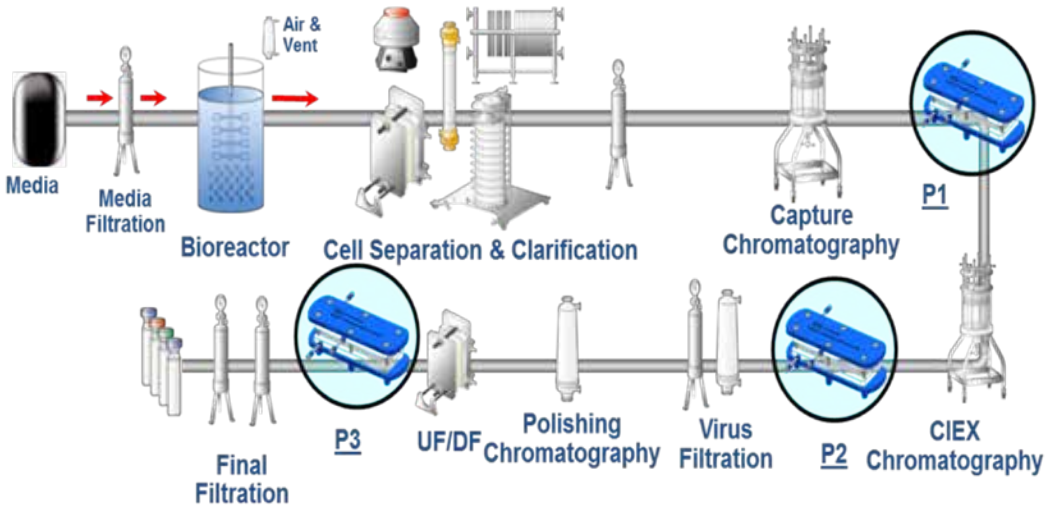
The same module was used for each test after cleaning with 0.3 M sodium hydroxide (NaOH) at room temperature. Normalized water permeability was measured before and after each session; observed data indicated that no significant fouling occurred and that the cleaning was effective. The module was equilibrated with respective buffer before each test.

To determine the capability of in-line concentration for each process step, feed-flow excursions at different feed concentrations were conducted while monitoring the VCF, retentate and permeate flows, and mAb concentrations. During these tests, the system was placed in total recirculation mode for the product. Feed flow was adjusted using the pump speed controller. The permeate, retentate, and feed flows were assessed using a scale with a stopwatch. A relative density of 1 gram per milliliter (g/mL) was applied to convert the gravimetric data to volume values. The feed and retentate concentrations were measured using a NanoDrop 2000c full-spectrum ultraviolet-visible (UV-Vis) spectrophotometer and the appropriate assay. Full single-pass operation was also evaluated for the volume reduction before the virus filtration (P2) and the final concentration after UF/DF (P3).

In addition, the effect of sample conductivity on concentration performance was investigated for volume reduction after the capture column (P1). It was expected that a higher salt concentration would increase the protein solubility and thus enhance ultrafiltration (UF) mass transfer, leading to improved ultrafiltration performance.

The pool sample from the capture step was mixed with salt (NaCl) to obtain a final concentration of 150 millimolar (mM) to increase the conductivity to 20.0 milli-Siemens per centimeter (mS/cm), and the pool sample from the cation exchange was diafiltrated with water for injection (WFI) until a conductivity of 1.9 mS/cm was achieved.

FIGURE 1: SCHEMATIC OF A MAB PRODUCTION PROCESS. THE CAPTURE STEP USES AFFINITY CHROMATOGRAPHY; THE POLISHING CHROMATOGRAPHY IS AN ION-EXCHANGE CHROMATOGRAPHY. THIS CONFIGURATION WAS TESTED FOR IN-LINE CONCENTRATION IN STEPS P1, P2, AND P3.



IN-LINE VOLUME REDUCTION AFTER mAb CAPTURE

The capability of in-line concentration to reduce the process volume after the capture step was investigated by Novo Nordisk because the company wanted to increase its storage capacity; a volume reduction of at least 3x was required to do so. Volumetric reduction just prior to the ion-exchange step was expected to optimize this step with shorter process times and/or reduced column volumes, both of which have the potential to reduce production costs.

Optimization: Feed flux excursions

Typically, the capture-step pool has a mAb concentration of approximately 7.0 grams per liter (g/L) and a conductivity of 3 mS/cm. Optimization studies were performed at mAb concentrations of 7.4 g/L and 9.9 g/L (Figure 2). A volumetric concentration factor of 3x was achieved at a feed flux of 36.7 L per square meter per hour (LMH), corresponding to a mass throughput of 0.27 kilograms per square meter per hour (KMH).

Notably, nearly the same retentate concentration was obtained even at a higher feed concentration at the same feed flux. Retentate concentrations of 22.2 g/L and 23.8 g/L, respectively, were obtained for mAb concentrations of 7.4 g/L and of 9.9 g/L at a feed flux of 36 LMH. In addition, the same VCF was achieved for the highest feed concentration when the same mass throughput was used.

These results suggest that controlling in-line concentration with the feed flux provides robust dampening for small variations in feed concentration while yielding similar retentate concentrations. If the objective is to obtain similar VCF values, however, the feed concentration and the mass throughput should be considered.

Feed flux was calculated by adding the permeate and retentate flows, then dividing the sum by the module area. VCF was calculated by dividing the feed flux by the retentate flux. Retentate concentration was determined by sampling the retentate stream and measuring the concentration using a full-spectrum UV-Vis spectrophotometer. The average of five samples taken during the optimization step was used for the feed concentration. Mass throughput was calculated by multiplying the feed flux by the average feed concentration. Importantly, retentate concentrations of the product stream calculated for each set point based on the VCF were in good agreement with the measured values.

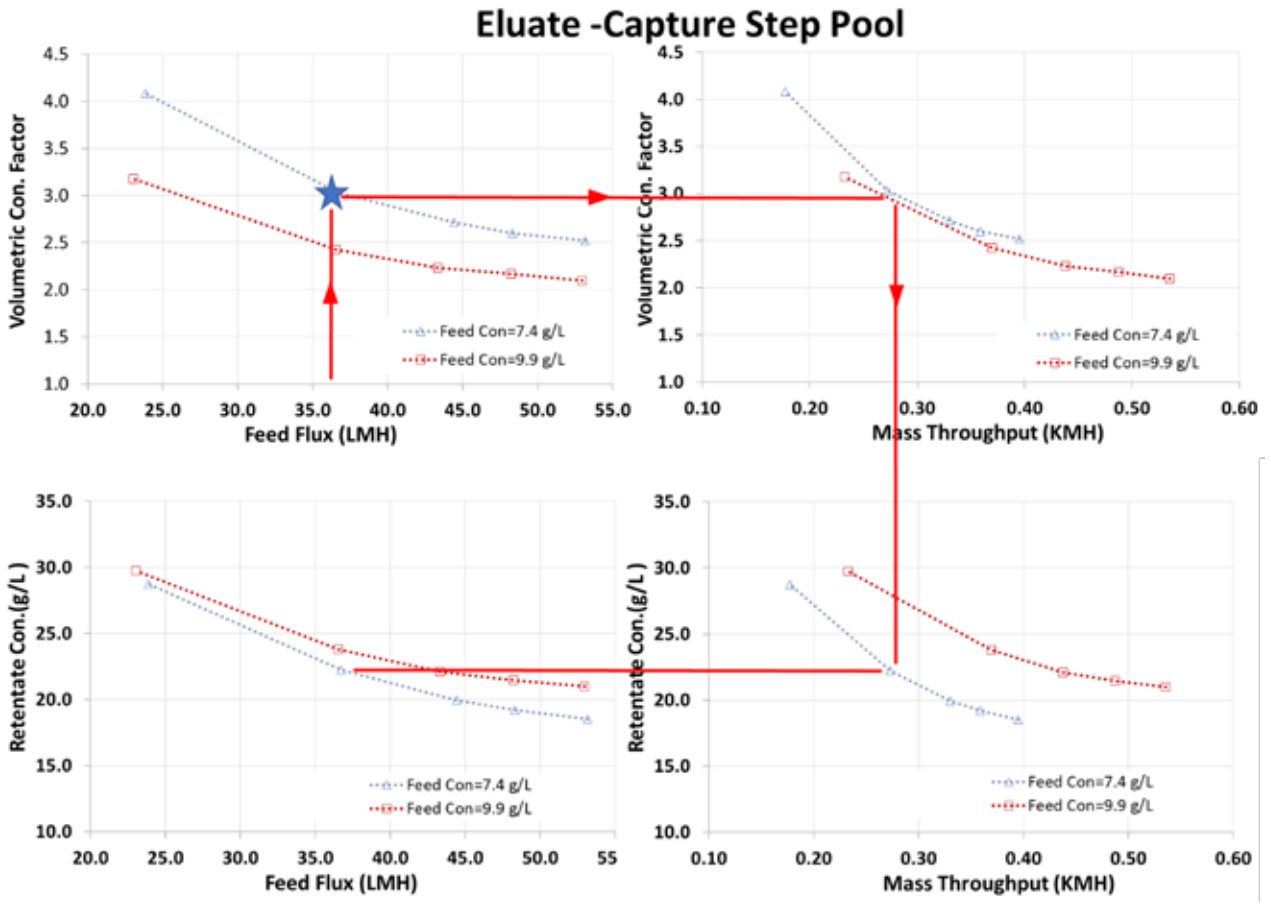
Effect of feed sample conductivity on flux

Typically, the eluate pool of the capture step has a very low salt concentration and consequently a low conductivity (2.9 mS/cm for the sample used in this study). Because salt increases mAb solubility, it may also affect protein concentration at the membrane surface. A decrease in the concentration polarization boundary layer thickness improves the ultrafiltration mass transfer coefficient.[6] A single-pass concentration step, operating primarily in the mass-transfer-controlled region where the permeate flux is independent of the pressure,[1–2] improves mass transfer and can result in higher permeate flux and an improved capacity for concentration.

To demonstrate the effect of improved solubility and to increase the mass transfer, the capture step pool conductivity was adjusted to 20 mS/cm by adding NaCl to achieve a concentration of 150 mM. For a mAb solution containing 150 mM NaCl, a feed flux of approximately 36 LMH provided a VCF of nearly 5.5x. The eluate pool without salt achieved a VCF of 2.5x at the same feed flux.

Possible aggregate formation caused by microcavitation induced by pumps and valves during product concentration was also investigated. Aggregate formation may be increased due to multiple passes in conventional tangential

FIGURE 2: VCF AND RETENTATE CONCENTRATION VS. FEED FLUX AND MASS THROUGHPUT FOR TWO FEED CONCENTRATIONS. ON THE VERTICAL AXES ARE VOLUMETRIC CONCENTRATION FACTORS (FEED VOLUME/ RETENTATE VOLUME) AND RETENTATE CONCENTRATION (G/L). THE HORIZONTAL AXES INDICATE FEED FLUX (LMH) AND MASS THROUGHPUT (KMH), I.E., THE FEED CONCENTRATION MULTIPLIED BY THE FEED FLUX.

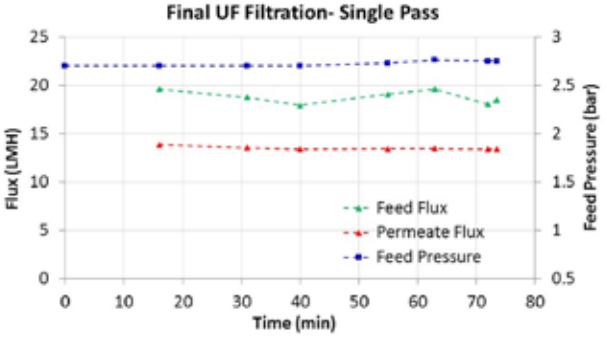


flow filtration (TFF).[3] Samples were collected during the process and analyzed via size-exclusive high-performance liquid chromatography for high-molecular-weight protein (HMWP) content. No increase in HMWP content was observed after concentration of capture pool samples with and without salt.

Scale-up to pilot scale

Using the results obtained for the feed-flux excursion experiments, throughputs and feed fluxes required to obtain desired VCF and retentate concentrations were calculated for volume reduction of a 200-L chromatographic capture step pool with a concentration of 7.4 g/L. It was found that this volume could be reduced in 1.6 to 2.5 hours using an in-line concentration module with an effective filter area of 3.5 m^2. In-line concentration also increases freezing storage capacity and creates opportunities to optimize the subsequent cation-exchange step without the need for a large hardware investment.

FIGURE 3: SINGLE-PASS RUN OF 1.51 L FEED VOLUME WITH A MAB CONCENTRATION OF 50 G/L



IN-LINE VOLUME REDUCTION BEFORE VIRUS FILTRATION

Virus filtration is costly and time-consuming for mAb production. In addition, the conductivity of the chromatographic pool after the ion exchange is often too high and must be diluted three times before the polishing chromatography step. The reductions in filter area and processing times possible with smaller filtration volumes reduce operating costs, not only during virus filtration but also in the chromatographic polishing step.

Optimization: Feed flux excursions

The ion-exchanger step pool had a product concentration of approximately 10 g/L and a conductivity of 16 mS/cm. To test the in-line concentration capabilities and process robustness, feed-flux excursions at three different pool concentrations (8.4, 10.4, and 12.1 g/L) were evaluated. For a product pool concentration of 10.4 g/L, a VCF of 3x was achieved using a feed flux of 57 LMH and a throughput of 0.59 KMH, approximately twice that observed for the capture step pool. The higher throughput can be explained by the higher conductivity of the ion-exchange pool.

As was the case for concentration of the capture step pool, nearly the same retentate concentrations were obtained for different feed concentrations (8.4 and 10.4 g/L) at the same feed flux. This finding provides further evidence that in-line concentration control by the feed flux provides robust dampening for small variations in feed concentration. Nearly the same VCF was achieved for all concentrations when the same mass throughput was used, however.

Single-pass run and product recovery

Next, a single-pass run was conducted with a feed flux of 57 LMH, using the ion-exchange pool with a starting concentration of 11 g/L to evaluate the stability of the in-line concentration process and determine the product recovery. Stable filtration without fouling was observed. Product recoveries of approximately 99.6% and 98.9% were obtained with and without (three hold-up volumes) system flushing, respectively.

Effect of decreased feed sample conductivity on flux

Although the same mAb was used, the mass throughput for the ion-exchange pool was nearly twice that of the capture step pool using a higher feed concentration. The main difference was the pool conductivity. To demonstrate that a higher pool conductivity (16 mS/cm) allows for a greater concentration factor, an additional test was performed using a product pool diafiltrated with WFI to a conductivity of 1.6 mS/cm. In this study's experimental setup, in-line concentration produced a sample with lower conductivity.

IN-LINE CONCENTRATION SOLVES PROBLEMS FOUND IN mAb PRODUCTION

With the diafiltrated sample (1.6 mS/cm), similar VCFs were obtained with a significant decrease in the mass throughput compared with the higher conductivity sample. In fact, it was not possible to achieve a VCF of 3x for the 1.6 mS/cm sample, even at a significantly lower feed flux. This can be explained by a decrease in mAb solubility at lower conductivity. Lower mAb solubility may lead to a higher protein concentration at the membrane surface, possibly increasing the concentration polarization layer thickness and decreasing the UF mass-transfer coefficient. Using an in-line concentration module with a single-pass concentration step that operates largely in the mass-transfer-controlled region (where the permeate flux is independent of the pressure) decreases the mass-transfer coefficient and can therefore decrease the permeate flow, limiting the VCF that can be achieved.

Scale-up to pilot scale

Virus filtration and polishing chromatography are intended to remove contaminants. Optimal impurity binding on the polishing chromatography column exchanger requires a decreased pool conductivity, which is achieved via 3x dilution. To maintain the same volume for both chromatography steps, 3x volumetric reduction of the ion-exchange pool was targeted.

Expected throughputs and feed fluxes required to obtain the desired VCF and retentate concentrations for volume reduction of a 200-L ion-exchange pool (10.4 g/L) were calculated using results obtained for the feed-flux excursion experiments. This volume could be reduced by a factor of three within 5 hours using one module with a filtration area of 0.7 m^2, or 1 hour using a module with a filtration area of 3.5 m^2.

IN-LINE VOLUME REDUCTION AND UF/DF

For final concentration, Novo Nordisk may currently perform up to three steps on the same UF system. The mAb is first concentrated to approximately 50 g/L, then diafiltrated with a suitable solution, and finally concentrated to > 100 g/L. A standard pilot UF system processes initial volumes from 600 L and provides final volumes of 12 to 15 L (VCF 40–50x). Such volume constraints may lead to poor product recovery and low yields, requiring product over-concentration.

The ability of this in-line concentration process to reach a mAb concentration > 100 g/L in the final concentration step (after initial concentration and diafiltration (DF) on the existing UF system) was evaluated. The goal was to achieve a significantly increased product yield.

Optimization: Feed flux excursions

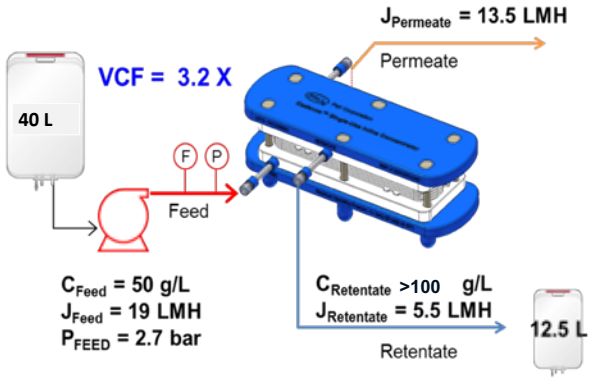
Feed flux excursions at feed concentrations of 49.4 g/L and at 59.2 g/L were conducted. The samples were previously concentrated and diafiltrated using a suitable buffer solution on the existing UF system. The feed flux, VCF, feed concentration, retentate concentration, and mass throughput were calculated or determined as described for the capture step.

For the two feed materials (of around 49 and at 59 g/L), the target retentate concentration was achieved at respective feed fluxes of 20 and 20.9 LMH. Once again, controlling in-line concentration via the feed flux provided robust dampening for small variations in the feed concentration (±10%).

Single-pass run and product recovery

A single-pass run was performed using a feed concentration of 50 g/L and

FIGURE 4: SCHEMATIC OF THE FINAL CONCENTRATION STEP



a total volume of 1.51 L with a 0.065 m^2 module to test the stability of the in-line concentration module and determine the product recovery (Figure 3). Single-pass operation was stable without any indication of permeate flux decreases or feed-pressure increases during the 75-minute run, indicating no membrane fouling.

A product recovery of 96.7% was obtained after flushing with an equivalent of two-system hold-up volumes—a significant yield improvement when compared with the current process.

Scale-up to pilot scale

Based on the test data from the single-pass run at a concentration of 49.6 g/L, the filter area for processing a batch volume of 40 L with a mAb concentration of approximately 50 g/L to a final concentration of > 100 g/L was calculated to take 3 hours using an in-line concentration module with a 0.7 m^2 membrane area—a potential improvement of the final UF yield compared to a conventional TFF system (Figure 4).[5]

CONCLUSIONS

For the tested mAb, the in-line concentration process performed in the present study reduced the capture step pool volume by a factor of 3x or 4x at respective feed fluxes of 36 to 22 LMH, meeting Novo Nordisk's requirements. To concentrate 200 L of the capture step pool starting from approximately 7.4 to 29.6 g/L within a reasonable processing time, an in-line concentration module with an effective filtration area of 3.5 m^2 would be required. The use of single-pass in-line concentration at this stage of the process increases binding capacity and creates an opportunity to optimize the subsequent ion-exchange step without a large hardware investment.

The ion-exchange pool was reduced by a factor of 3x with a feed flux of 57 LMH using in-line concentration, also meeting Novo Nordisk's requirements. Concentration of the 200-L capture step pool from approximately 10 to 34 g/L can be achieved within 5 hours using an in-line concentration module with an effective filtration area of 0.7 m^2 or 1 hour with a larger module (3.5 m^2 membrane area). The reduction in volume of the ion-exchange pool may permit cost and processing time reductions in the virus filtration and subsequent polishing chromatography steps.

Notably, the in-line concentration performance of this study's experimental setup was affected by the conductivity (salt concentration) of the chromatographic pools. At the same feed flux, adding salt to increase the capture step pool conductivity to 20 mS/cm increased retentate concentration to nearly twice that without salt. Conversely, removing the salt from the ion-exchange pool via DF significantly reduced concentration.

For final concentration after the UF/DF step, this study's in-line process increased a 50 g/L mAb solution to a final concentration of > 100 g/L in a single pass, with continuous concentration at a feed flux of 19 LMH. Processing 40 L with a mAb concentration of 50 g/L would be possible within 3 hours using a single-pass in-line concentration module with a 0.7 m^2 membrane area. Following these parameters for the final concentration step can significantly improve the final UF yield when compared with the conventional TFF system.

It was also shown that controlling in-line concentration by the feed flux provides a robust dampening effect for small variations in the feed product concentration. If the processing objective is to obtain a similar retentate concentration, the feed flux should be the controlling parameter. If the aim is to obtain a similar VCF, the feed concentration and the mass throughput should serve as the controls. ‹›

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Ole Elvang Jensen has spent more than two decades developing manufacturing processes for therapeutic proteins as a research scientist at Novo Nordisk. His work has played a key role in bringing drug substances forward for clinical trials. Jensen holds a master of science in organic chemistry from Aarhus University in Aarhus, Denmark; his core specialties include chromatography, ultrafiltration, and enzyme reactions. He is a published industry author.

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2013: Infliximab is the first monoclonal antibody biosimilar approved in Europe.

2015: Zarxio (filgrastim-sndz), a treatment for neutropenia associated with chemotherapy, is the first biosimilar approved by the FDA.

2017: Mvasi (bevacizumab-awwb), the first biosimilar for the treatment of multiple cancer types, is approved by the FDA.

Biosimilars by the Numbers

57%
Annual rate of biosimilars growth expected in the United States over the next five years

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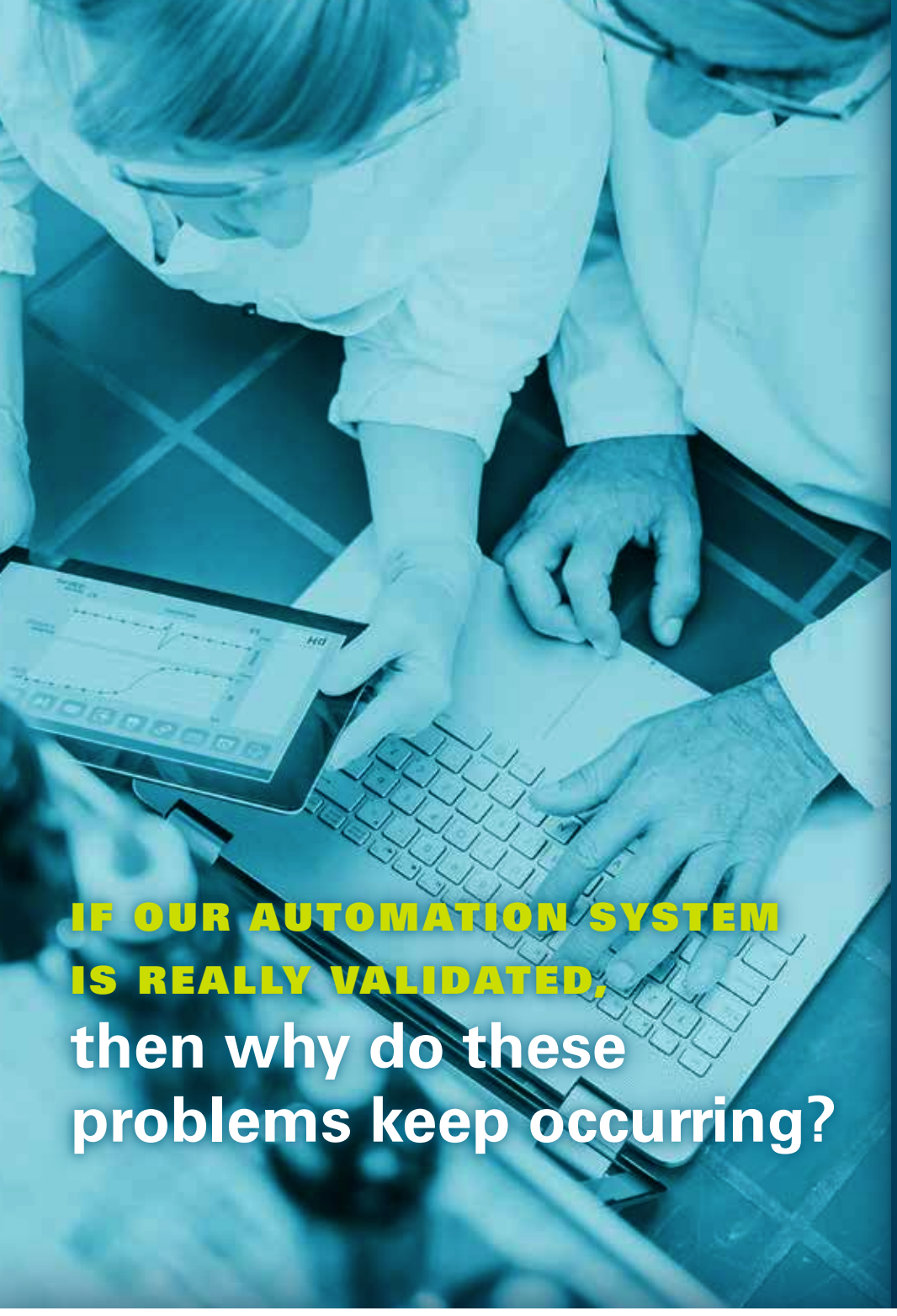
Research compiled by Scott Fotheringham, PhD



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