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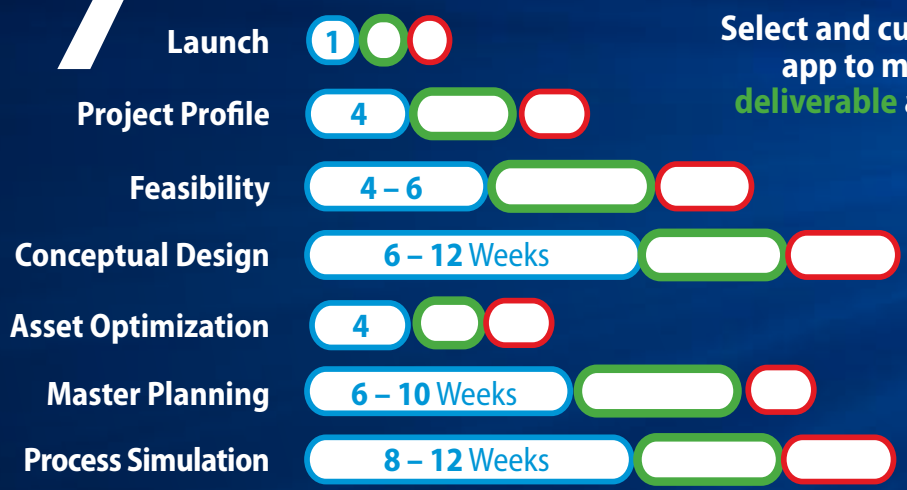

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12 SUSTAINABILITY AND THE LIFE SCIENCES INDUSTRY: A GLOBAL INTRODUCTION

This issue of *Pharmaceutical Engineering* looks at an array of sustainability topics. This introductory article surveys topics that will likely have a significant global impact on the way we conduct our business over the coming decade. We trace some of the history of sustainability in the life sciences industry and identify future issues of concern, including a number of areas where industry advancement cannot be made without true commitment to a full set of sustainable objectives.

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By Frances M. Zipp

What's Trending in the Pharmaceutical Industry?


Frances M. Zipp

WHAT'S TRENDING?

This is a very common phrase, one that's become part of the lexicon. You've probably heard it or read it countless times during the past year. I know I have.

So, from my perspective, it's natural to ask the question about regulatory trends in the pharmaceutical industry in 2020. There are two trends among many that have the potential to be a disruptive influence on healthcare and the life sciences: data integrity and Software as a Medical Device (SaMD). Their influence on each other is another relevant reason for me to share some thoughts and observations about them with you.

DATA INTEGRITY

In recent years, global regulatory bodies, including the US FDA, have heightened their focus on the significance of ensuring drug safety and quality through accurate and reliable data. In fact, the demand for data, in both quality and quantity, shows no signs of stopping in the near future. And with the rapid data-capture capabilities of SaMD, there's a broadening regulatory call to attention that we should expect to see trending this year.

ISPE's Pharma 4.0™ maturity model points to an end goal of digitalization for "smart facilities": drug production facilities where systems respond to changes in real time and prompt the needed remedial behaviors. To enable these corrective performance behaviors, organizations can be expected to rely greatly on quantifiable data that are both accurate and verifiable. This extent of digital maturation is on the horizon and trending, with many manufacturers starting to explore predictive quality techniques. Achieving the objective of predictive quality requires competency with large data sets, as well as data that accurately and rigorously reflect production and demonstrate competency with both AI and machine learning.

SOFTWARE AS A MEDICAL DEVICE

On the radar as another 2020 trend is the rapid advancement of technology in all areas of healthcare and the regulations governing it. Software has become an integral part of virtually every product. It has found its way into digital platforms that affect both medical and nonmedical purposes. Of particular note, the FDA has commented on the steady increase of SaMD and its use throughout a wide range of technology platforms, including medical device platforms, commercial "off-the-shelf" platforms, and virtual networks.

Because SaMD has the capacity to capture massive amounts of data quickly, it can also easily invite feedback from users—thanks to its availability on personal mobile devices, like smartphones and tablets—generating copious amounts of additional data. That's why the SaMD is inextricably entwined with data integrity. For companies using or developing SaMD, this fast response loop and the resulting data analysis can enable product iterations at an accelerated pace, reduce time to market, and propel more rapid innovation. How regulatory bodies and regulations can effectively address SaMD and related data integrity topics while serving all stakeholders presents an appreciable challenge.

The International Medical Device Regulators Forum (IMDRF) has noted that "the current application of regulations and controls may not always translate or address

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Throughout 2020, I look forward to seeing you at the many scheduled ISPE conferences and events.

the unique public health risks posed by Software as a Medical Device (SaMD) nor assure an appropriate balance between patient/consumer protection and promotion of public health by facilitating innovation"[1]. In acknowledging these circumstances, the IMDRF is working diligently to formulate and refine regulations that both maintain pace with the rapidly changing SaMD technology landscape and place the well-being of the patient as priority 1. How this trend of regulatory oversight unfolds in 2020 will be interesting to see. And it is one we shall all be watching closely.

These regulatory and innovation trends were front and center among the many topics at the ISPE Global Pharmaceutical Regulatory Summit in December 2019. Those in attendance also received valuable information regarding regulation of innovation in biotechnology, quality maturity frameworks, and innovation and quality during life-cycle management. The collegial and thought-provoking atmosphere proved to be a rewarding two-day experience for everyone. I hope you had the chance to be there.

Throughout 2020, I look forward to seeing you at the many scheduled ISPE conferences and events as we share our knowledge, opinions, and insights about the technologies, approaches, and solutions that drive innovation and quality for the medicines that serve patients. ISPE remains committed to providing our members with thought leadership and tools to understand and implement these technologies and approaches.

Reference

1. "Software as a Medical Device (SaMD): Key Definitions." International Medical Device Regulators Forum. 9 December 2013. http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-131209-samd-key-definitions-140901.docx

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

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KNOW YOUR WORTH

I recently had dinner with a friend and colleague who was looking at taking on a new job role. She asked me what I thought about her salary request as part of this new opportunity. I asked, "Is that what you think you are worth?" She looked very confused by my response, and I realized that many of us do not often step back and determine our business value.

For many people, talking about salary is taboo, and this is a delicate subject that should be approached with care and respect. However, it is smart to discuss your salary with appropriate individuals or look at market research. If we know our own value, could we negotiate for more? Not just more money, but more opportunity to grow? How does one navigate this tactfully?

STEP 1: KNOW WHAT YOU DO

Create a list of all your work activities, and then compare the list to your current job description. You might be doing more in one area but realize that you are neglecting another, or you could find that you are going far beyond your job role. I learned this early in my career: I like to help others, so this means that I often work outside of my job role. Talk with coworkers about what you are doing, as sometimes they can provide some additional insight.

STEP 2: UNDERSTAND WHAT YOU DO NOT KNOW

Understanding where you need to develop is a huge part of understanding your value. Admitting when you do not know something and seeking out the knowledge to fill that gap shows a great deal of self-acknowledgement and emotional intelligence. You can also loop this back to Step 1: if you are missing skills in an area of your job description, research ways to fill those gaps.

STEP 3: DO YOUR RESEARCH

Your list of responsibilities will make it easier to compare your job to others in the marketplace to know what others in similar roles are doing and how they are compensated. Use the list of your job responsibilities to compare your position with other roles' responsibilities and compensation. Be sure the site you use is a reputable one.

STEP 4: PRESENT YOUR CASE

I will often review my case with a trusted peer or colleague before I talk with my bosses. Make sure that you are clear on what your needs are and why. For example: "I have looked at my job description and feel like I am ready to move to the next level. Can we please discuss your thoughts on this and what that pathway looks like?"

Make sure that you are clear on what your needs are and why.

You should not go in with demands; instead, bring data to demonstrate your worth and understand that you might not get everything you ask for. After your meeting, determine if you are in a position and company where you can grow.

STEP 5: FULFILLMENT AND EXCITEMENT

Once you have determined your worth and presented your case, you will know your path within your company. There is no answer that is right or wrong, but you should always ensure that the work you do makes you feel valued and challenges you. When you do not feel fulfilled or excited by a position or a company, your growth will slow as you will feel less engaged and your desire to push further will diminish.

At the end of the day, you determine your self-worth by knowing your value and how you bring that value to your company and role. As Malcom X said, "We cannot think of being acceptable to others until we have first proven acceptable to ourselves."

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

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SUSTAINABILITY AND THE LIFE SCIENCES INDUSTRY:

A Global Introduction

By Robert J. E. Bowen, dipArch RIBA

In this issue of *Pharmaceutical Engineering*, we address an array of sustainability topics. This article surveys topics that will likely have a significant global impact on the way we conduct our business over the coming decade. We trace some history of sustainability in the life sciences industry and identify future issues of concern, including a number of areas where industry advancement cannot be made without true commitment to a full set of sustainable objectives.

The sustainability movement is now more than 50 years old; it was founded in the late 1960s and early 1970s by individuals concerned that the growing population, diminishing available natural resources, and the effects of pollution and waste could threaten the world population's ability to survive. One notable event in this social movement was the establishment in 1988 of a United Nations commission, the Intergovernmental Panel on Climate Change, to consider the science of climate change and sustainability.

Today, the sustainability movement is growing but controversial. Recently, divergent views on climate change were evident at the January 2020 meeting of world thought leaders at the Word Economic Forum in Davos. Some attendees called for urgent action to reduce our carbon footprints; others said there is no need for concern.

For those of us in the life sciences industry, the history of the sustainability movement has overlapped with our transition into a significantly more connected, scientifically and technologically advanced era. Throughout this period, we have commenced on the Fourth Industrial Revolution, with some areas pointing to a fifth level of industrial advance. For our industry to continue to advance, we must reflect and act on sustainability concerns such as energy, waste, and water reduction.

OVERVIEW

In the timeline to reduce carbon dioxide emissions, 2020 is a significant year. The United Nations Framework Convention on Climate Change (UNFCCC) has set this year as an initial waypoint in the push toward zero carbon dioxide emissions by 2050 [1]. The UNFCCC goals have been adopted by many life sciences corporations around the world [2, 3]. In nations where the drive toward carbon reduction is not as well as accepted, primarily in the US, Canada, and, to a lesser degree, Australia, the principles of sustainability are still relevant to pharma companies, which are setting goals for energy, water, and waste reduction.

The generally accepted definition of sustainability is "development that meets the needs of the present without compromising the ability of future generations to meet their own needs" [4]. How this definition converts into achievable, practical goals for the life sciences industry will inevitably vary depending on the part of the world, areas of industry focus, and a company's drivers.

INDUSTRY RESPONSE

Many multinational pharmaceutical corporations have adopted their own sets of engineering standards to ensure local compliance in a global context. These standards show a tendency of these large corporations to clearly adopt sustainable objectives.

Smaller company groups and individual companies are more likely to respond only to the expectations of their local legal and code environments unless there is a strong board or shareholder commitment or another driver, such as an ethical investor, to choose sustainable solutions. In many cases, companies may struggle to implement sustainability efforts because their facilities occupy older buildings rented or leased from third parties with

little interest in sustainable objectives unless the local government forces compliance.

In the UK, efforts to meet sustainable targets are driven by planning legislation and statutory building codes that include an expectation of achieving zero carbon dioxide emissions by 2050. However, the drive toward this goal for those committed to sustainable targets is accompanied by concerns that older facilities will not be updated, given that legislation is rarely retrospective. Therefore, the onus is on individuals and companies to decide whether to adopt sustainable objectives now or delay action until laws are enforced. Notably, the latter approach can damage the public image for companies with a patient focus—a commitment to sustainability can reinforce that a company is at the forefront of promoting health and well-being.

In general, the drive toward sustainable options has been considered to be a benefit to the pharmaceutical industry, although many companies face short-term pain to achieve long-term gain. Companies often, but not always, must invest considerable amounts of money up front to research, engineer, and implement sustainable options for processes and buildings. The results can provide large, lasting advantages for the company, such as process and operational improvements, upgraded environments, reduction of risks, and cost savings from increased efficiencies and cheaper facility operations; additionally, employees and the community can benefit from cleaner, more sustainable operations.

As companies commit to sustainability goals, they often seek out information resources and collaborative partners. Nonprofit organizations such as Science Based Targets [5] and Forum for the Future [6] are key players in noncompetitive, collaborative efforts on a global scale.

Science Based Targets has more than 700 corporate members worldwide, including AstraZeneca, Astellas, Biogen, Eisai, GlaxoSmithKline, NovoNordisk, Merck, Novartis, Pfizer, and Takeda. All have committed to zero carbon dioxide emissions by 2050.

Forum for the Future has similar sustainability commitments; its members include Walgreens, Boots Alliance, and Johnson and Johnson. The forum uses a "five capitals" model (i.e., natural, human, social, manufactured, and financial capital) to set sustainable development targets and manage improvement over time. It promotes the Net Positive Project, the Climate Futures 2030 strategy aimed at future business planning and debate, and the circular economy (which is discussed later in this article).

As Adrian La Porta, Technical Director–Process for Bryden Wood, noted in an email to the author, "Sustainability in the literature is more than carbon and water, not that these aren't important and extremely worthwhile in their own right. The five capitals model allows you to look at financial and social impacts at the same time as environmental impacts."

In recent years, companies aiming to manufacture and market cell and gene therapy products in the US and advanced therapy medicinal products in the UK and European Union have opened new facilities because older facilities cannot accommodate the scientific and manufacturing requirements for these types of products. The equipment needed to manufacture these new therapies is smaller than the equipment for older product types, which means the new facilities do not need to occupy as much space. Inevitably, the stakeholders involved in designing and constructing new facilities can see the benefits of adopting leaner, cleaner sustainable standards; however, existing facilities may maintain past inefficiencies because of the difficulties of retrofitting installed clean and black utilities, outmoded HVAC systems, and other systems and equipment.

In many environments, installing LED lighting and a few solar panels on the roof is not enough for a company to claim to operate sustainably. A true commitment is much more holistic. In this respect, it is beneficial to consider sustainability strategies on the basis of product, process, and facility requirements. The coordination of these variables to improve sustainability in even a single facility can provide long-term financial gains and other benefits.

In our industry, the ways that the cost of goods (COG) and return on investment (ROI) targets are derived are important considerations for those striving to meet sustainability targets. Each pharmaceutical or biotechnology product that reaches the market requires an up-front investment in research to develop the product and rounds of clinical trials; then, the company has a 20- to 25-year patent break in which to recover costs and provide payback for the shareholders before it faces a post-patent scramble for generic supremacy in the market, during which time shareholders continue to expect ROI.

These economic factors drive companies to set tight ROI targets and focus on controlling the COG. This makes sustainability targets tricky. From a facility perspective, ROI/COG priorities can seem to suggest that sustainability investments are "nice to have" but not cost-effective. Consequently, there is a risk that companies will lose sight of their ethical responsibilities as health providers, community members, and partners in initiatives to stop climate change. For these reasons, the success of sustainability in our industry may require national or international legislation, regulatory enforcement, or industry codes, or the strong drive and commitment of like-minded industry groups.

ISPE'S POSITIVE CONTRIBUTIONS

ISPE has taken a proactive role in promoting sustainability since Paul Malinowski and Nigel Lenegan established the Sustainability Community of Practice (CoP) in 2007–2008. The CoP subsequently merged with the HVAC CoP to form the HVAC and Sustainable Facilities CoP.

ISPE has recognized and rewarded achievements in sustainability since 2009, when the Society gave the first Facilities of the Year Award (FOYA) for sustainable projects, the Facilities of the Future Award. Almost every year since then, the FOYA program has presented this award; the most recent award recipient was Celgene Corporation's "Green Fairy Project" in Couvet, Switzerland. To see a profile of the Celgene facility and other Sustainability FOYA winners, go to https://ispe.org/facility-year-awards.

The ISPE *Handbook: Sustainability* [8] includes guidance on policy-making for sustainable objectives, along with practical suggestions for retrofit and new-build design principles and methodologies.

Pharma 4.0™, based on Industry 4.0 and the Industrial Internet of Things, refers to the ongoing revolution in our industry characterized by feedback/feed-forward data use, general improvements in in-process characterization, and advances in robotic options and equipment that are changing the face of pharmaceutical production.

Components of Pharma 4.0™ that are driving a more mature sustainable future with opportunities throughout the supply chain for improvement include:

- Advanced techniques that apply new and improved renewable materials and expand product options using additive manufacturing
- The integration of process analytical technology (PAT) in-process characterization and feedback/feed-forward data streaming to meet process integration and continuous manufacturing standards established in ICH Q13: Continuous Manufacturing of Drug Substances and Drug Products [9]
- Smart data applications, such as robotic process automation (RPA), that automate equipment for product manufacturing, storage, and warehousing
- Real-time particulate-level measurement and micro-metering of energy usage, which jointly provide information needed to effectively control energy use
- Improved patient-focused supply chains and drug product personalization, which minimize waste through better identification, serialization, and stock control
- System-based identification of disease outbreaks, which allows the facility to respond using modular formats and local micro-manufacturing

Collectively, these Pharm 4.0™ initiatives, along with innovations in facility and equipment design, data farming, cloud sharing, and human resources management, provide the capacity for a more focused, efficient, less wasteful, and sustainable pharmaceutical industry.

Furthermore, when Pharma 4.0™ is integrated with the circular economy concept described later in this article, this provides a new approach to manufacturing, facility design, and the supply chain as a whole. When managed correctly, this approach offers industry stakeholders the capacity to reassess existing products, their production processes, and overall supply chains and achieve significant gains in sustainability and other benefits.

In some areas, it will take time to implement such changes, and the changes may be costly at first. Companies may wonder, "If our current ROI is acceptable, why should we invest in changes?"

QbD AND IMPROVED PROCESSING

Quality by design (QbD), supported by ICH Q2(R2)/Q14, Q8, Q9, Q10, and Q11 [10–13] with guidelines on analytical procedures and risk assessment, is probably the most important factor when pharma companies seek to set sensible sustainability targets from the outset of a manufacturing process. Throughout a product's life cycle, two related issues—the technology transfer from candidate product through trials and scale-up, and, in particular, the way critical process parameters (CPPs) and critical quality attributes (CQAs) of the process are listed with the regulator—will be significant. If flexibility in the regulatory filing is unavailable, companies will be reluctant to change any aspect of formulation or method after the first regulatory clearance.

With older products, major changes to a manufacturing process usually require refiling. This is a costly exercise, which gives companies an incentive to not change the process, or to make only minimal changes so that refiling is not necessary.

Setting the correct path by responsible definition of CPPs and CQAs ensures that companies have the opportunity to move forward to sustainable/more advanced manufacture of a new product. In some instances, they may also be able to reengineer old processes. However, the introduction of continuous manufacturing, for example, may be challenging when older products are in constant demand and companies do not want to interrupt production. The incentives to stick with the status quo lead companies to retain inefficient, outdated, and wasteful equipment and processes, and resist changing process constituents to leaner, cleaner, and more sustainable process options that may be more beneficial over the long term.

These issues were clearly at play during a recent upgrade project, where the intention was to transfer an old solvent-based process with hydrogenation and other chemical risk issues to a new, safer, location with significant potential for process improvement and sustainable scaling of throughput. The transfer time required, the need for refiling, and the associated costs killed the project. With some process improvement through solvent-use/type reduction, the project remains in the same unsustainable position with similar locational risk issues and little opportunity for worthwhile scaling and associated multiproduct options. "Biting the bullet" to make sustainable changes is not easy without a value proposition.

SUSTAINABLY BENEFICIAL RISK REDUCTION

As indicated in the previous example, pharma industry stakeholders generally recognize that reductions in use of harmful solvents and their replacement with less-aggressive forms are beneficial and lead to easier, simpler, and safer transitions with less risk and operational cost, and without the downstream waste issues.

One tactic to reduce solvent use is to redesign elements of a process to use less. However, the better options are to look to for more beneficial methods of synthesis or to completely replace synthesis as a process with, for example, biosynthesis. Call it the "milding" of drug manufacture if the concept of "greening" is an anathema.

As Robert Dream, Managing Director of HDR Company LLC, suggested in correspondence with the author, "Let's abandon chemicals and use a substitute, recycle what is needed and not replaceable, and use our common sense for manufacturing."

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As cell and gene research projects advance globally, with drug candidates transferring into clinical trials and slowly clearing their regulatory processes, stakeholders are working on feasibility studies, facility design, and site searches for new builds and retrofits suitable for these projects. Projects underway include general-use viral vector and stem cell–based products, as well as personalized, oncology-focused products and interventions.

Given the processes and associated equipment involved, these projects are often based in small-footprint, efficient facilities, sometimes referred to as "labs+." These facilities can handle high-throughput, small-scale processes for clinical trials batches, and, where developed to larger scale, they can offer opportunities for using continuous, smart modular processes from inception and a smoothed-out supply chain overall.

As the process scale reduces, the facility scale can also reduce, thereby providing options for more sustainable solutions with greater resource control and the potential to manufacture local to need, including in hospitals or university-based retrofits or off-site modular construction.

In the future, some new product forms may even be manufacturable through the pharma/bioequipment equivalent of a bread-making machine. Active ingredients and excipients would be directly supplied to a hospital, pharmacy, or home to suit a patient's condition, with the machine providing the requisite dosage in a personalized form. This innovative technology would bypass the need for a facility dedicated to manufacturing, but, of course, it would still need to be fed with perfectly produced ingredients and meet rigorous standards for safe processing. Also, the sustainable benefits of such a device would need to be addressed.

Other sustainability opportunities associated with new product types may include switching to biosynthesis upstream and downstream intensification through continuous or smart batch manufacturing. These innovations would further allow reductions of scale while increasing response through process modularization combined with lean engineering techniques.

The last decade has seen the increasing acceptance and use of containment devices/isolators with better and increasing understanding of their efficient use. Drivers include the update of the European Medicines Agency EudraLex Volume 4 Annex 1 [14], which is anticipated to underline the need for maintenance of high-grade backgrounds for safety cabinets and RABS devices, forcing the consideration of closed process, contained isolator–based facilities supporting lower-grade backgrounds for the surrounding volume.

This shift might eliminate the need for Grade A and B room backgrounds as processes and products are fully contained with relatively minor volumes of once-through air and the potential, subject to correct risk evaluation, for partially or fully recirculated backgrounds two grades down from the enclosed/contained volumes. This would significantly reduce energy consumption and simplify the cleanroom requirement, building response, and staff risk. Inevitably, this could provide an overall more sustainable, controlled response to the environment.

The industry may also be able to realistically consider transitioning manufacturing to clean module-based facilities that are mostly constructed off site. This mode of construction takes advantage of the benefits of factory acceptance testing prior to site delivery and cuts down on time and resources needed to prepare and validate the site and construct the facility. These efficiencies are all sustainably beneficial.

Facility designs that aim to maximize sustainability goals allow companies to take a proactive, holistic approach to process and building assets. For example, a company could move beyond just monitoring overall energy usage to fully analyze micro-meter data on area-specific energy consumption. This more specific assessment helps target areas for improvement and can increase energy savings.

This approach to facility design, together with over 30 years of environmental assessments using tools such as Leadership in Energy and Environmental Design (LEED) [15] and Building Research Establishment Environmental Assessment Method (BREEAM) [16], has created a new sustainability-based norm for new and retrofit facilities. However, if carbon reduction ceases to be a priority, there is a danger that company boards and engineers may query whether in-depth design assessment and investments in sustainability features are necessary in facility design.

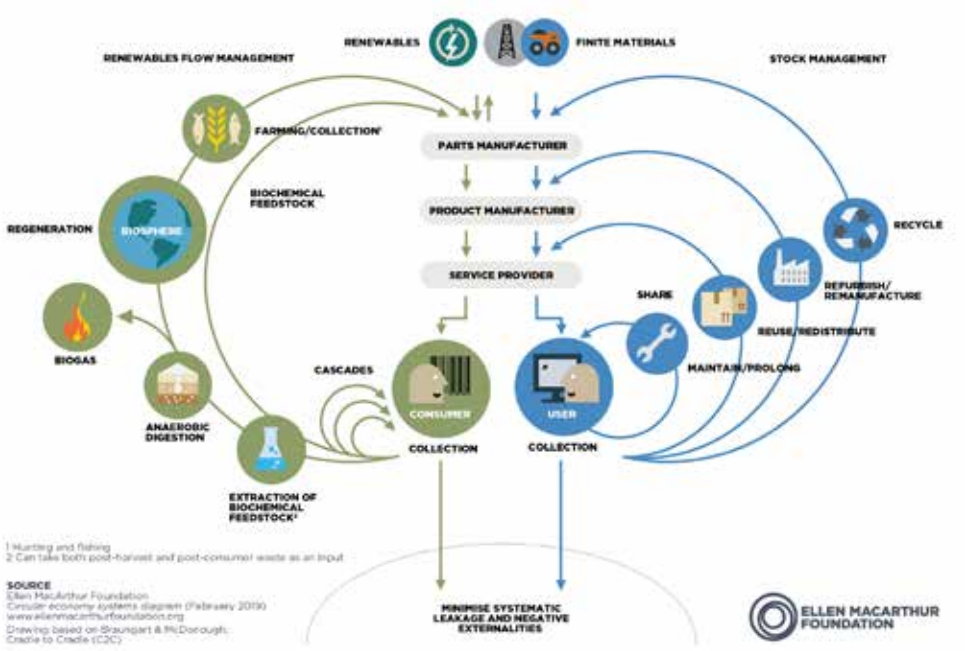
Still, sustainability advocates can take hope that sustainability will remain a design priority. Fortunately, the business case for sustainable design can be supported by build-before-you-build principles, the use of building information modeling (BIM) design software, and other applications that let designers and engineers model real-time scenarios and time-test designs for facilities and the environments they contain before construction begins.

As a part of Pharma 4.0™, operational control in facilities is being digitalized; fewer tasks on the floor are done by humans and the worker's primary role shifts to overseeing of digitally controlled processes within a PAT and real-time monitored space. The machine controls yield processes that are less variable due to the standardized operations inherent with automated control sequences. Such efficiencies can contribute to sustainability by reducing waste and resource consumption.

These changes to operations clearly have implications for human resources. In digitalized operations, basic human physical operational input is reduced, so fewer workers are needed. At the same time, expectations for workers increase; they must have greater skills and flexibility to run and oversee a clean, controlled facility from input to output. In sum, we can expect a transition to fewer, higher-grade staff working in smaller facilities and driving sustainable outcomes.

Although we have reviewed many ways that the manufacturing of drug products is becoming more sustainable, we have fewer insights about other areas such as warehousing, dispensing, and packaging. In these parts of the industry, priorities and incentives vary. For example, a primary incentive for companies to create new packaging forms is to gain advantages in the over-the-counter market; however, packaging that works well for the ROI may be

Figure 1: The circular economy principle. Reprinted with permission from the Ellen MacArthur Foundation (www.ellenmacarthurfoundation.org).



resource intensive to manufacture and create large amounts of waste, which runs counter to sustainability goals.

Another area needing further consideration is the cold chain. Many drugs must be retained within the 2°C–8°C range for all or part of their processing, which is obviously consumes considerable energy. There are still many areas for sustainability-focused engineers and process architects to improve.

FURTHER CHALLENGES

Traditionally, economic development has been considered as a straight line that moves from raw material to product to waste. In this model, there is little acknowledgment of responsibility in sourcing or disposal. In contrast to the linear model, another model, the circular economy, has been proposed by the UK-based Ellen MacArthur Foundation and other proponents of sustainability (see Figure 1). According the foundation's lead statement, a circular economy "is based on the principles of designing out waste and pollution, keeping products and materials in use, and regenerating natural systems" [17].

Applying the three principles of the circular economy to the life sciences industry presents a challenge that has been taken up by some significant players. Global partners in this campaign include Solvay and Unilever, and members of the Ellen A. MacArthur Foundation's CE100 (Circular Economy 100) Network include representatives of the life sciences industry such as 3M, NovoNordisk, and DSM, as well as significant contributors to our industry such as Microsoft, Apple, Philips, Dow, and DuPont [18].

Novo Nordisk and Novozymes are key partners and leaders in the Kalundborg Symbiosis, a partnership of nine public and private companies working together since 1972 to ensure that "the residue from one company becomes the resource at another," to the benefit of both the environment and the economy [19].

Adopting a circular economy approach challenges the principle of single-use plastics, where "single use" means use and dispose, mostly through incineration. Such a throwaway approach in the pharma industry may reasonably be considered to be too costly once sustainability is seen as a factor, especially given the expense of the specialist medical plastics used and wider concerns about incineration as a solution to pollution.

According to a *National Geographic* article on hospital single-use products and the resultant waste, "In 2018, China announced it would no longer buy two-thirds of the world's waste. That's leaving facilities little choice but to toss their mingled plastic waste into landfills or incinerators. PVC that ends up in incinerators can release toxic chemicals" [20]. According to Plastics Recycling Update, roughly 30,000 tons of biopharma single-use products are landfilled or incinerated each year [21].

We cannot use plastics once and dispose of them in these ways without facing the consequences. One bright spot is that MilliporeSigma has tackled the issue directly and offers a significant service by working with their clients to eliminate waste. To quote their website, "We faced this challenge by working together with customers and the waste management industry to provide a unique process and first-of-its-kind single-stream recycling program. Our U.S.-based programs are able to recycle almost 100 percent of the products with the added benefit of traceability" [22].

CONCLUSION

Whether by default or design, the scientific and technological advances reviewed in this article, many of which were developed over the last 10 years, provide us with an array of sustainable solutions, including:

- Changes in product formulation
- Process improvement and simplification
- Scale reduction and opportunities for continuous processing
- Data-fed automation
- Air volume reductions through use of isolation techniques
- Build-before-you-build simulation via BIM and process simulation software

Further, we can be encouraged by global agreements on strategies for sustainable solutions and the commitment of governments and organizations to timelines for major initiatives to achieve a "no waste" future and zero carbon dioxide emissions by 2050.

In the life sciences, there is the hint of a bright horizon. We were late in accepting the issues associated with sustainability, and because the ROI is uncertain, many of the feeder and front-end processes in our multifaceted industry continue to rely on old techniques that would be costly to change. We also understand that much of what is necessary to achieve successful outcomes, such as introducing a circular economy, depends on political forces that our industry can influence but can't control. However, after a slow start, we can be proud of most of the global players in our industry for their adoption of sustainable principles. Going forward, it is important that start-ups, individual companies, and small groups participate to ensure that sustainability is a total success in the life sciences industry sector. Although sustainability issues are complex and often politicized, we can and should commit to the premise of sustainable design, construction, implementation, and operation in the pharma industry.

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TWO REAL-WORLD EXPERIENCES in Global Sustainability

By Keith Beattie

The article appraises the real-world experiences of two pharmaceutical companies approaching the rollout of energy- and water-reduction programs to selected facilities around the world. It is the result of more than two years of collaboration between the company corporate teams, individual site teams, and an external specialist consultant.

Company A is a leading research-led pharmaceutical company that operates globally and is in the top 10 pharma companies in terms of sales revenue. It has a mix of operations, such as vaccine production, other biotechnology processes, solid oral product manufacturing (tablets and capsules), and research facilities. The company has sites around the globe, with a large footprint in North America.

Company B is a top-20 global manufacturer of consumer products (mainly over-the-counter medicines and some prescription medicines). They also contract manufacture products for other companies. Many of the brands are well known. Their processes are solid and liquid oral dose, with a limited amount of sterile product manufacturing.

COMPANY A

This company has had a long-standing commitment to sustainable operations, which is supported at the highest level in the organization. However, because of other priorities, they had made limited progress on reaching targets for energy use and water reduction. That started to change in 2016 and 2017, when they made structural changes and set aside a capital budget specifically targeted at supporting manufacturing sites with implementation of energy-, water-, and waste-reduction projects. Access to this fund was contingent on completing a standardized-methodology energy and water assessment using a specialist external consulting firm with expertise in the sector. This supported overall objectives of targeting capital spending to have the biggest impact and proceeding in a coordinated way.

The initial program was sponsored by the corporate operational finance team, who were championing cost reductions within the supply chain. The stakeholders recognized that cost and carbon (energy) reductions are synergistic, which meant the program could support a number of strategic objectives, including cost of goods, sustainability targets, operational excellence, and personnel engagement/talent retention.

In the first phase of this assessment, 11 sites were assessed (audited) for both energy- and water-saving opportunities over a two-year period (2017–2018). The sites ranged from small packaging/distribution operations to large multiproduct manufacturing campuses.

Figure 1 summarizes the findings from these energy and water assessments. Over 270 specific project opportunities were profiled for cost and carbon savings, capital implementation cost, and risk/benefit analysis. In addition, savings for more than 140 low- or no-cost ideas were not quantified, as these initiatives could to be pursued with very little effort.

In Figure 1, the bubble size represents the relative estimated cost reduction for each utility category. The total savings identified exceeded $6 million per year, equivalent to 25% of the annual utility costs for all sites. Notably, at the time of the audits, all sites were already well maintained and operated, with great technical team knowledge and expertise; therefore, this high level of opportunity was not a result of neglect or lack of knowledge. Instead, it was the result of taking a specific, focused approach and challenging the accepted practices through the lens of sustainability.

It was no surprise to find that HVAC and associated building management system (BMS) controls presented the most attractive investment opportunity. This category was by far the greatest energy-saving opportunity—around 50% of total savings identified. See Figure 2 for data on Company A's investments relative to the carbon savings for various initiatives.

Interestingly, although behavioral change actions were a

Figure 1: Company A energy audit summary (annual carbon savings by utility category).

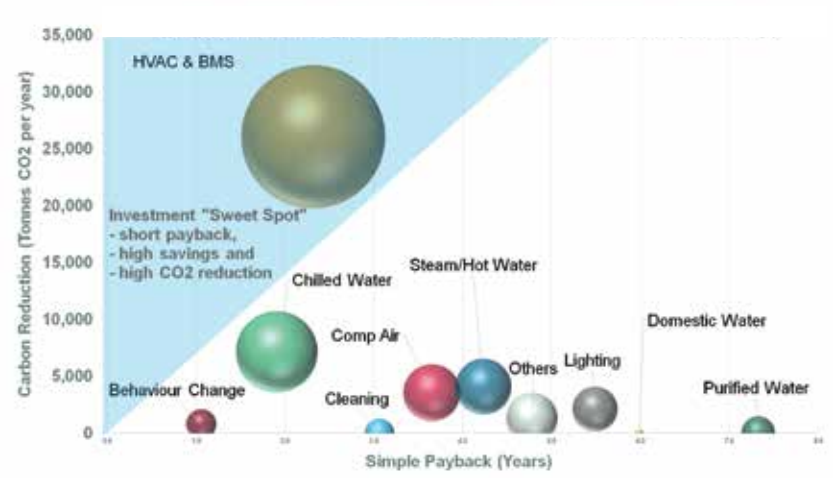
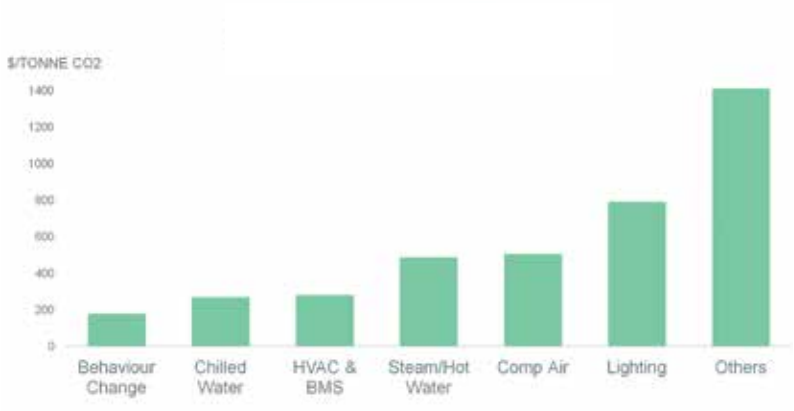


Figure 2: Company A's estimated one-time capital investment per tonne CO_2 reduction (annual) by utility category.



relatively small contributor to energy savings , they were found to offer the highest return on investment (ROI). These are small, low-cost operational management/staff awareness actions that individually contribute a very small benefit but have a sizeable result when scaled across an organization. Examples would be turning off packaging conveyors when the line is down, shutting down computers at night and on weekends, and switching off unneeded lighting.

Raising awareness simply by communicating the scale, cost, and impact of a site's energy footprint can have a positive impact on staff behavior, but only if sustainability messaging is supported by consistent leadership policies and actions. Leaders have to walk the talk! A positive employee response to sustainability initiatives can also impact many other utility categories by reducing the "friction" and inertia of making improvements in other areas—if a majority cohort supports the objectives and understands their impact and benefits, that can make investment approvals and project implementation somewhat easier.

Chilled water generation and distribution systems were the second-largest category of energy-saving opportunity. Simple changes such as raising the chilled water setpoint (either continuously or based on seasonal variation) can be easy to make and provide good savings with little or no cost. There were also good opportunities for pump motor efficiency upgrades and introduction of a variable flow system. In many cases, chilled water systems had been expanded and evolved over time, but little consideration had been given to the cumulative impact of these changes on efficiencies; hence, system optimization, rationalization, and chiller sequencing offered common opportunities for system improvements. Finally, cooling tower web bulb control of fans, fan staging, and variable speed drives were all found to be viable options for saving energy.

HVAC is by far the largest single utility consumer on most pharmaceutical manufacturing and research and development (R&D) sites. The energy required to move, filter, heat, cool, dehumidify, and, in some cases, humidify the air is responsible for between 45% and 70% of a site's total energy demand. We can often assume that this energy expenditure is inevitable in the pharma industry because cleanroom environments are needed for manufacturing, and it is true that cleanrooms and laboratories require more energy than an office space. However, the question is: Do they need quite as much energy as they did 5 or 10 years ago, given our improved understanding of cleanroom performance and the availability of much more efficient technologies at lower cost? Indeed, as unit energy costs increase, efficiency investments in HVAC can demonstrate a greater ROI. Figure 3 illustrates the recommended priorities of energy-reduction initiatives for HVAC to achieve the maximum savings and ROI.

When we looked more closely into the types of savings available in HVAC, we found that approximately 60% of the savings opportunities were in GMP spaces (cleanrooms—controlled not classified [CNC], Grade D, and some in Grade C). Grade B cleanrooms were evaluated for savings but were not included in the project proposal because of their relatively low contribution to

Figure 3: Recommended priority for HVAC energy reduction strategies (© EECO2, reprinted with permission).

energy expenditure and challenges in managing and qualifying changes in these spaces. Viable energy-saving opportunities for Grade B cleanrooms were found, but it is always better to focus first on the more easily delivered CNC and Grade D spaces.

More surprising than the ROI on cleanroom efficiencies was the scale of the opportunities available in non-GMP spaces (offices, laboratories, warehousing), which accounted for 40% of the energy savings for HVAC utilities. This included projects such as time-scheduling systems in offices, supply air temperature reset (a big opportunity at US sites), and demand-based ventilation in warehouses. These types of changes are relatively easy to implement and require small investments relative to the savings available.

Why are many organizations overlooking these easy wins? One of the reasons is resourcing. A site's technical resources and expertise focus primarily on supporting the manufacturing and GMP spaces. Therefore, companies have limited capacity to look at improvements in noncritical areas. Notably, when organizations have adopted an integrated facilities management model for outsourcing asset maintenance, typically for non-GMP or non–business critical assets, they do not achieve improvements in energy efficiency. This finding is likely a result of contract arrangements (and would be an interesting topic for another article).

Key Themes

Although there were many different project opportunities at each audited site, some key themes were common across most of the 11 sites.

Metering, Monitoring, and Targeting

There was almost a complete absence of submetering of utilities at most sites, and those sites that had some submetering were not actively using the data to inform decisions. Having the right level of information is helpful to target interventions in the right area and to measure the impact of these interventions to validate the business case.

Company A recognizes that investment in this area is needed to help them reach their overall goals.

Meaningful Key Performance Metrics

It is typical to compare this year's metrics on energy and water consumption performance to metrics from the same periods last year. Although this comparison is of some interest, it does not help when actively managing energy consumption with a goal of improving efficiency. In the pharmaceutical industry, with HVAC being such a key energy consumer, the impact of outside conditions can dramatically affect energy consumption from year to year. For example, it is hard to make conclusions about energy efficiency when simply comparing HVAC energy-use metrics from a particularly hot summer and a more temperate one.

There are techniques that can eliminate (or substantially reduce) the influence of variables such as weather conditions to compare like-for-like consumption. These techniques can also be used to derive meaningful performance metrics that help an organization determine progress and where resources need to be employed for best effect.

The recently published ISO 14644-16 standard for energy efficiency in cleanrooms provides examples of performance indicators specifically for cleanrooms [1], and there are many other publicly available resources giving guidance on energy metrics for other contexts. The key point is the metrics should be specific to the individual site, the buildings, and even the process level if that is relevant.

Sharing with and Learning from Others

At the time of the audits, many sites already had good practices in some areas of their utility system. It was recommended that these practices be shared more widely within the business so that personnel at all sites can learn and improve. Company A had forums for sharing knowledge; however, these were criticized for being at too high a level to be practically beneficial. Sharing of experiences between sites and with other similar companies can be a good way to continually improve and to challenge and try new ideas.

Results in Practice

An energy audit is a tool to prioritize and focus investment decisions. It does not in itself reduce energy consumption. However, when done well, it can promote different ways of thinking and acting within the site team. The best audits also incorporate some element of training such that the site teams obtain tools to look at sustainability opportunities with a different perspective and challenge out-of-date thinking and ineffective approaches to problem-solving.

Results are what really matter: Can you put into practice the audit recommendations, and do they broadly achieve the expected results? It is critical to get this right. Success follows success, so having a good first few projects, well delivered, that meet stakeholder expectations is a key component of a successful program.

For example, Company A planned the execution of a pilot project at one site. They chose to implement several HVAC control improvements in four areas of the site that included offices, warehousing/distribution, and technical spaces. The objectives were to optimize the controls of heating and cooling, introduce demand-based control, and eliminate other inefficiencies in the systems while maintaining a comfortable environment for occupants. The actions taken included:

- Introducing a time schedule to switch off HVAC during unoccupied times
- Recommissioning a strategy to reset the supply air temperature controls to allow the discharge air temperature to increase when there is no cooling demand
- Introducing a deadband to room temperature setpoints
- Installing CO2 sensors through the open-plan offices to reduce the airflow when occupancy levels are low or temperature and CO2 standards are satisfied
- Reducing airflow volume flow rates

On completion of the improvements, the initiatives were evaluated to confirm the results and measure energy consumption. The pilot project confirmed annual savings of over $190,000, and the project implementation costs were around $100,000. A six-month simple payback exceeded the expected ROI, and the occupants noticed no difference to their environment or comfort.

Company B

Company B wanted to take a more targeted approach to identifying energy- and carbon-reduction opportunities. They opted to focus the audits only on HVAC and associated BMS controls to maximize the efficiency of this utility. The company's initial objective was to reduce operating costs; however, as they have simultaneously been developing their sustainability strategy, they are shifting priorities to reducing carbon emissions. This change in priorities affects the strategies they can employ.

Initially, two sites were selected for piloting the focused HVAC/BMS energy audit, one in the Europe and one in the US; these sites were chosen primarily because of their high energy spending. The European site opted to focus narrowly on opportunities that would pay back their investment within one year. This need for a quick ROI presented a challenge and limited the range of project opportunities that could be proposed. Following the success of the pilot audits, five more sites were assessed in 2019.

One of the excellent cost-saving opportunities at a US site was combined heat and power (CHP), also referred to as cogeneration. In fact, there was also a possible viable opportunity for combined heat, power, and absorption chillers (trigeneration). This was due to the low relative cost of natural gas (compared with electricity).

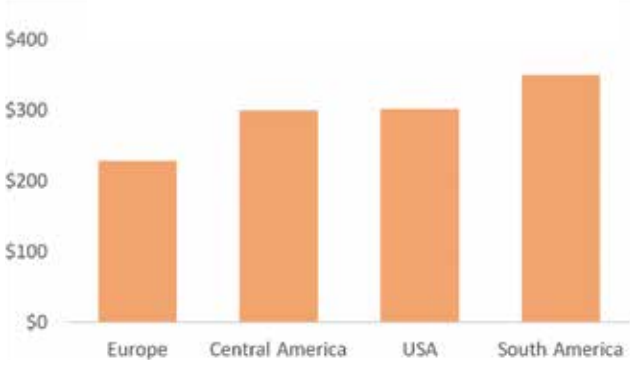
However, this proposed project may work against Company B's new carbon-reduction objectives for the following reasons.

- CHP would offset the higher carbon factor of purchased electricity with the lower carbon factor of onsite-generated electricity.
- Part of Company B's future strategy may be to purchase 100% renewable electricity, with a carbon factor close to zero. That would negate the carbon benefit of CHP—in fact, it makes the situation worse because the company would need to burn more gas to run the CHP. There is likely still a cost benefit from CHP, but the carbon benefit will disappear.
- Even without purchasing "green" electricity, many electricity grid systems are reducing their carbon intensity by increasing the mix of renewable generation. In a few years' time, many regions of the world will have grid electricity carbon factors much lower than they are today, which puts into question the long-term carbon benefit of CHP.

Therefore, we can see the subtle conflict between a cost-led strategy and a carbon-led strategy. However, what is clear is that simple, effective energy-efficiency improvements (reducing demand) work in all circumstances and are a key component of an effective sustainability strategy.

Figure 4 shows regional variation in the investment required to abate 1 tonne of CO2 emissions. The relatively high cost in South America is attributed to the lower carbon content of grid electricity in this region (due to extensive use of renewables, specifically wind and hydroelectricity, in the generation mix).

Figure 4: Company B's estimated one-time capital investment per tonne CO_2 reduction (annual) by region.



Therefore, an investment of similar value to investments in other regions would be expected to reduce energy consumption by an equivalent amount; however, the carbon content of that energy in South America is much lower. The difference between Europe and the US can be attributed to the relatively higher cost of project implementation in the US in this example.

Results in Practice

Because the focus of the first European site assessed was to identify rapid payback opportunities, the assessment team was limited to opportunities associated with control optimization and demand-based ventilation. The team identified a very good opportunity to convert a large 100% fresh air system to recirculation. Within six months, the first site assessed delivered €120,000 ($130,000) of annual savings by implementing only some of the identified projects. This reduced annual CO2 emissions by approximately 400 tonnes.

The strategies employed included:

- Air change rate reduction
- Demand-based ventilation based on occupancy and temperature demand
- Converting 100% fresh air systems to recirculation
- Switch-off and setback (turndown) during unoccupied periods
- Return air humidity control

The total estimated annual savings from all projects with the potential to pay back investment in less than one year was €180,000 ($200,000). The site continues to implement the remaining opportunities and has not yet assessed their results.

Compared to the European site, the US pilot site consumed much more energy, in excess of 70 GWh per year, of which approximately 60% was attributed to HVAC consumption. The US site had an ongoing asset renewal program that identified integration of sustainability opportunities to enhance the business case. Challenging current standards and design approaches led to a range of additional options with total savings of almost $500,000 per year, with a simple payback of 2.5 years.

CONCLUSION

These two real-world examples demonstrate that effective management of resources (electricity, fuel, and water) can have a major, positive impact on sustainability and operational cost efficiencies. It is simply good business sense to make efficient use of all resources. It is no longer acceptable for any organization to continue to operate in a wasteful way. The public and market expectations are that major corporations lead by example and set high standards, with investors now taking account of a company's ability to mitigate the impact of climate change.

Companies A and B are reaping the rewards of their investments in the form of tangible economic and strategic benefits. Many other pharmaceutical companies are also taking positive steps in the right direction. But the pace of change in this area is much slower than the accelerating demands for increased sustainability performance. The solutions that Companies A and B are employing are not "magic"—they are based on sound engineering practice and data, are well proven, and lead to predictable outcomes.

Finally, undertaking an energy or water audit/assessment and implementing a selection of easy initiatives does not mean you have "done" sustainability. Sustainable development should be considered a journey of continuous improvement, with a goal to integrate sustainability thinking and practice into business as usual. This is a fast-changing field: Technologies are becoming cheaper and better; energy and water costs are rising; and company business models changing. The cumulative effect of these forces can dramatically change the economics of efficiency projects from one year to the next. The best performers know this and employ the plan-do-check-act cycle in their energy- and water-efficiency audits on a three-year rotation.

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Keith Beattie is a Director with Energy Efficiency Consultancy Group Limited (EEC02), a specialist life sciences energy-efficiency consultancy with an expertise in laboratory and pharmaceutical cleanroom sustainability solutions. He and his team use their technical expertise to help clients such as AstraZeneca, Bayer, Eli Lilly, GlaxoSmithKline, Pfizer, Sanofi, and others apply best practices and innovation to reduce energy costs and maintain or improve safety and quality compliance. A leading practitioner in his field, Keith is a member of ISPE's global HVAC Sustainability Community of Practice Steering Group. He is also a member of the ISO TC209 Committee and has contributed to the development of the ISO 14644 standard for cleanrooms and associated controlled environments, as well as other standards, training, and code of practice guidelines in the discipline. Keith has been a member of ISPE since 2013.

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IMPLEMENTATION OF A FORMAL ENERGY-EFFICIENT DESIGN PROCESS

By Aoife Hamill, BEng, MSc, John Hanley, PhD, MPhil, CEng, and Vincent Lane, MSc Eng

Sustainability is a key principle for pharmaceutical companies in 2020. However, translating corporate goals into meaningful improvements can be a challenge, particularly when competing factors such as complex technical requirements or ambitious project schedules are involved.

This article describes a formal energy-efficient design (EED) process that has been in use across all industries in Ireland since 2014 and addresses the benefits of integrating this type of study into the design process. Improving efficiency in a highly regulated environment can be a challenge, but companies in even the most regulated industries in Ireland (e.g., pharmaceutical, biopharmaceutical and semiconductor manufacturers) are adopting the methodology.

This article was derived from the authors' experiences across many projects and in the development of the Irish standard I.S. 399 [1], which establishes EED as a management system (complementing ISO 9001 and ISO 50001). It provides companies with a robust strategy for delivering energy, environmental, quality, and competitiveness objectives.

WHAT IS EED?

An EED study is a plan-do-check-act management method, much in the same way ISO management standards are; however, an EED study can be applied by an organization for single projects or it can be used on an ongoing basis. The philosophy at the core is to benchmark the asset being procured, built, or retrofitted from an energy standpoint and to try to reduce energy use in a practicable and affordable way.

The EED methodology works well for organizations that are used to management systems–type thinking even if they do not have formal certification.

When the project team adheres to EED principles early in the project timeline, this often leads to significant capital savings, which, in some instances, can be greater then the energy savings from more efficient operation. A further benefit of EED is that it often delivers improvements in plant throughput. For example, heat-recovery projects, especially when applied to the main process, can deliver reductions in heat-up and cool-down times in addition to energy savings.

The challenge and analyze parts of an EED study are analogous to a hazard and operability (HAZOP) study—a methodical, logical process with clearly defined steps and outcomes.

EED IN IRELAND

In Ireland, EED for industry has been developed by the Sustainable Energy Authority of Ireland (SEAI) over the course of the last 14 years. It was originally intended as a check on the project design from an energy- and water-consumption perspective.

Published in 2014, the Energy Efficient Design Management standard I.S. 399 [1] was developed by SEAI, the National Standards Authority of Ireland (NSAI), and energy-efficiency industry experts. It helps raise energy issues early in investment projects and aims to control energy consumption across the project's life cycle. The I.S. 399 approach can be applied in all sectors, organizations, and projects.

Like other energy-management system standards, I.S. 399 certification is possible but not obligatory. Some organizations get I.S. 399 certification to demonstrate they have implemented an energy-management system; others decide to implement the standard solely for the benefits it provides.

In Ireland, implementation of the EED process in line with the SEAI Excellence in Energy Efficiency Design (EXEED) program [2] supports funding of energy-saving measures in large capital projects. SEAI has formally run the EXEED program since 2016. Before then, EED was implemented by a small group of companies (e.g., Pfizer, Novartis, Leo Pharma, Astellas) on a project-by-project basis.

Table 1: The effects of starting EED at different project stages.

	Project Stage	Typical Team	Comment
1	URS	EED team, designers, and client	Highest impact for lowest capital cost
2	Precontract	EED team, designers, client, and supplier	Still good commercial leverage with preferred supplier
3	Postcontract/detailed design stage	EED team, designers, client, and supplier	Usually carried out at piping and instrumentation diagram (P & ID) finalization/HAZOP stage

The Irish Environmental Protection Agency Act of 1992 requires companies to adhere to the use of best available technology to reduce or eliminate emissions from an activity, and the use of EED complements this requirement.

WHEN IS EED APPROPRIATE?

EED is appropriate in the following scenarios:

- There is significant energy use.
- There is planned investment that will result in energy consumption.
- Improved corporate image and credibility among customers, clients, and stakeholders are desired.
- There is planned investment that will result in an asset consisting of significant amounts of embodied energy in its manufacture.
- Value engineering is planned (EED complements this process).

WHEN IS THE RIGHT TIME TO COMPLETE EED?

The earlier that EED is implemented for a project, the greater its potential impact on both capital and life-cycle costs will be (see Table 1). Ideally, EED should commence at the user requirement specification (URS) stage and be updated continually as new information becomes available.

It is important to note that the EED expert (a person competent in the EED process, technology, and target areas of the project) does not need to have all the information (i.e., a fully detailed design) to have a positive impact. The first energy-balance evaluation is often approached as a Fermi problem to determine the magnitude of energy consumption and demand, and to identify the significant energy users. This allows progression to the challenge and analyze steps in as short a time frame as possible to allow the maximum number of opportunities to be included in the project scope. Refinement of the energy-balance study can then follow, and the energy-savings register (a live document) can in turn be updated.

OTHER SUSTAINABILITY PROGRAMS

Leadership in Energy and Environmental Design (LEED) and Building Research Establishment Environmental Assessment Method (BREEAM) are well-known rating systems for the certification of sustainable buildings. LEED was launched by the US Green Building Council in 1998 and has become increasingly popular internationally, including in Ireland [3].

Because these rating systems were designed for construction of sustainable buildings, their processes do not include detailed process interrogation. For example, using LEED will help justify using the most efficient chiller in its class, but the LEED process will not lead to the question of whether glycol at –30°C is actually required. The expertise at the core of LEED is in construction, whereas the leaders of an EED project will have expertise in the specific process area of the project. There is no reason that EED and LEED cannot be used for the same project as they have very different areas of focus.

RENEWABLES AND EED

Renewable (and low-carbon) energy options should be reviewed after the initial design for energy performance review is completed (i.e., once all the opportunities that will reduce the asset's energy consumption have been identified and the key ones put in scope); then, the most appropriate renewable energy technology can be selected and sized. If the order of these steps were reversed, the renewable selection might be unsuitable (e.g., biomass steam boiler instead of hot water heat pump/solar) or too big (if the baseload is substantially reduced, the turndown is not enough in the renewable technology and inefficient operation ensues).

STEPS IN THE EED PROCESS

The key stages of the EED process are outlined in Figure 1.

Asset Definition

The asset being analyzed in the EED process should be well defined and encompass all energy services associated with the project (i.e., desired outcomes that necessitate the consumption of energy). Also, where possible, it should be defined by a physical boundary. The defined asset can be extended beyond the specific project (e.g., it could extend to a whole building or site rather than the room in which new equipment will be installed).

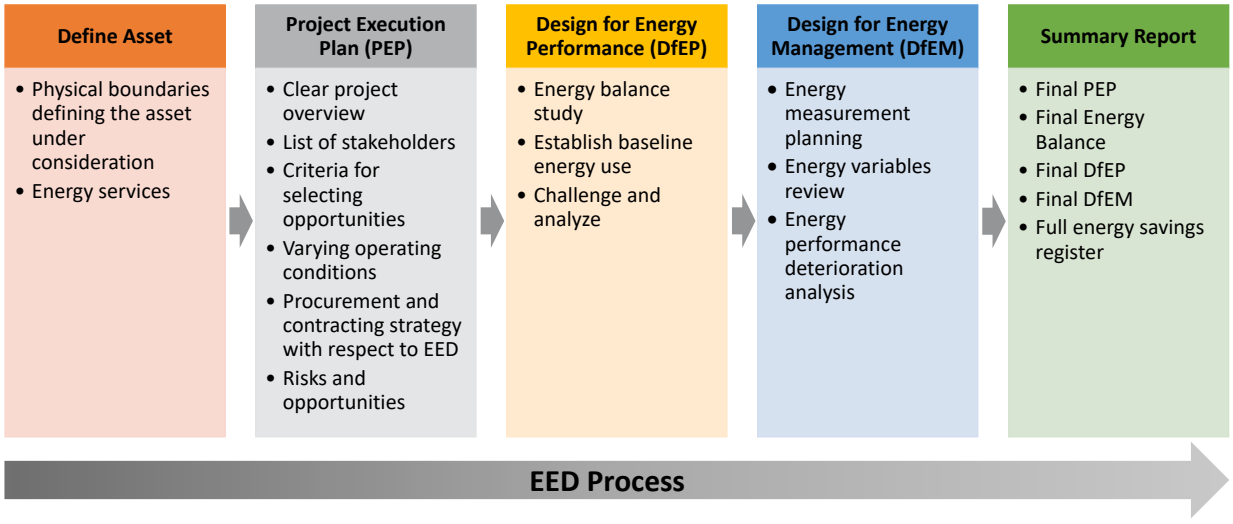
Project Execution Plan

The project execution plan (PEP) is a revision-controlled document that provides a clear overview of the project. It should contain the requirements for design for energy performance and energy management, and list the EED project objectives and requirements for energy measurement, monitoring, and reporting.

The PEP presents an initial EED assessment of the project, including:

- Project timelines for the delivery of EED objectives, with a schedule of meetings or reviews where the overall project design will focus on EED

Figure 1: EED process steps.



- The requirements for lines of communication between the EED owner, expert, and project design team as well as other interested parties
- Varying operating conditions
- Criteria for identifying significant energy users
- Criteria for determining if EED opportunities will be incorporated into the project scope and design, and how they will be proven to be successful
- Criteria for how the procurement and contracting strategy will support EED
- Reference national policies or other mechanisms that could support the viability of energy performance opportunities
- Risks and opportunities related to the project

In particular, the list of identified risks and opportunities is a useful precursor to the challenge and analyze process. This analysis is the first chance to challenge the process design and is the earliest point in the process where meaningful change and the benefits of EED can be achieved.

Design for Energy Performance

Design for energy performance (DfEP) is a process comprising an energy-balance study stage, a challenge and analyze stage, and an implementation stage for design projects.

The energy-balance study should be completed at the URS stage and updated continually as new information becomes available. It provides a baseline against which the EED savings are usually recorded, and it should use whatever information is available to maximize return on the EED effort. The point at which the baseline is taken depends on the type of project (e.g., Greenfield, Brownfield, or replacement) and at what stage EED is implemented (e.g., pre- or post-URS, pre- or postcontract). In the analysis, the process is reviewed, and significant energy uses are identified—these will provide the focus for the challenge and analyze stage.

When carrying out the energy-balance study, the challenge and analyze phase should be kept in mind. Initial questions may concern the following issues:

- Storage—thermal storage, battery storage, etc.
- Heat recovery
- Plant turndown
- What grade of utility is required?
- What is the energy service for the project?

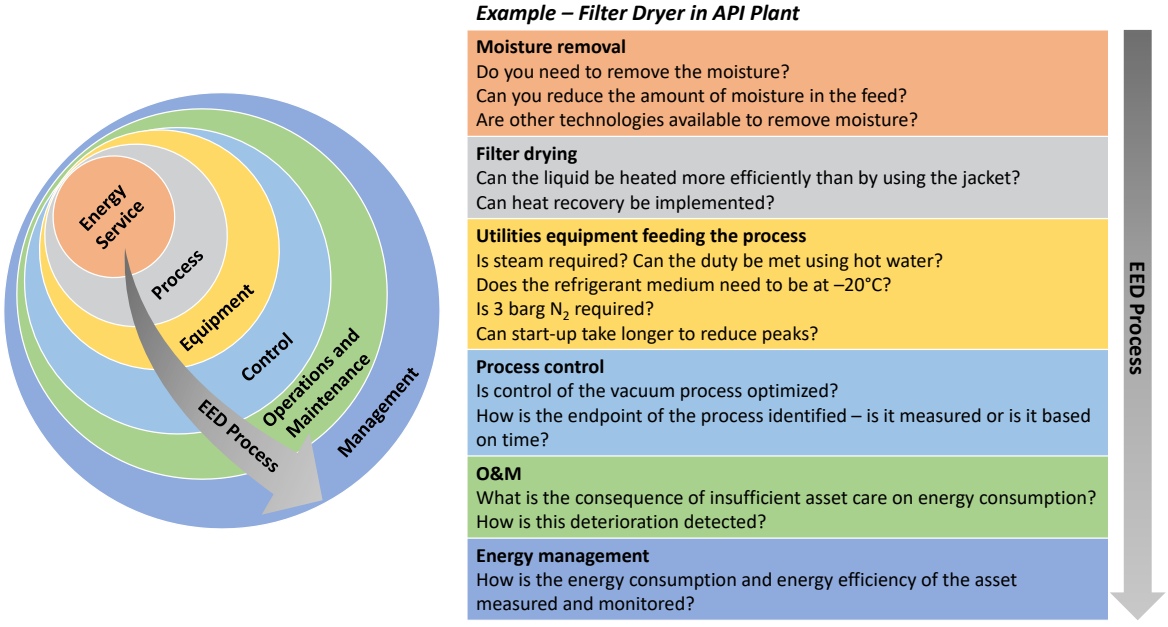
Identifying the correct energy service takes a particular skill set or mindset. The challenge and analyze work builds on the outputs from the energy-balance study. It is ideally completed as early as possible, over the course of several workshops. For each significant energy use, the energy service is established and then challenged as per each layer of the Venn diagram (Figure 2). The process and equipment layers could potentially have Venn diagrams of their own if it is deemed appropriate to analyze the system to this level of detail.

Key questions in the challenge and analyze process are as follows:

- What is the energy service?
- How can the energy service be met?
- What are all the energy uses and energy sources?
- What are the significant energy uses?
- What are the expected running hours?
- What is the annual consumption?
- What is the peak demand for each utility?

The energy-savings register is output from the challenge and analyze stage. The energy-saving opportunities are then assessed and

Figure 2: Energy Venn diagram (per I.S. 399) and filter dryer example.



accepted or rejected by the stakeholders. The best EED analysis ensures opportunities can be disseminated outside of the project group to the relevant stakeholders.

Opportunities selected for implementation should be reviewed and integrated into the design, construction, and commissioning project stages.

Design for Energy Management

The aim of design for energy management (DfEM) is to ensure that best practices in energy management are included at the design phase. DfEM ensures a systematic approach within the design life cycle to manage energy consumption in operations and is intended to support the energy management requirements of ISO 50001.

DfEM should broadly take place in the same timeline as DfEP. DfEM consists of energy-measurement planning, energy-variables review, and energy-performance-deterioration analysis.

Energy-measurement planning defines requirements for energy measurement and reporting and an energy-metering plan to deliver these requirements. This can be used to form the basis of measuring energy performance indicators (EnPIs) for project validation and postproject tracking (e.g., ISO 50001 management system).

Some common mistakes in energy-measurement planning include:

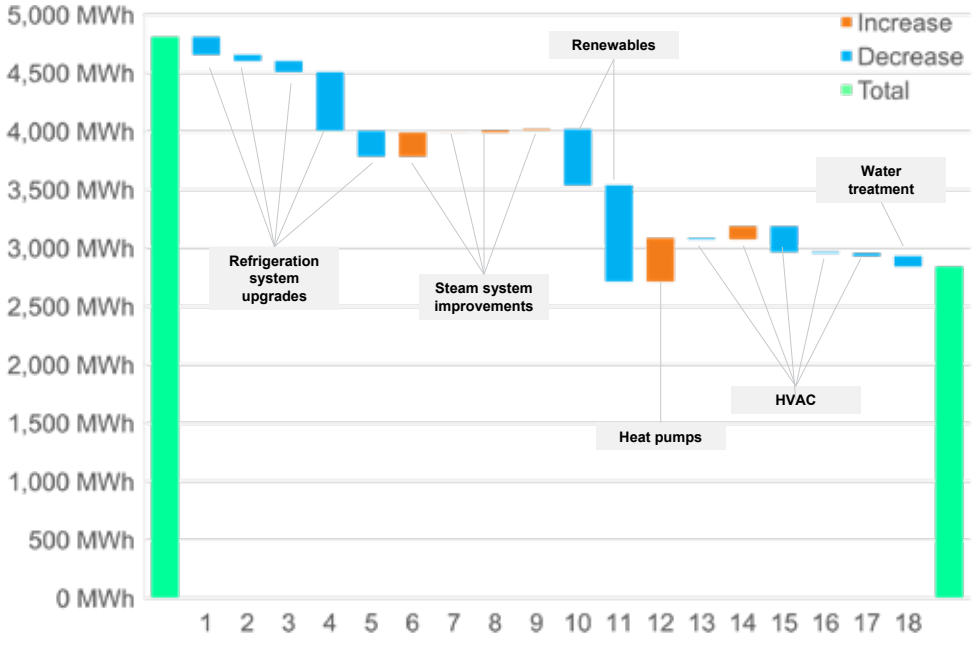
- Setting EnPIs and key performance indicators (KPIs) that are difficult to measure
- Basing EnPIs on peak plant output even though the plant never achieves that peak
- Selecting meters with insufficient accuracy or turndown
- Not considering parasitic load from services
- Not considering heat from pumps into liquid, which has a negative impact on cooling consumption
- Not considering heat load from lighting into the environment
- Not setting benchmarks for "baseload" operation
- Potentially missing the opportunity for economy mode
- Using too many meters, which makes analysis cumbersome

An energy-variable review of the significant energy uses is completed to understand how energy performance is affected by varying operating conditions. An energy variable is defined as a "quantifiable variable that impacts energy performance" [1]. These variables include production parameters (production, volume, production rate), weather conditions (outdoor temperature, degree days), operating hours, and operating parameters (operational temperature, light level). In this review, the design is challenged to ensure that it will operate efficiently under expected or planned variability in operating conditions.

Energy-performance-deterioration analysis examines the potential for deterioration in energy performance during operations and ensures that appropriate measurement and mitigation of this potential deterioration shall be considered during the design stage. Examples of deterioration include fouling in heat exchangers, blocking in HVAC filters, and bearing wear. The output of this analysis may include design changes, metering, and operations and maintenance (O&M) procedures.

Ideally, the outputs of the DfEM are implemented in same time

Figure 3: Electricity waterfall graph.



frame as those from the challenge and analyze stage, and the outputs are captured in the energy-savings register.

Summary Report

The EED summary report should include the following sections:

- Executive summary
- Project description and asset definition
- Comparison of the EED design process to baseline
- Energy-savings register, noting opportunities identified and which opportunities were implemented
- Savings achieved or projected

The report appendixes should include:

- Final PEP
- Final energy-balance study
- Final DfEP
- Final DfEM
- Energy-savings register

CASE STUDY I: API PLANT

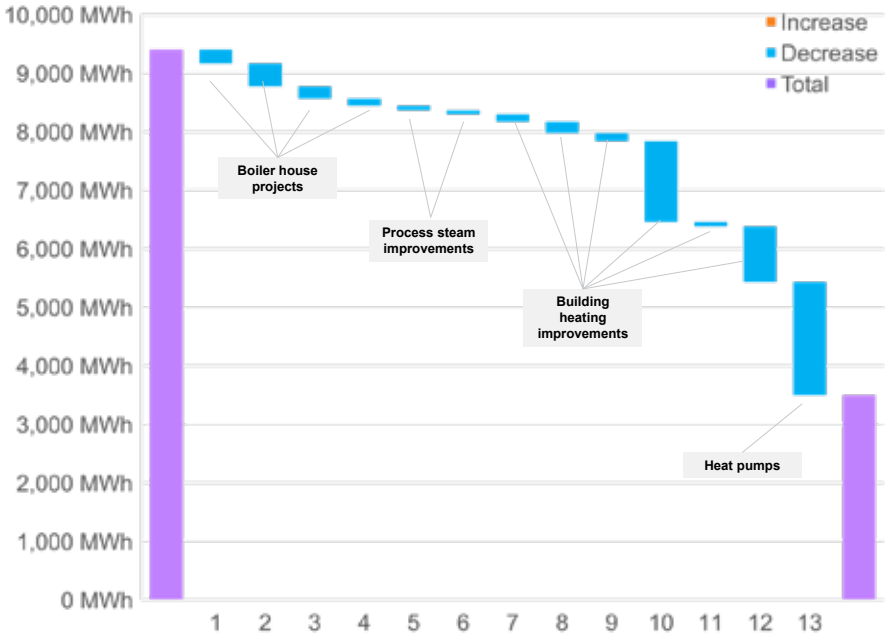
In 2019, an EED study was completed for an active pharmaceutical ingredient (API) plant in Ireland. The asset was defined as the entire site, including all production and nonproduction buildings and utility systems. The aim of the study was to provide a framework to ensure energy efficiency was maximized for upcoming capital projects.

An energy-balance study was completed for the site and two challenge and analyze sessions were held. Opportunities that seemed to be feasible were scoped and costed for review by site management.

The feasible electrical and thermal savings identified are represented in waterfall graphs (Figures 3 and 4, respectively). The initial baseline (annual energy usage) is shown as the bar on the left, and the incremental change associated with implementing each opportunity is shown. The bar on the right side is the calculated site baseline if all opportunities were implemented. In some cases (e.g., introduction of a heat pump or changing from a steam-driven condensate return pump to an electrically driven one), a thermal energy–saving opportunity will result in an increase in electricity consumption. These increases are also included in the waterfall graphs.

Refrigeration system improvements (including a more efficient plant and a control upgrade) are expected to result in a 20% reduction in site electricity consumption. Chiller replacement is under consideration for the site because the present refrigeration system may be obsolete, but the EED exercise identified several refrigeration-related efficiency measures that would have a substantial impact on site energy use. A suitable heat sink (suitable baseload, physically close to the chillers, and already using hot water as a heating medium) has been identified for a heat pump, which can be installed in conjunction with the new refrigeration system. Thermal savings of 20% for the site are

Figure 4: Thermal energy waterfall graph.



expected from this upgrade. The overall refrigeration capacity that will be installed is likely to be reduced as a result of the study, which will lead to a capital saving.

The plant currently uses glycol at –25°C for all process cooling. The requirement for this temperature was challenged. The lowest temperature process application on site at present is –3°C. The annual saving available from moving to a higher-temperature system was estimated at €120,000. In practice, this change may be difficult to achieve—for example, additional heat transfer area may be required to fulfill the same process loads, and there may be additional validation requirements. The scale of saving, however, means that this is something that will be explored prior to any refrigeration upgrade.

Boiler house upgrades (metering upgrade, automatic firing control, economizer) are expected to result in a further 10% thermal energy saving for the site. One of the two boilers is maintained on "hot standby" to quickly provide steam in the event of an issue with the lead boiler. The energy cost for this was calculated to be at least €6,000 per year. An alternative recommended for consideration was the installation of a steam generator, as that type of generator can provide steam from cold start-up (assuming a charged hot well is available) in under five minutes.

If all the opportunities were implemented, site energy usage would be reduced by more than 50%. Suitable opportunities will be selected based on practicality of implementation, capital cost, carbon saving, and investment per tonne of carbon saved, and in line with the site's strategy. The site masterplan will be updated to include these projects.

CASE STUDY 2: TABLETING PLANT

In 2017, I.S. 399 was implemented for a tableting plant in Ireland as part of the development of its new pilot plant facility. The company's stated rationale for the EED project was as follows:

- To use the methodology to ensure that new infrastructure is efficient and low cost to run
- To use the project as a way to test out the methodology so that perhaps it can be used in future projects and/or become a corporate standard for new capital expenditure projects
- To ensure that the pilot plant is efficient, which will allow it to be fed from the existing site utilities, which (for some services) were almost at maximum capacity

The pilot plant was built in a corner of the existing facility that was fallow and was to be supplied with the existing utilities. A meeting took place during the predetailed design phase to discuss the impact of this on the current facility. The EED project looked at the following utilities: chilled water, low-pressure hot water (LPHW), hot and cold process water, purified water, and ventilation (HVAC).

In addition to applying the principles of EED and I.S. 399, the goals of the project were as follows:

- To assess the impact of the pilot plant on the existing utilities

- To limit the pilot project's impact on these utilities by using the principles of EED
- To ensure that staff understand the I.S. 399 process, and to be able to replicate this process, if desired, in future capital expenditure projects

The designer completed a high-level demand estimate for the pilot plant's utility consumption, and this was scrutinized in detail as part of the energy-balance study.

The calculated annual energy-consumption figure included thermal energy (LPHW, steam, and clean steam) from gas consumption and electrical energy consumed directly by process equipment and indirectly through utility provision (purified water, process water, compressed air, and chilled water).

In addition to this, a study of the baseload energy consumption was also completed. A large part of the energy consumption in the baseload design was found to be the consumption outside of production hours. Thus, one of the main interventions suggested and implemented was a setback mode for nights and non-production weekends, while still allowing the plant to operate within the GMP remit.

A large part of the exercise was the DfEM process, a review of the energy variables and energy-performance-deterioration analysis. In addition, it was important that all the utilities' consumptions and demands were metered and visible for staff to understand the impacts of the extension.

Energy efficiency and lifetime cost were considerations in plant selection, and optional features offered in tenders from prospective contractors were assessed using the most economically advantageous tender (MEAT) criteria.

Factors that determined whether an EED opportunity was progressed included:

- Simple payback (anything with payback of five years or less will be subject to detailed assessment)
- Health and safety
- Throughput (e.g., if the opportunity leads to improved operational efficiency)
- GMP requirements

The identified opportunities that qualified under these criteria had thermal savings of 148,000 kWh (43% steam saving, 57% hot-water saving) and electricity savings of 104,000 kWh. The annual operating cost savings were calculated as €17,000. The cost of implementation (largely associated with the additional automation scope) was €67,000, and the calculated payback was four years.

CASE STUDY 3: TOPICAL PRODUCTS MANUFACTURE, FILLING, AND PACKAGING PLANT

In 2008, an EED study was carried out for a planned combined heat and power (CHP) project. The initial proposal was to install a CHP system with electrical output capacity of 2 MW and providing heat and cooling (using a new absorption cooler) to the process.

One of the outcomes of the challenge and analyze stage was that onsite measurements were carried out to validate the existing heating and cooling baseloads, which had been used in the design.

The outcome of the EED study was that electrical capacity of the system was reduced to 1 MW because the thermal demands used in sizing were overstated. Had this study not been completed, the plant would have run inefficiently after installation because all the heat would not have been used.

Capital savings of more than €500,000 were achieved through use of the EED process.

EXPERIENCE IN OTHER INDUSTRIES

Table 2 summarizes selected opportunities identified in recent EED studies in other industries for sites in the EU and in Africa.

CONCLUSION

Although it is preferable to start EED early, carrying out EED at any stage has always been found to yield benefits, even on smaller projects. It can be difficult to ensure the EED process is followed strictly in some circumstances (e.g., if a project has an accelerated schedule and opportunities to reduce energy consumption have been missed). However, once the process starts, there are usually opportunities to be unlocked. Barriers that may need to be overcome to maximize EED benefits can include:

- Specifications
- Timelines
- Budgets
- Contracts
- Perceived "hassle" factor for client or supplier

From experience, the following factors are important for the success of EED for a project:

- Having a client sponsor with influence on capital spending is a key criterion for success of EED in any project.
- It is important to review the register of opportunities with the project manager before formally issuing the study. The project manager will ultimately be held to account for any proposed savings, so they need to be comfortable with the calculations and assumptions used.
- EED principles should be applied to a project as early as possible. Applying the principles early in the project life cycle affords greater opportunity to significantly impact the energy service. Sometimes, this can be difficult in practice—many projects do not get engineering funds approved until the business case has been approved, and by the time this happens, the URS may be "locked down."
- Once the supplier understands EED, they are generally positive—briefing them in advance of a workshop is a good idea.
- Capturing the EED outputs from projects and applying them to subsequent projects is important. By doing this, EED becomes as routine an element of the project life cycle as a design risk assessment or HAZOP.

Table 2: Sample opportunities from EED studies in other industries.

Industry	Key EED Opportunity	Annual Energy Saving	Capital Investment	Other Impacts
Distilling	Use alternative source of cooling for process cooling	26.5 MWh electricity 180 tonne CO_2	€300,000 saving	Security of cooling supply Instant cooling start-up Reduced noise
Semiconductors	Dual setpoint chilled water	398 MWh electricity 212 tonne CO_2	€1,000,000 investment	Greater redundancy
Brewing	Modify heat recovery to maximize benefit, design steam out of conversion process	5,000 MWh thermal energy 1,300 tonne CO_2	€600,000 investment	3 tonne/hour reduction in steam demand Water saving of 30,000 m^3/year
Shipping	Redesign of reefer metering and reporting	300 MWh electrictiy 385 tonne CO_2	€700,000 investment	Allows inefficient container cooling to be easily identified
Packaging	Alternative sourcing of raw materials and air recuperation from bottle blowing	200 MWh electrictiy (EED study showed that raw material selection had the biggest impact on overall line energy consumption)	€100,000 investment	Changes in supply chain strategy

- The key process requirements (energy services) must remain a priority. Opportunities must be practical and not have a negative effect on the required energy service.
- Peak calculations and future expansion allowances should be challenged to make sure that the right-size process and utilities will be installed.

Each of the steps described as part of the EED process is common sense and part of good design practice; however, without a formal process, it is difficult to ensure that each will be completed for a project.

The advantages of implementing a formal EED process can be substantial, ranging from large capital, energy, and carbon savings on the project itself to potentially significant opportunities outside of the core project scope. The process provides a useful cross-check and due-diligence tool for any project.

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BIOREMEDIATION OF PHARMACEUTICALS

By Bilgen Yuncu, PhD, PE

Medical treatments and pharmaceuticals are indispensable in improving quality of life. In recent years, however, pharmaceutical compounds have become a significant group of environmental pollutants, shown to pose risks to human health and have adverse environmental effects.

PHARMACEUTICALS AS POLLUTANTS

Pharmaceuticals have been detected worldwide in wastewater, surface water, ground water, and soil. North American, Canadian, Japanese, Korean, and European waterbodies contain relatively low amounts (nanograms to micrograms per liter) of various pharmaceutical compounds such as antibiotics, painkillers, hormones, and anti-inflammatory and chemotherapeutic drugs. About 700 different pharmaceuticals were detected in the aquatic ecosystems of 71 countries, according to aus der Beek et al. [1]. These compounds enter the environment as byproducts of human and veterinary use through manufacturing waste, human excrement into septic tanks/sewage systems, animal excrement on soil combined with surface or agricultural runoff, household and hospital solid wastes that end up in landfill leachates, and disposal of unused or expired medicine through sewage systems and landfills (Figure 1) [2].

REMEDIATION METHODS

Among the major contributors of pharmaceutical compounds found in the environment are wastewater treatment plants (WWTPs). Although some compounds (e.g., acetaminophen and caffeine) have been reported to be removed by WWTP processes, most pharmaceuticals reported in the literature are not completely removed by WWTPs, which means they are being discharged into the environment in the treated effluent.

Treatment of pharmaceuticals can be a challenge due to the large quantity, their complex and highly stable chemical structure, and their hazardous nature. Currently available physical and chemical remediation methods—including coagulation/flocculation, filtration, and advanced oxidation processes such as application of ozone, hydrogen peroxide, and ultraviolet light—are not always applicable, can be cost-prohibitive, and may produce secondary pollution. With the increased detection of pharmaceuticals and their metabolites in the environment, the need for more efficient and low-cost remediation technologies such as bioremediation is becoming apparent.

BIOREMEDIATION

Bioremediation is the use of naturally occurring or genetically engineered microorganisms (bacteria and fungi) to consume and break down pollutants in contaminated media, including water, soil, and sediment. The US Environmental Protection Agency defines bioremediation as "an engineered technology that modifies environmental conditions (physical, chemical, biochemical, or microbiological) to encourage microorganisms to destroy or detoxify organic and inorganic contaminants in the environment" [3].

A well-established technology, bioremediation has been used for decades as an effective method of degrading various forms of chlorinated solvents and petroleum hydrocarbons in groundwater and soil. Bioremediation can be accomplished through natural attenuation, biostimulation, and bioaugmentation in groundwater and soil. Natural attenuation corresponds to the natural remediation capacity of a microbial community present in a contaminated site to achieve contaminant removal. Biostimulation consists of adding nutrients or electron acceptors to encourage indigenous microorganism growth and thus enhance the rate and extent of biodegradation of target contaminants. Bioaugmentation is the inoculation of contaminated sites with strains or microbial consortia (a group of two or more different microbial species that work together) with biodegrading capacities when an appropriate population of microorganisms does not exist or is too slow to stimulate complete remedial of the existing contaminants.

Over the past three decades, bioremediation has been widely studied in environmental biotechnology, and it has been shown that microbial communities in various environments can metabolize a wide variety of chemicals into environmentally acceptable end products. For example, although conventional WWTPs are not designed to remove micropollutants such as pharmaceuticals, the potential for attenuation and degradation of these compounds during the biological treatment processes has been investigated in several studies [2, 4, 5]. A manufacturing facility in Arkansas contaminated with chlorinated solvents implemented bioremediation

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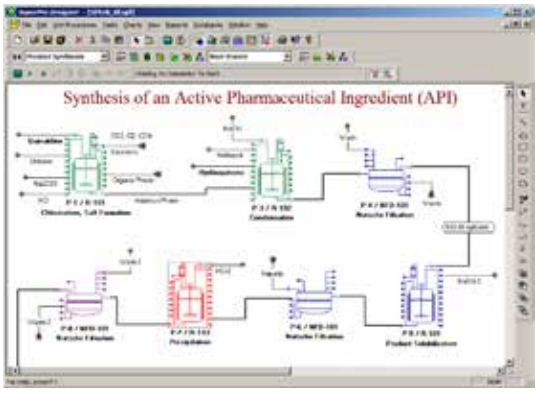
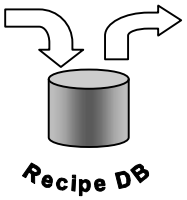
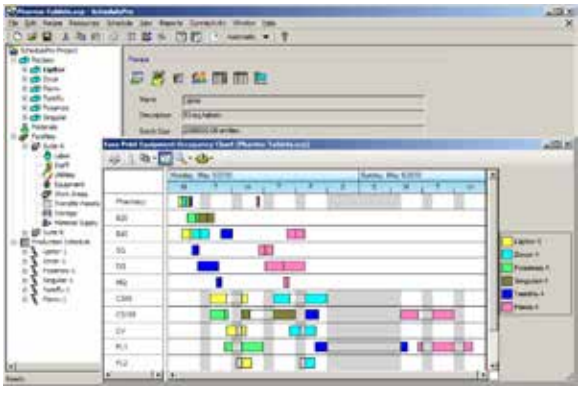


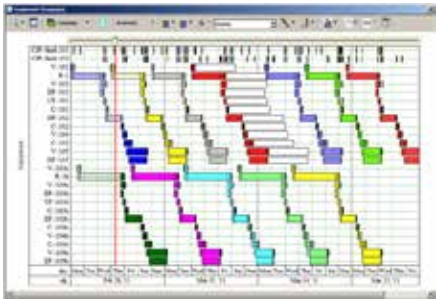
Use SuperPro Designer to model, evaluate, and optimize batch and continuous processes



SchedulePro®

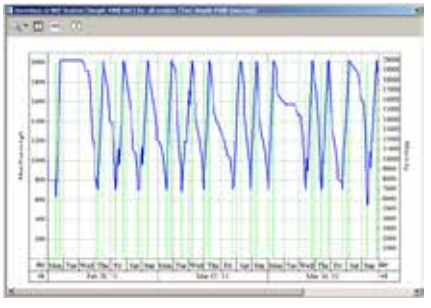


Migrate to SchedulePro to model, schedule, and debottleneck multi-product facilities



Easy production tracking, conflict resolution and rescheduling

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



Managing inventories for input, intermediate, and output materials

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

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

Visit our website to download detailed product literature and functional evaluation versions of our tools

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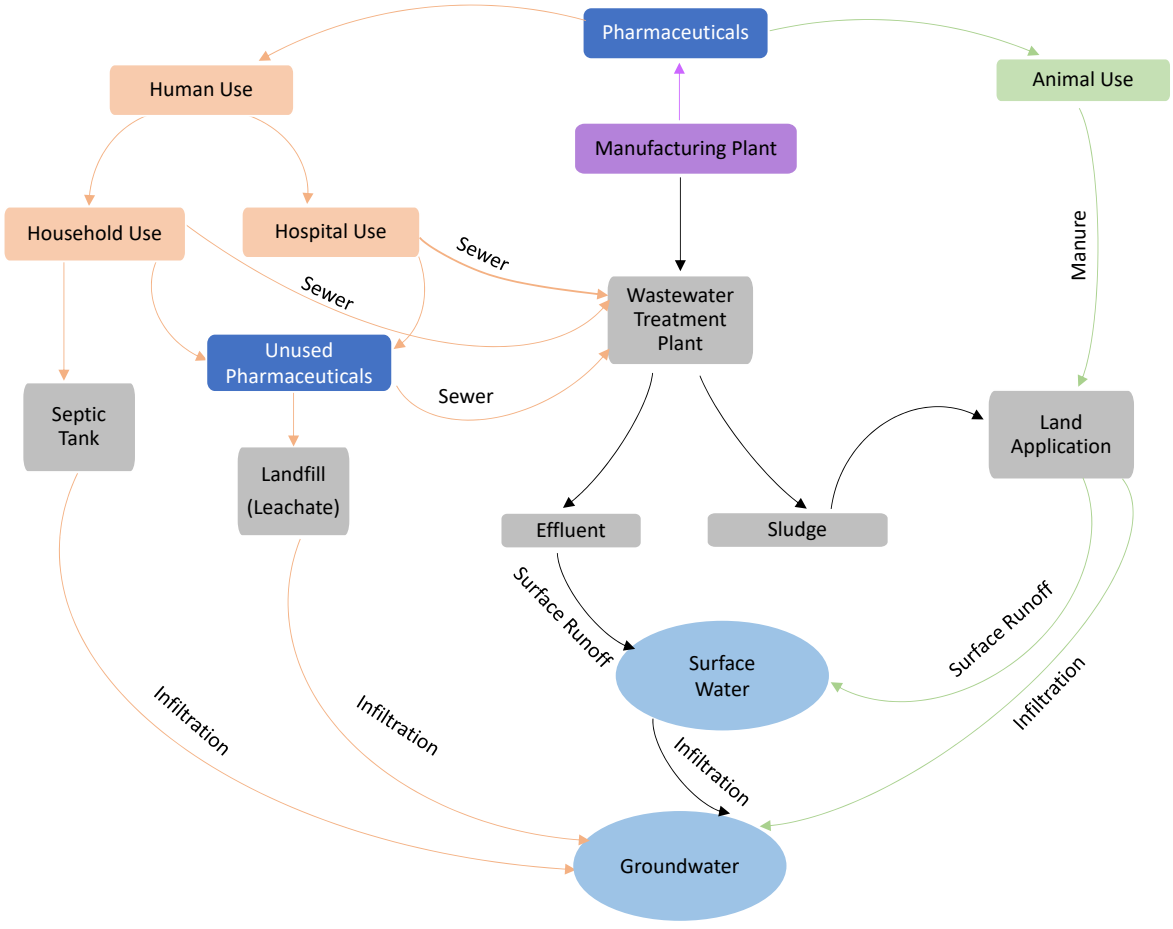
Intelligen also has offices in Europe and representatives in countries around the world

Figure 1: Sources of pharmaceuticals in the environment. Adapted from reference [2].



through subsurface injection of emulsified vegetable oil as an electron acceptor (biostimulation) and reduced contamination by more than 90%. Similar bioremediation strategies could be effectively applied to pharmaceutical waste streams and at contaminated sites.

Numerous studies have documented the use of microorganisms and bacterial isolates to break down pharmaceutical waste in WWTPs and in the environment, respectively [6–8]. One study [9] evaluated the treatability of bulk drug pharmaceutical wastewater using an activated sludge reactor with acclimatized mixed consortia by integrating with chemical coagulation as the pretreatment process. An 86.6% reduction of chemical oxidation demand (COD) was achieved in pharmaceutical industrial wastewater with the help of the biodegradation process. In another study, modified activated sludge and multistage biofilm processes with microbial consortia involving fungal and bacterial cultures for treatment were found effective in removing toxicity in wastewater from a pharmaceutical company in Sweden [10]. Additional research, especially on the isolation and characterization of pure cultures for the degradation of pharmaceutical compounds, could provide the necessary insights to enhance the effectiveness of bioremediation of these compounds.

It is essential to understand the biological transformation of pharmaceuticals and determine the biological mechanisms and degradation pathways responsible for removal to accurately track the ultimate environmental fate of these compounds, and hopefully lead to improved removal of them. Significant progress has been made in understanding the role of microbial metabolism in the transformation and removal of pharmaceuticals in WWTPs and other aquatic systems.

CHALLENGES

Although bioremediation could be a cost-effective technology for removing pharmaceutical waste, biodegradation of pharmaceutical compounds can be challenging, given their diverse and complex chemical structures and relatively low environmental concentrations. Some pharmaceutical compounds, such as ibuprofen, are readily biodegradable, whereas others, such as carbamazepine

and trimethoprim, tend to be recalcitrant. Furthermore, biological treatment methods can be sensitive to changes in environmental conditions such as pH, temperature, oxygen, and nutrient levels, as well as sudden changes in the influent's toxicity levels. These conditions must be optimized and monitored carefully during any bioremediation operation because the treatment's efficiency directly depends on their stability. An uncontrolled environment may result in the transformation of the pharmaceutical compounds into harmful end products.

GREEN APPROACHES

Pharmaceutical waste management can also be improved by using "green chemistry" or "green pharmacy" approaches in which the production routes and entire life cycle of a product are monitored to make them as sustainable as possible by requiring less energy and material, producing fewer undesirable byproducts, or making byproducts easily biodegradable. Many recalcitrant pharmaceutical compounds can now be developed into more biodegradable forms using biologically derived catalysts. Biocatalysts are isolated enzymes and microorganisms that are used as catalysts to produce pharmacologically valuable materials (biopharmaceuticals). Using biocatalysts is not only environmentally beneficial but also cost-effective and therefore more sustainable than using synthetic catalysts.

CONCLUSION

Ultimately, the pharmaceutical industry and those responsible for risk management would be wise to explore bioremeditation strategies to address pharmaceutical contamination in the environment. As the provided examples highlight, bioremediation offers significant advantages and a cost-effective approach, especially when working to remediate contamination at current and former manufacturing sites.

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About the author

Bilgen Yuncu is an Environmental Engineer with Draper Aden Associates, a mid-Atlantic engineering, surveying, and environmental services firm, and she serves as a project manager and remediation group leader. Bilgen specializes in bioremediation strategies of hazardous compounds in soil and groundwater. She is the lead engineer on many of Draper Aden Associates' in situ bioremediation projects. She received her PhD in civil, construction and environmental engineering from North Carolina State University and worked as a postdocto,ral research scholar in the same department. Her PhD work has been mainly focused on taste and odor removal from drinking water by adsorption and ozone oxidation. As a postdoctoral scholar, she conducted research on biodegradation-sorption barriers for munitions constituents. Bilgen holds a North Carolina Professional Engineer license and is a Project Management Professional.

A CAREER OF QUALITY CONTRIBUTIONS:

2019 ISPE Member of the Year Award Recipient, Charlie Wakeham

By Paul J. Cumbo, MS, MLitt

The 2019 ISPE Max Seales Yonker Member of the Year Award was presented to Charlie Wakeham, a data integrity and compliance specialist based in Sydney, Australia, who has played an instrumental role in the development of GAMP®.

Charlie, a Regional Informatics Computerized Systems Validation Consultant with Waters Corporation, is a Chartered Engineer and a Fellow of the Institution of Mechanical Engineers. She holds a postgraduate degree in advanced manufacturing technology (with distinction) from the University of Portsmouth in the United Kingdom. A member of ISPE GAMP® since 1999, she serves on the GAMP® Data Integrity Leadership Team as well as the GAMP® Global Council. She has been a key contributor to documents and guides, and she has offered training and presentations to professionals and regulators around the globe.

Charlie received the ISPE Max Seales Yonker Member of the Year Award at the 2019 ISPE Annual Meeting & Expo in Las Vegas. This award honors the ISPE member who has made the most significant contribution to the Society during the past 12 months.

When *Pharmaceutical Engineering* asked her to reflect on the award, Charlie said that "to actually receive the award felt like a vindication, confirming not only that all my personal time working on GAMP® was worth the sacrifices, but also that I was seen as a worthy contributor to the Society. My GAMP® associates have always been tremendously supportive, and I am so fortunate to work with them, but now the wider ISPE community was granting me recognition. The award ceremony may be long over, but the satisfaction and immense gratitude remain." She also expressed gratitude for the many kind words of congratulations from others in the community. "So many people in my network have reached out to me since the award, and it's been wonderful to have renewed contact with former colleagues and customers."


Charlie Wakeham

A PERSONAL COMMITMENT TO QUALITY

For Charlie, the production of quality pharmaceuticals is a personal matter as well as a professional vocation. She realized early in her career the centrality of her work to her own well-being, along with that of others.

"The very first process system I ever built was destined for a production line making a medication that I needed then—and still need now. It wasn't about protecting some faceless end user. If my process system failed, I would suffer the consequences directly. Since then, I have always understood that every action I take must protect patient safety first and foremost." Today, Charlie remains focused on quality. "I'm at a time of life when a lot of people I know are on blood pressure medications and statins. With concerns about potential carcinogenic effects of nitrosamines in sartans,

for example, it all comes down to the fact that you know somebody who might be impacted."

FROM RACE CAR DREAMS TO FILTRATION SYSTEMS

Charlie's engineering ambitions weren't always quite so solemn. As she explained, chuckling, "I graduated university with a bachelor's degree in mechanical engineering, a master's degree in advanced manufacturing technology, and dreams of working on a Formula One racing team." Soon, however, she realized that those dreams were unrealistic. "You look at the numbers and realize there's a lot of engineering students and not that many gigs in Formula One." And even if she were to have landed one, Charlie acknowledged, "it's also incredibly intense, with weeks and weeks of travel and working through the night. It's not fame and glory. It's just insane, hard work."

As reality set in, she was happy to accept a position with Pall Corporation, where she began building automated filtration systems for pharmaceutical production processes. As a project engineer, she was responsible for the process design, functional specifications, build, testing, and validation of the systems. "That was in 1997, and it was quite soon after that I came across *GAMP® 3*—a tremendously helpful guide to validating computerized systems, which, strangely, could be read back-to-front and upside down." In the UK, her career encompassed working with a wide variety of process systems for fixed plants, lab-scale process equipment, filter integrity testers, and single-use bioreactors. When she moved to Australia, she took on a role with Waters Corporation, where she focused on providing validation assistance to regulated customers implementing informatics software, such as the Empower Chromatography Data System used in many quality control labs in the industry.

The work is "not as sexy as Formula One, but I get to contribute to global health," Charlie said. "It's a contribution to something that matters. I help pharma make better medicines in order for patients to get better therapeutics."

NETWORKING, VOLUNTEERING, AND LEARNING

Charlie's relationship with ISPE has spanned 20 years, beginning with her first ISPE conference in 1999. In 2001, she attended the launch of *GAMP® 4* and her first GAMP® Forum. In 2003, she volunteered to join a GAMP® Special Interest Group (SIG) on testing GxP systems, and taking on that role was transformative. "In reality, volunteering taught me more than I could have learned in 10 conferences, as a SIG comprises industry workers sharing real-life experiences." According to Charlie, her involvement with ISPE GAMP® over the years has enabled her to have a notable impact within her own company and in the broader industry, with a level of reach that wouldn't be possible without ISPE.

Networking has been central to Charlie's ISPE experience. "I met and forged relationships that are still strong today, such as with Kate Samways, the Testing SIG leader who mentored me through other SIGs and nominated me for my first GAMP® committee, and with Karen Ashworth (a true subject matter expert [SME] in process control systems), with whom I would later co-lead the second edition

"I help pharma make better medicines in order for patients to get better therapeutics."

of *GAMP Good Practice Guide: Testing GxP Systems* (published 2012) and work on the *GAMP® RDI Good Practice Guide: Data Integrity—Manufacturing Records* (published 2019). I've had the privilege to serve on SIGs and GAMP® committees with so many of the industry's and ISPE's great key opinion leaders—Michael Rutherford, Siôn Wyn, Chris Reid, Lorrie Vuolo-Schuessler, to name a few—all of whom have not only been mentors to me but also become personal friends and close colleagues within ISPE."

WOMEN IN LEADERSHIP

When Charlie was a university student, she was one of three female engineers in a class of 150 students. "I never felt that being female was a disadvantage," she recalled. "Although I still occasionally encounter pockets of discrimination, my own experience has been that if you are professional and competent, the discrimination fades away. I do, however, strongly sympathize with women who have faced tougher discrimination challenges."

Charlie noted that in 2019 the Global Chair and Secretary of GAMP® and the Chair, Co-Chair, and Secretary of GAMP® Americas were all women. This was "not because of any skewed selection criteria, but simply because the committees appointed the competent and willing volunteers best suited to take on the roles at that time," she explained.

Addressing gender issues more broadly, Charlie said, "I think women are now empowered to enter roles and careers that interest them and, therefore, any prior male bias is ending through natural progression. I do believe, however, that the gender pay gap is a fundamental issue that still needs to be addressed throughout our industry and beyond."

COMPOSITION, QUALITY, AND INTEGRITY

Over the years, Charlie has made her home in a range of locales. "I've had the privilege to live in different places through my life—early years in Scotland and Germany, my school years in the United Arab Emirates, and then my university education and much of my working life were spent in the UK. In 2013, my husband, Kevin, and I, along with our cat, Pippin, emigrated to Australia to explore new horizons."

The unspoiled scenery of New South Wales inspires Charlie and her husband, both amateur photographers, to practice their hobby. Charlie enjoys nature photography the most. She began taking traditional film photographs at a young age, and

> "Integrity comes from the honesty of the data."

transitioned to digital about eight years ago. Whether shooting on film or digitally, her fundamental approach to photography remains the same: "It's about composing an image that captures the feeling of a moment," she said. "Composition is the key—it's what comes in that determines the quality." Notably, these words about quality in image composition are analogous to Charlie's principled focus on quality in pharmaceutical manufacturing.

In her interview, Charlie also emphasized the importance of integrity. "Integrity comes from the honesty of the data," she said. "The oldest maxim in the world is, 'if it looks too good to be true, it probably is.'"

That's one of her concerns about digitalization, in both photography and manufacturing. "There's an immediacy in digital photography versus the delay in the old model—with film, you were more or less stuck with whatever you had. But with digital, you can see the result immediately, and you can tweak it. You have the option to fix some of the flaws in the short term, such as underexposure. But I don't really embrace the massive postprocessing that people do. Images look amazing, but they've lost integrity."

She expressed similar concerns about data integrity in current pharma manufacturing. "Being able to fix an issue in real time is great, because you should get a much higher yield of quality product. But the concern is that there exists the ability to manipulate the data. There are tremendous benefits in terms of process yield and continual improvement possibilities, but we have to be careful. With improved flexibility comes increased risk to data integrity."

When thinking about the benefits and potential disadvantages of digitalization, Charlie frames the issue as a generational one. Indeed, as a self-described "midcareer professional," she seeks to bridge the gap between older and younger workers—and their divergent ways of working. "Veterans of the pharma industry are familiar with working to rigorously defined processes, 'because that's how it's always been done.' Young Professionals [YPs], especially Millennials, have grown up with supreme flexibility—the ability to instantly bring in a new app to solve a problem; to apply a filter or retake a poor photo—without necessarily being accountable for how changes are made. It will take collaboration between these extremes, facilitated by the midcareer professionals, to fully realize the benefits of digital transformation and to embrace and manage flexibility within a controlled framework." This collaboration calls for leadership from people who can combine "old school" quality and integrity principles with an understanding of, and an appreciation for, digital agility.

ADVICE FOR YOUNG PROFESSIONALS

Asked to provide some advice to industry colleagues, and especially YPs, Charlie emphasized the importance of volunteering. "You don't have to be an expert to volunteer, but volunteering can help make you an expert," she said. "For every guide I've worked on, and every conference I've been involved with, I have gained more than I have given. In preparing the guide or presentation content, I have improved my knowledge, which I've been able to share with my networks. And then these networks put me in contact with more SMEs, and these SMEs often became close colleagues and friends."

Charlie is dedicated to helping guide younger colleagues. "When I look at the boost to my capabilities, my confidence, and my career that has come from involvement with ISPE, I know I have to pay it forward. So, to all the YPs in ISPE, the first-time conference attendees, and the want-to-be volunteers who feel anxious that they don't have enough to offer—please speak up, join in, and be part of something special."

THE PATH AHEAD

"To me," Charlie said, "The Fourth Industrial Revolution can be simply represented as joined-up thinking supported for the first time by a level of technology interconnectivity and interoperability that allows us to leverage significant process, efficiency, and quality gains." She described a new era in manufacturing in which the whole picture is visible. "We can see the relationships among the component parts in the process, and the impact any part can have upstream or downstream in that process. For pharma, I believe this provides the opportunity to implement a paradigm focused on maximizing data integrity, product quality, and patient safety. This is a dramatic improvement over the previous focus on compliance for compliance's sake."

Despite receiving the Member of the Year Award, Charlie remains humble. "One person changing the industry is a big challenge, and I don't think I could claim anything close to that. I do hope, however, that the extensive training and consultancy in computerized systems validation and data integrity that I've delivered over the years to regulated companies and health authorities across the Asia Pacific region are of value. I hope I have helped raise awareness of the risks to product quality arising from poor data integrity and, in some measure, helped others see the importance of protecting patient safety."

About the author

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

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FOCUS ON BALANCE:

Profile of the ISPE Delaware Valley Chapter

2019 ISPE Affiliate and Chapter Excellence Award Recipient

By Mike McGrath

As one of the larger and older ISPE Chapters, the ISPE Delaware Valley Chapter (DVC) is admired by other Chapters and Affiliates around the world.

DVC's success was recognized at the 2019 ISPE Annual Meeting & Expo in Las Vegas, where it was awarded the Affiliate and Chapter Excellence Award. In addition, DVC member Emilie Pelletier was one of the authors who received the *Pharmaceutical Engineering* 2018 Roger F. Sherwood Article of the Year Award, and DVC Board Secretary Dennis Gross received the Joseph X. Phillips Professional Achievement Award for his significant contributions to the pharmaceutical industry.

"Our members are our heartbeat," said DVC President Eleanor Small as she spoke about receiving the Chapter award. "This award is recognition of everything we do together, including our contributions to guidance policies and international CoPs. It's about speakers, how our members participate at the Chapter level, and how we do our volunteer work. It really is an all-around award, and it would not have been possible without the collective contributions of all our members."

SUCCESSION PLANNING

Founded in 1982, DVC was the second Chapter created at ISPE. It covers eastern Pennsylvania, southern New Jersey, Delaware, and part of Maryland, a region that is home to a vibrant pharmaceutical and biotechnology sector and several top-tier universities. "I've heard people call this 'Cellicon' Valley. It's a funny play on words, but there really is something to it. The number of start-up companies and the incubator space we have in this area is pretty phenomenal," said Small.

The location within this pharma belt provides DVC access to one of the world's highest-density areas for pharmaceutical professionals. The Chapter currently has close to 900 members, with a high retention rate of 78%. When membership declined slightly in recent years, the Chapter successfully reversed the trend through a program focused on new membership and a simple yet effective effort to email former members whose memberships had expired.

Maintaining continuity while bringing in new people and ideas can be a challenge for leadership of any organization; however, DVC's structure seems to encourage smooth transitions. To become DVC President, a member must first serve on one of the Chapter's seven committees (Programs, Education, Marketing & Communications, Membership, Young Professionals, Students, and Symposium), rise to the position of and serve at least a one-year term as Vice President of a committee, and then serve a one-year term as Executive Vice President. The Executive Vice President succeeds the current President for a one-year term. The President stays on the DVC Board for one year in the Past President role.

VALUE FOR MEMBERS

The DVC annual event calendar is an active one, with three types of activities: education, programs, and member events. The four education events held per year offer in-depth training on various topics for pharmaceutical engineers. "Anyone with a professional engineering license is required to maintain professional development hours, and our education sessions meet all of the professional development hour requirements for PE licenses in New Jersey, Delaware, and Pennsylvania," explained Small. "If members attend all four events, they can earn their 12 professional development hours and stay on the cutting edge while having great networking opportunities."

Programs provide attendees a higher-level learning experience, mostly focusing on hot topics. "These events cover what's new in the market, and sometimes we use them as teasers, where if we see a lot of interest in a topic, we can build an education event from it," said Small.

Although education and program events provide networking/social opportunities for members, member events are the most focused on that DVC benefit. "We want our members to be able to connect on a deeper level," said Small. "We have a holiday party, and we always do an end-of-year event like going to a Phillies [baseball] game, which we often use for recruitment. We also do service events, such as Habitat for Humanity or the Future City Competition, which provide members an opportunity to give back to the community."

On 14 May 2020, DVC will host its Annual Symposium and Exhibition at Lincoln Financial Field, home of the Philadelphia Eagles football team. The event features education opportunities,

Quick facts about the Delaware Valley Chapter

- Founded: 1982
- Region: Delaware Valley
- Membership: 900

OFFICERS

- President: Eleanor Small, PhD, Johnson & Johnson
- Executive Vice President: Marvin Royal, STEQ America
- Secretary: Dennis Gross, MS, PhD, PA Drug Discovery Institute
- Treasurer: Amy Markey, Carisma Therapeutics
- Vice President Programs: Michael DeBellis, Jacobs
- Co-Chair Programs: Sawyer Romich, Hargrove Life Sciences
- Vice President Education: Brendan Bradley, Vanrx Pharmasystems
- Co-Chair Education: Daniel D'Aquila, GlaxoSmithKline
- Vice President Marketing and Communications: Michelle Santoro, CPSM, Skanska USA
- Co-Chair Marketing and Communications: Tieg Murray Rustam, Skanska USA
- Vice President Membership: Laura-Ann Chin, MSc, Genesis Engineers, Inc.
- Vice President Young Professionals: Jenna Eicherly, Laporte Consultants
- Vice President Students: Jon Becker, RPA Engineering
- Vice President Symposium: Jill Clark, CRB
- Co-Chair Symposium: Sandra Bones, CPSM, IPS
- Directors: Michael Faia, Jazz Pharmaceuticals; Greg Sabatino, MBA, Eisai Inc.; Peggy Del Fabbro, M. Davis & Sons; Bill Dugary, Applied Control Engineering, Inc.; Glenn Lawrence, Merck & Co.
- Past President: Kristina Pumphrey, Precis Engineering

a career fair, an academic pathway to ISPE, and networking. "We have a speaker stage, and this year we did a call for abstracts and received a lot of submissions, and we are going to select some good quality talks for our members," said Small.

FINDING BALANCE

When Small became DVC President, she decided on a mantra to follow: balance for better membership value. "We need to balance what we are asking of our members," she said. "I don't want to flood members with emails or have so many events that they can't attend them all. I do want to provide value for the money they are paying for their membership. So, we established a pattern of alternating between education, programs, and member events."

ISPE Delaware Valley Chapter's ISPE Women in Pharma Learning to Lean-In in Today's Business Environment conference on 4 December 2019 in Conshohocken, Pa. Left to right: Moderator Eleanor Small, ISPE-DVC President, Johnson & Johnson Inc.; speakers Kristen Duffy, Chief of Staff, Global Biologics and Sterile Operations, Merck; Laura Flessner, Director, New Venture Insights Lead, GSK; Meryl Towarnicki, President, Genesis Architects; Jing Yang, People and Business Resource Group Lead, Pan Asian Network, Bristol-Myers Squibb; and Rachel Haddock, Vice President Technical, Biopharms and Steriles, GSK.

"We also have to find balance for our volunteers. The last thing you want is to have someone who is enthusiastic and wants to be part of the Board, and then you burn them out in two years. Volunteers are a precious resource and need to be protected. So, by alternating when we do education, programs, and member events, we are also spreading out the monthly responsibilities between our committee members."

Small's other focus has been to improve the Chapter's performance with Young Professionals (YPs) and students. "I brought in two people who have the right skill set and asked them to think outside the box and build things from the ground up," she said. Some YP events have included social get-togethers involving activities such as axe throwing or meet-ups at local breweries. This year, the Chapter will be introducing lunch-and-learn events because DVC's YP survey showed that many members don't want to go to events after work.

On the student side, DVC is taking a different approach by focusing on students at the graduate level and those in the sixth, seventh, and eighth grades; the strategy recognizes that middle school students are at a critical age for deciding whether they will follow a STEM path. "We feel like this is an opportunity to really engage the students and help them make the decision to stay in STEM," Small said.

The Chapter also encourages its members to stay connected with the professional student societies at their alma maters, especially the ones not associated with pharmaceutical engineering. Small's reasoning is that many future pharma professionals are studying other disciplines, such as chemical or mechanical engineering. "We are trying to create adjacent benefits where we participate in career events hosted by professional societies like the American Institute of Chemical Engineers and try to engage the students by giving them the pharma perspective."

About the author

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

GLOBAL REGULATORY TOWN HALL:

Answers to Key Questions

By Susan Sandler

The 2019 ISPE Annual Meeting & Expo plenary featured a global regulatory town hall addressing a wide range of information about trends in regulations and other developments in the pharmaceutical industry. The town hall format offered attendees the chance to ask a panel of regulators about issues such as harmonization initiatives and information sharing among industry members and regulators. As Sara Pope Miksinski, PhD, Senior Director of Global Regulatory Affairs at AstraZeneca and session leader noted, "Big-picture thinking is the idea of this town hall."

OVERVIEW PRESENTATIONS

The plenary began with short presentations by four of the panelists on activities and forward-looking focus for their respective regulatory agencies and organizations.

MHRA

David Churchward, Expert GMP Inspector at the MHRA, noted that as one of its current key areas of focus, the agency is involved with various international harmonization initiatives including ICH, ICRA, and PIC/S.

Digital health and Pharma 4.0™ are another area of focus; MHRA recently set up an expert tech group tasked with horizon scanning and ensuring they are ready for the future. A team is also looking at artificial intelligence (AI), especially in medicine and software as medical devices, blockchain, and rapid data capture systems. He noted that use of technology to perform regulatory functions is on the rise, with a lot of opportunities for big data in regulatory oversight throughout the drug life cycle in the years ahead.

Personalized medicine is increasing, and MHRA has an innovation office to engage with this area and clinical trials. In the future, MHRA will work to address regulatory and supply chain challenges such as manufacturing at point of care, making medicines in centralized premises, and making medicines fit for administration or true manufacture at point of care if a product may be less stable and manufacturable for stock. Regulations to accommodate these new supply chains are an area of focus.

WHO

Joey Gouws, PhD, Lead, Inspection Services, Regulation of Medicines and Other Health Technologies, World Health Organization (WHO), noted that health and medicine are a key priority for WHO's Director-General. Gouws is in the essential medicines and health products program of WHO, which has two strategic roles: facilitator, focusing on innovation and increased access to medicine and health products, and guardian, focusing on regulatory capacity building and practices in WHO member states. Her department looks at innovation, access, use of healthcare, and the regulation of medicines and other health technology. The focus is on outcomes, she noted, including harmonizing norms and standards; standards and practices across the globe; and international pharmacopeia, among other areas. Her unit "wants to be sure everyone has access to quality essential meds, vaccines, and other products."

FDA

Lawrence Yu, PhD, Deputy Director, Office of Pharmaceutical Quality, CDER/FDA, shared that the FDA's strategic priorities for the next five years will be collaboration, innovation, engagement, and communication. The agency has two major initiatives for premarketing assessment. The first, launched in 2015 for drug products and biopharma, seeks enhancement and collaboration with team members and assessment/inspection. The second, launched in 2018, is the Knowledge-aided Assessment and Structured Application (KASA) initiative to provide the FDA with more information "at our fingertips." A postmarketing initiative in quality metrics is underway, with the first report focused on state of quality of facilities in the current space. Inspections with specific timeline and a 90-day about the state of the facility have been added. The FDA is also working in investigation digitalization and continues to make significant process in continuous manufacturing.

ANVISA

Raphael Sanches Pereira, Health Regulation and Surveillance Specialist with ANVISA, Brazil's regulatory agency, gave an overview of ANVISA's goals. The priority is to make of drugs available in Brazil as quickly as they come to the US and Europe. An important strategy in realizing this goal involves harmonization as well as recognition of and reliance on the agency's work. For reliance, there is a need for equivalency of rules (harmonization) or mapping of differences; trust and relationships (at the reviewer's level); and equivalency of documents submitted (or mapping of differences). Challenges for harmonization include fitting guidelines

into the Brazilian legal framework, which is different from the framework in the US or Europe; interpretation; discussion with stakeholders; workforce limitations; knowledge; and sponsors' submission equivalency.

PANEL Q&A

Moderator Roger Nosal, PhD, Vice President and Head of Global Chemistry, Manufacturing & Controls (CMC) at Pfizer Inc., led the question-and-answer panel discussion. Churchward, Gouws, Pereira, and Yu were joined by Renata de Lima Soares, Regulatory Specialist, ANVISA; Commander Emily Thakur, RPh, Team Leader, Drug Shortages Staff, FDA/CDER; and Rapti Madurawe, PhD, Director, Division of Process Assessment I, Office of Pharmaceutical Quality, FDA/CDER.

Update on MRA: Will the EMA and FDA share progress/metrics? Also, with MHRA leaving, what impact will this have on the EMA annual inspection plans?

Churchward responded to the first two points only, noting that the mutual recognition agreement (MRA) is fully functional between the EU and US. The impact of the MHRA leaving the EU is unclear. In practice, there has been active use of the MRA with Europe-focused facts in the agreement, which came into force in October 2017. As a result, there has been a 75% reduction in EU inspections performed in the US. Nationally, MHRA has had 28 inspection requests from the FDA, and MHRA provided responses to 75 information requests, showing that there has been a good start to the MRA.

For Yu and others: What is the knowledge structure investment? Are there any potential opportunities for industry to be in discussions with the FDA around what they are doing?

Yu noted that the KASA initiative mentioned in his presentation is a way to make knowledge available, and the FDA is always glad to talk with industry. There has been significant progress, especially in generics and, soon, new drugs. He noted that the FDA is seeking more digitalization and also would like to be able to read and store data digitally.

Nosal added that a discussion point during some meetings in which KASA has been introduced is, how does the FDA want to use the data and why is it valuable in a structured format?

Yu responded that assessors look at the data, specifications, etc., and sometimes have to retype or cut and paste the information. Removing these extra actions would be a good step, and it would be helpful to have digital information for life-cycle management so changes can be automatically saved and dated where needed. Digitalization of submissions is the next level. Nosal observed that many companies in industry are also struggling with data management.

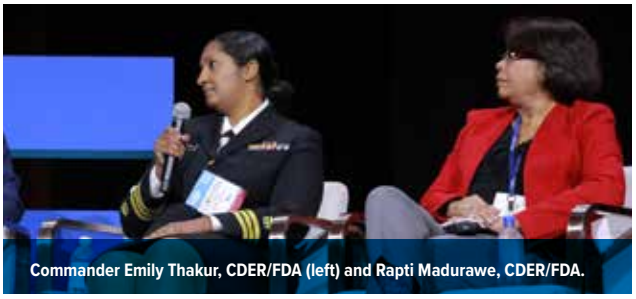
Would ANVISA be willing to expand upon the current status of ICH integration now that they are members of ICH? What do you see as opportunities and challenges for harmonization?

Pereira responded that ANVISA wants to expand its status in ICH, and that he hopes to be on the management committee. There are some efforts to implement the guidelines, although there are difficulties, mostly about interpreting old guidelines: newer guidelines are easier to implement because ANVISA participates in their elaboration. He noted that ANVISA is applying for PIC/S membership, and Lima Soares added that Brazil's specifications may limit implementation of guidelines. She also said that other issues in Brazil include the need to adjust to change and necessary training to adopt new guidelines.

ICH membership will help with applications for Brazil, Pereira said. "We need to participate in early stages of development and need flexibility because early-stage drugs are not the same discussion as already developed drugs. It's a huge advantage for our patients." Expanded capacity will be needed for this growth.

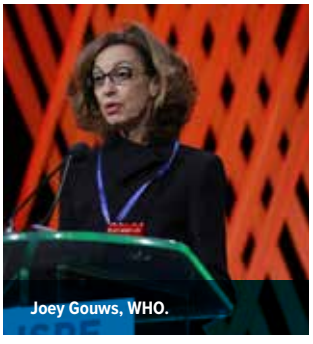
In the CAR-T presentations [during the conference], it was stated that production batches were "released" with OOS [out of specification], and deviations. It was said FDA/EMA is okay with this to get drugs to patients quickly. True?

Churchward said, "Be clear: Are we ok with products going to


Commander Emily Thakur, CDER/FDA (left) and Rapti Madurawe, CDER/FDA.


Lawrence Yu, CDER/FDA (left), Raphael Sanches Pereira, ANVISA, and Renata de Lima Soared, ANVISA.


David Churchward, MHRA.


Joey Gouws, WHO.

2019 ISPE Annual Meeting & Expo Highlights: New Leadership and Awards

ISPE's 2019–2020 Chair, Frances Zipp, took the helm of the organization during the 2019 ISPE Annual Meeting & Expo Membership and Awards Breakfast on Tuesday, 29 October 2019, from outgoing chair James E. Breen, Jr., PE, 2018–2019 International Board Chair and Vice President, Lead Biologics Expansion at Janssen Pharmaceuticals. Breen continues to serve ISPE's International Board as immediate Past Chair.

Breen introduced the 2020 Board Officers: Fran Zipp, Chair; Tom Hartman, Vice Chair; Joanne Barrick, Treasurer; Jörg Zimmermann, Secretary; and Jim Breen, Past Chair. Directors are Vivianne Arencibia, Gunter Baumgartner, Scott Billman, Chris Chen, Ylva Ek, Lou Kennedy, Stephen Mahoney, Christine M.V. Moore, Alice Redmond, Caroline Rocks, and LeAnna Marcum (Young Professionals Representative).

Breen and Zipp presented the following awards during the session:

Max Seales Yonker Member of the Year Award
Charlie Wakeham

Richard B. Purdy Distinguished Achievement Award
Christopher Reid

Joseph X. Phillips Professional Achievement Award
Dennis Gross

Company of the Year Award
CRB

Facility of the Year Award (FOYA) Overall Winner Award
Kantonsapotheke Zurich

Affiliate and Chapter Excellence Award
Delaware Valley Chapter

Committee of the Year Award
2019 ISPE European Annual Conference Programme Committee

2018 Roger F. Sherwood Article of the Year Award—*Pharmaceutical Engineering*
"Continuous Manufacturing in Biotech Processes: Challenges for Implementation" by Robert Dream, PE, CPIP; Christoph Herwig, PhD; and Emilie Pelletier

Global Hackathon
Team 4

patients with OOS and deviations because the system is poorly controlled? Absolutely no." However, the unique properties of advanced therapies, especially life-saving therapies using the patient's own blood or tissue, may not meet existing specifications. "Starting material from the patient is highly variable, so you end up with a variable product—but not because of a variable process. We want to meet needs of patients. Often these products have very short shelf life." He noted that guidance provides for proceeding in agreement with the treating physician and letting the regulatory authority know. The patient needs to be treated; depending on the deviation from the specifications, the patient may be excluded from the trial. There is a need for balance here, he noted.

Thakur agreed that this can be very difficult. "We must balance the risk of the patient not having the product to the risk of the product itself." Working with the agency is indicated in these instances. Gouws said this is the WHO approach as well: "Look at the risk to the patient. Will we have no product on the market? Look at additional testing, quality control, and additional requirements for that batch. We'd rather have some product than none."

As we look at repurposing older facilities and bringing in new modalities like viral vectors, what are the expectations of segregation between viral vector technology and a mature product?

Madurawe replied that this is hard to answer. "We are not in the biotech space; we are with small molecules, not viral. With repurposing an old facility, you need to meet current cGMP requirements. Most older facilities are being morphed into smaller, more agile, more advanced facilities." Pereira agreed. "My experience is more in small molecules, but we have had some discussion recently regarding where this kind of process will be analyzed: In the same office as biologicals? A different office? Some of these products have so many specificities. We need to train and have a better understanding of the product."

What is the most important aspect of ICH Q12? What will be most difficult aspect to introduce within your agencies?

ICH Q12 is very forward thinking, and it will be very useful for the FDA to manage the postmarketing workload that is "ballooning," Madurawe said. "We do see challenges: Getting an application to approval status in the review cycle is difficult enough. Now, we are looking at the postmarketing/change management perspective—this is another layer. Also, we struggle with huge reliance on quality management systems. Many

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METTLER TOLEDO

A key part of effective implementation of Q12 is ensuring a QMS is in place through the supply chain. — David Churchward, MHRA

regulators, not just the FDA I am sure, would accept a lot of change management ideas if they had full confidence in the quality management system (QMS). It is hard to tell how good the quality management system is—there is no metric right now. Also, QMS is subject to change through the product life cycle."

Nosal asked Churchward about QMS and how more confidence can be had in it. Churchward replied that a key part of effective implementation of Q12 is ensuring a QMS is in place through the supply chain. This is a challenge because if one part of the supply chain is not in an ICH region, how can it be certain that the QMS is in place? Many territories do not have, or have different, marketing authorizations, which is adds additional complexity. Communication of marketing authorization and communication between regulators are needed. "If a product is registered in the US, we need to know the change management protocols in use."

Pereira said he hoped Q12 will help with current challenges concerning postapproval change workloads. "We understand Q12 is very important in solving this. We don't have as many postapproval changes as Europe or the FDA, but we have many more than Australia, for instance."

This is also a huge challenge for WHO, Gouws said. "When we look at the way WHO operates, we prequalify or register products for purposes of UN agencies to buy/deliver products to low- or middle-income countries. If you look at the life cycle of products, we receive applications for change management and variations and evaluate and approve those; then, when you go into the distribution chain, the product could be delivered to a country with no regulatory system. How can we make sure the prequalified product is the one actually reaching that country? A UN agency may have a quality system to address this. Going forward, it will be a challenge."

Yu noted that a common theme in FDA meetings is the challenge of postmarketing management. "I truly believe Q12 is a significant advancement compared to the current system. Regulators do need to embrace it because it is an advancement."

With the industry moving forward with new innovative technologies and biotechnology, please reflect on quality systems and accelerated filings in these new areas.

Madurawe said that with implementation of advanced technologies, "we see the facility aspect and actual technology get closer and closer together. It is no longer sufficient to consider submission reviews from facility aspects; we must link them together holistically. Old quality system elements may be there, but specifics for that particular technology may not be, so we need to update, train the people, have the right documentation, etc."

Although elements of the system may be the same, the way the system is used needs to be different, Churchward said. Control strategies, not just control measures, should be discussed. Careful consideration of process and how to design and monitor with feedback through the quality system will ensure the state of control is maintained.

Pereira added that quality review is able to evolve a lot. The move is to holistic review: a pharma quality system with documents and a system as a whole. "Have this in mind. More and more we will get deeper into quality systems; new technologies will allow you to have better evaluation. ICH Q8, Q9, and Q10 have a different approach to quality system; have that in mind, too."

A few examples of some reliance activities: How far can it go? What are some challenges? Commonality of information in postapproval change is one. What else?

"Regulators around globe realize you cannot do everything on your own anymore—you must tap into knowledge that is out there, must tap into other regulatory authorities," Gouws said. "You must trust them and first must understand how they do what they are doing in order to trust. Common standards and guideline documents become more and more important. If we look at information available on specific aspects under consideration, a regulatory authority will have to look at it and make an informed decision if it addresses the issues important for WHO. Then decide to accept or not accept."

Churchward said, "We need to go big on ambition but delivery [may take time]. Work toward harmonization. Have the political will to do it. Harmonizing standards and approaches will take give-and-take among all regulators. It's a bigger conversation, but that is what we need to be aiming for."

About the author

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

ISPE GLOBAL HACKATHON 2019:
Report from the Winning Team

By Sarah-Catherine Dannelly, Elice Kitchen-McKinley, and Phuong (Sophie) Le

The first ISPE Global Hackathon was held at the 2019 ISPE Annual Meeting & Expo with six teams and 36 participants, including 19 undergraduate students, 11 graduate students, and 6 Young Professionals (YPs). Three members of the winning team, Team 4, named Team Mini Xoom, shared insights about their Hackathon experience with *Pharmaceutical Engineering*.

Members of Team Mini Xoom at work on their solution.

OVERALL CHALLENGE

It's 2030 and you have just been employed with Xoom Pharma, a new, innovative biopharmaceutical manufacturer. You are placed in a multidisciplinary technical team to develop a strategy for a new multiproduct manufacturing facility. This facility is going to be state-of-the-art and will produce the next generation of medicines for patients around the world. You and your team will create a presentation to give to the company Board on your topic to request funding to accomplish your team's objective for the new facility.

TEAM 4 CHALLENGE

Future Flexibility: To be sustainable in the long-term, an effective facility must be able to weather changing trends in drug technology, manufacturing technology, workforce dynamics, and global markets. Design a plant that is well-equipped to adapt to future challenges in any or all these areas.

DEFINING FLEXIBILITY

Team Mini Xoom's challenge, Future Flexibility, provided a wonderful opportunity to learn more about the innovations happening upstream of the pharmaceutical supply chain, where medications are manufactured.

As we read through our challenge, we discussed what flexibility currently means in the pharma industry. We see companies using contract manufacturers and manufacturers using ballroom-style and single-use technology to allow for changes in their process or product. Stephen Hall, PE, Chief Process Engineer at Genesis Engineers, provided a great deal of insight from his experience in process engineering. We spent most of the morning discussing the restrictions and pain points of the current processes.

We kept the threat from natural disasters and climate change in mind as we drafted our presentation. One of the first things we agreed on was to create a group of mini-facilities that could be dispersed geographically so a single natural disaster would not significantly disrupt supplies. We spent most of our first day brainstorming and researching a wide variety of options that are currently available or in development to help us find a way to quickly scale up or scale down manufacturing capabilities. We also debated incorporating cutting-edge technologies—such as 3D-printed medications, robotics, and automation—into the manufacturing process and to what extent we might use these approaches. However, all of them came with the significant costs of capital acquisition, installation, and maintenance. Many concepts that we initially considered also depended too much on external electricity and water infrastructure, which would not be available in areas of the world where those infrastructures are limited or nonexistent.

Our idea of future flexibility meant the ability to adapt to the ever-changing market of human disease in order to treat diseases that will crop up in the future, and do so with a short lead time to approve both product process and quality. This meant being able to adapt to different regulations around the world, reach populations in countries that are usually difficult to treat, and adapt an already

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existing facility to a new process without the usual years of planning, constructing, commissioning, validating, and running conformance lots. This facility would need to be transportable as well.

In the end, we determined that future flexibility meant that the both the facility and the process had to be dynamic. We didn't want to build a single static facility because then it would be restricted to the resources and demand within a specific area. Building a dynamic facility meant we could react to the unforeseen demands and adapt to available resources.

DEVELOPING THE SOLUTION

We spent most of the day discussing current methods and challenges in drug technology, manufacturing technology, workforce dynamics, and global markets.

We developed a solution as a group, brainstorming all possible paths. We first looked at our objectives—including marketplace, workforce, scale, and facility needs—and decided what each of these meant to us and which should be our areas of focus. We defined "marketplace" to be about serving the needs of genetic disease treatment that would arise in the future, as well as outbreaks that happen in rural areas. We then asked, "How could we transfer a facility quickly and easily?"

We came across the concept of the modular/podular pharmaceutical manufacturing process, which uses multiple miniclones of the same self-contained cGMP facility deployed to remote areas where the medication products are needed, such as rural areas or areas ravaged by a natural disaster or a disease outbreak. With each Mini Xoom pod, we can quickly bring our products close to patients while reducing unnecessary costs, satisfying multiple regulatory standards, and minimizing our footprint. A "landing pad" would provide each pod with critical utilities such as HVAC, gas, water, and electrical supplies, so each pod can initially make a small supply of medications right away. Then the pod could ramp up or wind down production based on current local needs. When the manufacturing technology or product becomes obsolete, this independent facility can be repurposed to adapt to new technology and demands.

We further refined the presentation based on the available information and research articles on podular and portable continuous processing systems, as well as feedback from coaches and additional group discussions. To adapt to the workforce of the future, we discussed developing mission-based rotations to provide on-the-job training as well as increasing capabilities and responsibilities at work to attract and retain talented and motivated employees from diverse backgrounds.

We made a huge pivot in our solution in the midafternoon. Coach Wendy Haines, PhD, DABT, ASQ CQA, Associate Director of Technical and Scientific Services at PharmENG Technology, encouraged us to be creative and push the boundaries, so we went back to an earlier idea. We originally didn't use it because we were unsure how feasible the execution would be, based on where pharmaceutical technology is now and where we think it could be in 10 years. We were inspired by G-CON and Germfree's work in pod technology. Our solution was to use pod technology to create mobile, portable, self-contained facilities that are essentially miniature versions of the parent facility. Our versions of pods and miniature technology would allow us to be faster to market while lowering the cost and reducing the footprint. We spread the project across multiple phases, starting with a pilot pod that was followed years later by globalization.

Each coach gave us insightful comments and suggestions based on their expertise in facility architecture, bioprocessing, manufacturing, and quality assurance. Their feedback helped us further evaluate and articulate our ideas, and we were able to continuously improve and refine them until we finalized our presentation.

One of the judges questioned our timeline, because our "completion" date was almost 2040, noting that the pharmaceutical industry is known for being slow to adopt new technology and our timeline suggested that we did not see that changing. He made an interesting point because our solution required Xoom to quickly embrace new manufacturing technology, but we didn't expect the industry to adopt our model quickly.

We struggled with the conflict between the ethical and business purposes of the company. We ultimately embraced the mindset that Xoom Pharma would not be restricted by the tension between profitability and patient well-being. Our primary objectives were to reach more patients, adapt to novel therapies and technologies, and reduce unnecessary expenditures. To support Mini Xoom, we worked under the assumption that Xoom Pharma was a well-established and profitable company.

TAKEAWAYS

The ISPE Hackathon was a fantastic event that brought together students and YPs from around the world. The Hackathon sparked thoughtful conversations among professionals, YPs, and students. We're grateful for the incredible coaches who took the time to work with us and provide their unique perspectives.

The best part was getting to know other students and YPs on our team. Each of us contributed different perspectives and skills to the team. And we still keep in touch after this Hackathon! Overall, the Hackathon was a great experience. It was well designed, fun, and engaging for all participants. Thank you to ISPE for making it happen!

About the authors

Sarah-Catherine Dannelly is a Project Manager, Sales, with GEMÜ Valves, Inc. After graduating from Georgia Institute of Technology as a Biomedical Engineer, she joined GEMÜ. She supports engineering and OEMs with valve design and bid through production. She has been an ISPE member since 2017.

Elice Kitchen-McKinley will receive a bachelor of science in bioprocessing sciences with a minor in biomanufacturing from North Carolina State University this year. She is the NCSU-ISPE Student Chapter president. Elice has been an ISPE member since 2019.

Phuong (Sophie) Le is a student at the University of Minnesota College of Pharmacy, Twin Cities campus, and a member of the AMCP-UMN Chapter. Before graduate school, her work included three research labs and volunteering at a hospital. Her interests include pediatrics, oncology, supply chain, and health economics. Sophie has been an ISPE member since 2017.

GROWING MOMENTUM:

2019 ISPE Europe Pharma 4.0™ Conference Report

By Thomas Zimmer, PhD, Hans Heesakkers, Christian Wölbeling, and Teresa Minero

The 2019 ISPE Europe Pharma 4.0 Conference held in Manchester, UK, on 20–21 November 2019 was attended by 300 participants, all of whom contributed to the growing momentum for Pharma 4.0™ initiatives. The Pharma 4.0™ Special Interest Group (SIG) and the Program Committee collaborated with the ISPE UK Affiliate and ISPE staff in the US and Europe to create an extremely interesting program featuring high-quality speakers and presentations.

The conference gave all the attendees the opportunity to share strategies, discuss planned and realized projects, and hear the opinions of regulators, industry leaders, and technology providers.

During breaks in the programming, visitors headed to the booths of key Pharma 4.0™ suppliers to touch, see, and better understand how traditional and new enabling technologies can support the Pharma 4.0™ revolution.

PROGRAM HIGHLIGHTS

Mike Phillips from McLaren Applied Technologies, United Kingdom, opened the conference with an inspiring speech in which he pointed out parallels between Formula One racing and the pharmaceutical industry. In both racing and pharma, "safety is a given, and performance is expected," he stated. Also, both Formula One racing and pharma are technology-driven, regulated, competitive, cost-constrained, and under public scrutiny.

Recently, the Fédération Internationale de l'Automobile introduced new regulations for Formula One racing, triggering additional testing. McLaren explained how Formula One teams are using data-driven simulations in a "digital twin" of their vehicles to quickly and extensively conduct testing at reduced cost.

A car, like a production line, is a physical system, which can be modeled and validated. A Formula One car pushes the limits of performance, Phillips noted. The goal in modeling and validation of these cars is to explore the design space and help maximize performance outcome. It is of vital importance that the "human factor" is embedded in this process, he said.

On a Formula One team, a network of experts collaborates to maximize performance. The driver, the race engineer, the strategist, data analysts, and others work together to populate data in a decision support tool that provides recommendations and visualizes simulations. Although these tools can accomplish many things, the final decisions are made by humans.

Taking a comparable approach, stakeholders in the pharma industry can use the analytical maturity assessment scale to evaluate digital maturity levels within the industry. These levels start with the descriptive stage (what happened?) and progress through the diagnostic stage (why did that happen?), the predictive stage (what will happen?), the optimization stage (how can we optimize what happens?), and, ultimately, the adaptive stage (how do we learn?). The Pharma 4.0™ working group linked the stages with the specific digital maturity attributes to the pharmaceutical industry.

Phillips closed his speech by outlining the elements of the Formula One performance model impact assessment:

- Performance—Key performance indicators
- Interventions—Core decisions and processes for decision-making, risk, and governance
- People—Roles, responsibilities, accountabilities, behaviors, motivations, and incentives
- Tools—Technology landscape, visualization, decision-making tools, and hardware
- Data—Data architecture, data quality, and communications
- Sensors—Data capture/telemetry
- Other—Organizational structure, head count, operational footprint, and regulatory and fiscal structures

Collectively, this seems very similar to the holistic control strategy in Pharma 4.0™!

Mike Houghton from Siemens Digital Industries, United Kingdom, presented about the Industrial Strategy Challenge Fund (ISCF), a UK government initiative to improve competitiveness through digitalization. He stated that more than 50% of the world's data were created last year, but less than 0.5% were analyzed or used. Because access to data is critical to establishing new business models and transforming traditional markets, ISCF is

supporting new business models in a range of industries. ISCF-supported projects must aim for short-term support and should fit in one of the following four topic areas:

- The smart, connected factory, including use of real-time data to optimize efficiency and capture, analyze, and visualize manufacturing processes
- The connected and versatile supply chain, including information integration, communication, traceability, and trust
- "Design, make, test," including transforming product design through digital technologies, virtual product testing, verification and modeling, quality monitoring, and inspection
- Adaptable flexible manufacturing operations and skills, including culture change and skills development, and human-centric automation and autonomy

The expected benefits of the projects are reduced time to market, enhanced flexibility, increased productivity, and greater efficiency.

Jean-Marie Bouvier from Merck KGaA in Darmstadt, Germany, shared insights from a case about how a digital transformation becomes a reality on the shop floor at Merck companies.

As a first step, an overview of the digital plant architecture is developed. All systems for supporting processes are mapped, as well as all systems dealing with manufacturing and laboratory execution and batch disposition. The completed map includes systems for end-to-end planning as well as systems with advanced analytics for plant performance monitoring, deviation analytics, and continued and advanced process monitoring.

Next, four visions are developed.

- Manufacturing execution vision:
  - The manufacturing execution system (MES) is fit for the future, fully deployed, sustainable, and scalable.
  - Batch record review is done by exception.
  - All in-process controls equipment is connected to the MES.
  - Exhaustive automated process verification is done for all processes.
  - Real-time multivariate analysis is used extensively.
- Quality management vision:
  - Quality control is completely paperless, with zero data integrity risk.
  - Machine learning technology is used to reduce recurring issues.
  - The company is capable of paper-free quality process management.
  - A disposition-readiness dashboard is validated.
- Maintenance and engineering vision:
  - Equipment and the system validation process are digitalized.
  - An automation system historian is centralized, which is a prerequisite toward predictive maintenance.

Figure 1: Decision committee for digital plant organization at Merck KGaA, as presented by Jean-Marie Bouvier, Merck KGaA.

Merck's digital plant organization is based on GAMP® 5 governance concepts supported by a decision committee:	
Site Process Owner	**Site Systems Owners**
Manufacturing execution	Manufacturing execution system Distribution control systems
Batch disposition	Manufacturing execution systems
Quality testing management	Laboratory information Management system
Continued process verification	Scientific data management system
End-to-end planning	Enterprise resource planning Real-time modeling system
Qualification and validation	Validation life-cycle management system
Documentation and training	Learning management system Documentation management system
Quality compliance	Quality management system

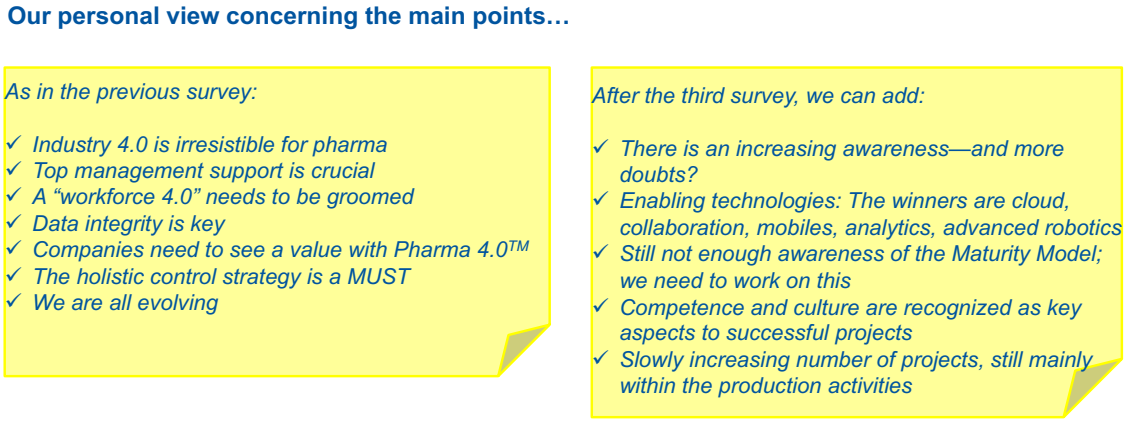
- People and culture vision:
  - Efficient methods of onsite information sharing are employed via extensive use of classic tools.
  - Workers have access to effective and popular e-learning to facilitate self-learning and training qualification.
  - Site culture improvements are made via cognitive science, games, and artificial intelligence (AI).
  - Performance management is automated to enforce the data-driven mindset.

The digital plant organization is based on GAMP® 5 governance concepts supported by a decision committee (Figure 1).

The key takeaway messages to make the digital transformation a reality are as follows:

- A strong digital organization is able to understand user requirements and manage information technology and computer system validation constraints.
- Top management must support and fund local leadership.
- The organization must have a clear and stable roadmap with a strong project management execution focus.
- The organization must develop its digital culture, leverage existing data, encourage a "source of truth" mindset for decision-making, and effectively train and communicate with its employees.
- It is important to establish clear and simple roles, responsibilities, and decision workflows.
- The digital transformation should be system- and governance-agnostic; involve best-in-class specialized external partners; and have well-managed local, corporate, and multisite projects.

Figure 2: Conclusions from the third survey by the ISPE Pharma 4.0™ SIG.



Teresa Minero, Chair of the ISPE Italy Affiliate, Pharma 4.0™ SIG member, and Founder and CEO of LifeBee, a firm specializing in digitalizing life sciences, gave an update on the Pharma 4.0™ SIG's third annual survey of Pharma 4.0™ stakeholders, including manufacturers, technology developers, suppliers, regulators, and consultants. Specifically, she focused on responses from the survey conducted in October 2019 (316 participants) and how they compared to findings from the 2017 survey (about 300 participants) and 2018 survey (more than 400 participants).

The 2019 survey, which added questions about organizational aspects of Pharma 4.0™ and the skills and abilities required to deliver Pharma 4.0™ projects, included the following 10 questions:

1. Rate a set of statements, mainly regarding the meaning and approach to Pharma 4.0™.
2. Rate the impact on Pharma 4.0™ on a set of main issues currently at the center of debates within the pharma industry.
3. Pharma 4.0™ prospects: Trends, specific needs, regulatory enforcement and constraints, operating model.
4. What is the Pharma 4.0™ maturity level you see in your organization? Not started, just starting, pilots, or systematic ongoing actions?
5. What is your company's interpretation (technical, tactical, strategic) of the Pharma 4.0™ perspective?
6. Which Pharma 4.0™–enabling technologies are the subject of adoption in your company?
7. In the event of active projects, specify the area you are either working or planning to work on.
8. Please describe one to three Pharma 4.0™ projects your company has been working on.
9. Who is involved in Pharma 4.0™ projects within your company?
10. For of each the following competencies, please rate its relevance for carrying out a successful Pharma 4.0™ project.

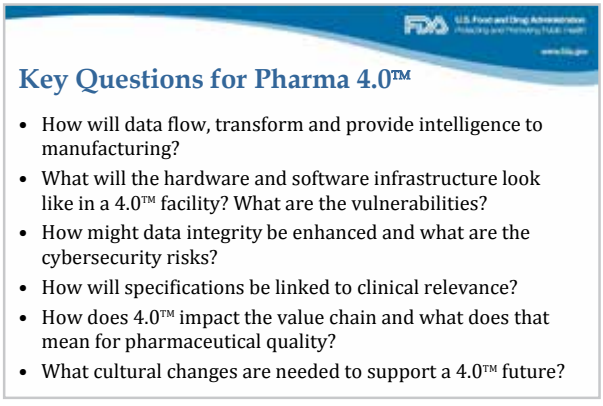
Figure 2 summarizes findings of the most recent survey. Additionally, the following points about the survey deserve elaboration:

- Pharma 4.0™ is increasingly seen as a strategic matter (by 49% of respondents in 2019 compared with 31% in 2018); the percentage of respondents who categorized it as a mere tactical option declined to 22% from 38% in 2018.
- There was a slight but meaningful increase in project implementation; the percentage of companies with systematic ongoing actions and/or pilot projects rose from 38% in 2018 to 44% in 2019.
- Recognition of Pharma 4.0™ is widening, but perception of the maturity model can be improved—the ISPE Pharma 4.0™ SIG is continuing to work on it!
- More than 90% of respondents said that culture and resources are always relevant or key relevant factors for the ISPE Pharma 4.0™ operating model.
- All organizational roles from middle to top management are involved in Pharma 4.0™—and this is good news!
- Respondents consider professional and personal skills to be central to a successful Pharma 4.0™ project, affecting factors such as data-driven decision-making, effective communication about results, management of project teams, scheduling, and stakeholder awareness of the relationship between business processes and the transformation project.

Christian Wölbeling, Senior Director, Global Accounts, at Werum IT Solutions, Germany, and Founder and Chair of the ISPE Pharma 4.0™ SIG, gave an overview about the accomplishments and ongoing efforts of all Pharma 4.0™ SIG subgroups.

He focused on issues related to quality, explaining that regulators in various countries are not fully satisfied with the manufacturing and quality performance of many drug substance and drug product manufacturers, QC laboratories, and contract

Figure 3: Key questions from regulators about Pharma 4.0™ (source: "A Perspective on the Future of Pharmaceutical Manufacturing," presentation by Sarah Arden, PhD, Office of Pharmaceutical Quality, US FDA, Center for Drug Evaluation and Research, at the ISPE Europe Annual Conference Dublin, April 2019.)



laboratories, for a variety of reasons documented in publications and inspection statistics. Quality deviations can even result in drug shortages, he noted.

According to Wölbeling, the SIG is actively pursuing answers to key questions that have been posed by regulators such as Sarah Arden of the US FDA (Figure 3). For example, the ISPE SIG has developed the Pharma 4.0™ operating model and created subgroups to define the roadmap to Pharma 4.0™ along the pharmaceutical life cycle and in accordance with the ICH Q10 pharmaceutical quality systems digitalized elements and enablers (Figure 4). Notably, the digital transformation to the Pharma 4.0™ operating model is not an IT project; rather, it is a reorganizational Lean/change management project.

Kevin Bailey, Good Manufacturing and Distribution Inspector from MHRA in the UK (Figure 5), delivered his perspective on the future of pharmaceutical manufacturing.

He explained that one of the drivers for the next generation will be the changing spectrum of medical product activity from large-scale stable batches to the single-person "batch," and from a small number of centralized manufacturing sites to a large number of point-of-care manufacturing sites. Production could combine partial central manufacturing with diversified local finishing at sites of product use. In such a model, quality oversight by a qualified person (QP) must be differently organized.

Pharma 4.0™ approaches can help design and manage this transition, Bailey said, as new modes of production affect many key parts of the industry, including electronic batch records, maintenance, training, factory investigations, security of the pharmaceutical supply chain, data integrity controls, and process monitoring.

AI will play a role in supporting QP certification decisions. However, to ensure the safe implementation of algorithms, workers will need new skills to help them understand the AI model,

Figure 4: The ISPE Pharma 4.0™ operating model with enablers and elements. The tracks of the 2019 ISPE Europe Pharma 4.0™ Conference are noted.

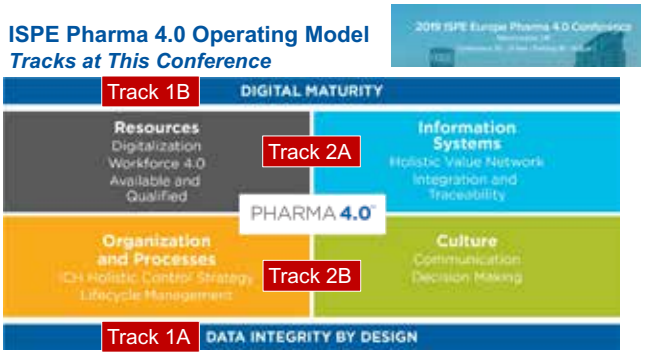


Figure 5: The MHRA inspectorate has identified Pharma 4.0™ as one of their top four priorities, as Kevin Bailey, MHRA Inspector (below), explained.

control outsourced technology, and guarantee cybersecurity.

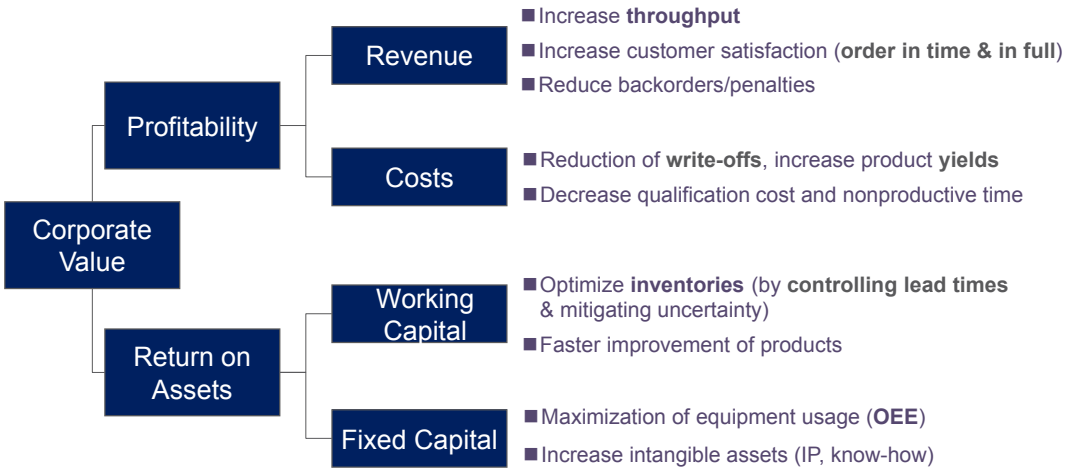
After Bailey's presentation, the conference split into parallel tracks (see Figure 4). Some highlights from these tracks are described next.

DIGITAL MATURITY

Romain Bourgin, Manufacturing 4.0 Program Director at Sanofi Pasteur, explained the company's manufacturing strategy in motion program.

Before the program started, stakeholders identified five roadblocks to digital maturity: a lengthy decision-making process; insufficient IT delivery and support; funding constraints; challenges in securing resources; and organizational silos and resistance to change. The top five key enablers were identified as strong governance and sponsorship; commitment from employees on the shop floor and in middle management; a dedicated digitalization team and funding; an effective change management strategy; and proper staff training or recruitment to implement new competen-

Figure 6: Sanofi Pasteur digitalization program's performance drivers, as presented by Romain Bourgin.



cies and technologies.

The program has five missions:

- Improve products and manufacturing processes to increase yield and reduce write-offs.
- Facilitate decision-making and increase predictability, lowering inventory levels and optimizing costs of goods and services.
- Improve building and equipment design and use.
- Align and streamline documentation flow for product and quality management.
- Enhance shop-floor personnel qualifications and improve workstation ergonomics.

Figure 6 identifies the digitalization program's performance drivers. This program focuses on seven digital capabilities: big data collection, machine learning/AI, release by exception, deviation intelligence, multilayer digital dashboard, augmented operator, and e-maintenance.

The strategic intentions are to unleash full potential of big data, implement paperless processing, streamline the value chain, democratize access to data, empower the workforce, and increase engagement. The program's roadmap has defined 10 projects: bulk manufacturing; formulation; filling; packaging; final release; training; quality control/quality assurance; maintenance; supply chain and logistics; and health, safety, and the environment.

THE ISPE OPERATIONS MODEL—RESOURCES AND INFORMATION SYSTEMS

Simon Webb, IT senior director, EMEA and APAC, at AstraZeneca, USA, described how the company defines "digital" in operations. It focuses on process digitalization; connectivity and sensing; big data analytics; robotics and automatization; AI; and business model innovation. These priorities require new ways of working, a shift in culture and mindset, changes to the operating model, and new capabilities and underlying IT platforms.

Strategically, the company is shifting from technology-led efforts to vision-led innovation—in other words, from IT-driven strategies to a business and IT partnership.

AstraZeneca's factory of the future will be based on visualization of data analytics; capturing big data from shop-floor sources; reducing human intervention through advanced automatization; Internet of Things (IoT) methods to trace and control batch processing through real-world data; digital twins; and AI applications to analyze big data and predict ways to optimize manufacturing or proactively detect safety problems in operations.

AstraZeneca plans to start with digital lighthouse projects to demonstrate the business impact of digitalization, increase the company's understanding of technology, and determine the best ways to integrate the new way of working into business processes before scaling up the project. Simon showcased one of these lighthouse projects, batch release visualization. The proposed solution is the real-time visibility of all release processes, process performance measures, and process improvement strategies. Business benefits such as process efficiency, reduced workload for employees, and an earlier launch of a new product have been achieved in this project.

Mareile Fuss, Head of Business Process Excellence/Strategic Projects at Boehringer Ingelheim, Germany, reported about usage of smart glasses by packaging-line workers. Eighty different packaging operations were created, and the employees' feedback about the technology was positive: they reported that the smart glasses technology was comfortable, useful, and well supported. This shop-floor pilot program achieved 30% savings in job training,

Voices from the Conference

The 2020 ISPE Europe Pharma 4.0™ Conference will be held in Cork, Ireland, in November 2020. We hope these comments about the 2019 conference inspire you to join us there!

"The manufacturing and control of biopharmaceutical products is at the dawn of a profound transformation, where we will move from document-centric to data-centric processes. This will require a joint effort from manufacturers, regulators, and suppliers. The ISPE conference in Manchester was a great forum to address the challenges and opportunities with the right mix of industry presentations, supplier viewpoints, and interactive workshops."
—Romain Bourgin, Program Director, Manufacturing 4.0, Sanofi Pasteur, France

"For us as exhibitor and sponsor of the Pharma 4.0™ conference, the event in Manchester was very valuable. We were stunned by the quality of the visitors. As solution providers, we saw a good mix of possible clients and partners alike. The booth was never overcrowded but always busy. Pretty much every conversation we had was worth a follow-up. We already booked our booth for the European ISPE conference in Madrid next spring."
—Robert Hoffmeister, CEO, Goodly Innovations, Germany

"Though I live in the US, I attended the ISPE Europe Pharma 4.0™ Conference in Manchester, UK, to network with others involved with Pharma 4.0™, to find out how I can contribute more, and generally to get more involved in Pharma 4.0™. The conference was well worth the trip. The sessions and speakers provided great insight into where the industry is, where it is going, and what challenges it faces in implementing Pharma 4.0™. The exhibition space, coffee breaks, and networking dinner provided a great opportunity to get to know others involved in the movement, and to meet some of my fellow Validation 4.0 SIG members in person."
—Chip Bennett, Assistant Director, CAI–USA

"As a Young Professional participating for the first time in an ISPE conference, I had a very rich and inspiring experience. The two-day conference was full of knowledgeable people sharing their experiences and showing how it is possible to successfully adopt Pharma 4.0™ and what the challenges and next steps are. A highlight of the conference is all the people I met. At an early stage of my career, it's fundamental and very interesting to meet people from all around the world who share a passion and interest for Pharma 4.0™, and are always willing to share their advice and experiences. I look forward to keeping contact with many of the people I met, and to meet all again at the next ISPE conference!"
—Jessica Luzio, Young Professional, Tenthpin Management Consultants, Portugal

and processes were faster and more flexible. The initiative took about two years to show a return on investment, and broader usage of smart glasses by packaging-line employees is anticipated.

Smart glasses were also tested in manufacturing for on-call services during night and weekend shifts. The glasses allowed the on-call employees to receive video transmission at their homes. In this pilot, too, the employees' feedback was positive, and faster processes and greater flexibility were noted. At a strategic level, smart glasses enable implementation of a network strategy.

Notable technology-related lessons learned in the projects included the following:

- IT server connection to the devices is key.
- Know-how sharing between IT service and user needs to be a common learning.
- Good WLAN coverage is needed.

Lessons learned at a management level were as follows:

- Before the project launch, stakeholders must clearly define the project of scope, achievable targets, roles and responsibilities, and realistic timelines.
- Highly motivated local management is key to project success.
- The expectations of all involved parties must be well managed.

Fuss noted the considerable challenges of running a pilot in a productive environment but said that she anticipates more smart glasses applications will be implemented.

ORGANIZATION, PROCESSES, AND CULTURE

Heike Roeder, Head of Process and Knowledge Management for Bayer AG, Germany, and **Zam Tahir,** an ISPE Young Professional working for Thermo Fisher Scientific, UK, used Alexa, the digital assistant by Amazon, to help them act out a scenario about standard operating procedure (SOP) management of the future. In this show, they illustrated the transition from documents in binders or files, more or less isolated from each other, to data integrated and cross-referenced within a connected, always up-to-date system optimized for training processes.

In the demonstration, SOPs were centralized in a SOP chatbot, a technology that allows open learning because the entire community of users can correct and comment on answers and add new variations to problems. The learning could be made available to other chatbot users as soon as it was

saved, meaning that all members of the user community can be teachers as well as students.

The presenters acknowledged that it is a challenge to harmonize this new way of working with current principles of quality management, which need authorization and release processes. They also noted that chatbot and smart glasses technology might be combined to facilitate learning.

CONCLUSION

It is fitting that the site of the 2019 ISPE Europe Pharma 4.0™ Conference was Manchester United Stadium, where many historic football games have been played, because Pharma 4.0™ undoubtedly represents a championship-level contest for the pharma industry's future.

The stakes in this Pharma 4.0™ "match" are high. Together with all our stakeholders, from shareholders to patients, we need to make our industry faster, more competitive, and more sustainable in delivering high-quality, safe, and effective drugs and medical devices to the public.

About the authors

Thomas Zimmer, PhD, held numerous positions at Boehringer Ingelheim between 1981 and 2013: pharmaceutical development, pharmaceutical production, international production, quality management, quality standards, Corporate Lead Auditor GMP, implementation production alliance Europe, product transfers, transition management from national to international supply, Plant Manager of Pharmaceutical Production in France, Senior Vice President of Global Quality, Qualified Person, and Senior Vice President of Environment, Health, and Safety and Sustainability. Since November 2013, he has served as the Vice President of ISPE's European Operations. Thomas has been an ISPE member since 2005.

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

Christian Wölbeling is Senior Director Global Accounts at Werum IT Solutions in Lueneburg, Germany, part of the Körber Medipak Systems Group. He has a master's degree in mechanical engineering and more than 28 years of experience working in life sciences manufacturing IT, including all GMP-related processes. Christian is Founder and Chair of the ISPE Pharma 4.0™ SIG, Co-Chair of the ISPE "GAMP® MES SIG, Member-at-Large of the ISPE GAMP® European Steering Committee, Chair of the ISPE Knowledge Network Council, Steering Member of the ISPE PAT & Lifecycle Control Strategy Community of Practice, and a Board Member of the ISPE D/A/CH Affiliate. Christian has been an ISPE member since 2001.

Teresa Minero is Founder and CEO of LifeBee, a business consulting and digital company dedicated to life sciences since 2004. She has more than 30 years of experience in managing international consulting and digital innovation projects for production, logistics, quality, regulatory, and R&D, and managing start-ups and business divisions for international consulting groups. Teresa has worked in the life sciences for more than 25 years. She is currently the Chair of the ISPE Italian Affiliate, part of the ISPE European Leadership Team, and a member of the ISPE Steering Committee for the Pharma 4.0™ Global SIG. She has been Lecturer and Chair at many conferences and is the author of articles on digitalizing life sciences and Pharma 4.0™. Teresa has been an ISPE member since 1996.

FROM WEST TO EAST AND BACK:

ISPE Japan Affiliate Sees Excellence on Its US Plant Tour

By Akihiro Matsui and Michael J. Lucey

Before traveling to the 2019 ISPE Annual Meeting & Expo in Las Vegas, the ISPE Japan Affiliate held its annual pharmaceutical plant tour over five days (21–25 October), visiting two plants in Los Angeles, one in Boston, and one in Indianapolis.

ISPE Japan Affiliate members visiting Eli Lilly's continuous manufacturing facility in Indianapolis.

Among the 19 professionals from across Japan who participated in the tour were Head of Secretariat Akihiro Matsui and Adjunct Director Michael J. Lucey, who jointly planned the tour with the Japan Affiliate's Organizing Committee led by Affiliate Vice Chair Hiroshi Sakai and Director Hirokazu Kisaka. Industry representation on the tour was broad, with seven members from pharmaceutical manufacturing companies, nine from the engineering/construction sector, and three from equipment manufacturers.

The following are highlights from some individual plant tours.

TAKEDA (FORMERLY SHIRE)

The tour's first stop was the Takeda Los Angeles manufacturing plant. Tour members saw the large-scale quality control (QC) laboratory as well as the Building 8 purification manufacturing facility. These facilities were selected as ISPE 2018 Facility of the Year Award (FOYA) category winners for Operational Excellence and Facility Integration & Overall, respectively, with Building 8 selected as the overall 2018 FOYA winner. The QC lab functions as a control lab for next-generation plasma-derived therapy, for which global demand is increasing. An optimized developmental environment has been realized by incorporating an effective flow and an improved work environment into the facility design. The manufacturing facility was designed using building information modeling (BIM). The underpinning philosophy of BIM is that maintainability and operability should be considered at all times. On such basis, an optimal facility was realized through real-time review work during the construction, with feedback to the designers.

CONTINUUS PHARMACEUTICALS

The tour's third stop was the CONTINUUS Pharmaceuticals facility in Woburn, Massachusetts, just outside of Boston. CONTINUUS is a spin-out company from a multiyear collaboration between the Massachusetts Institute of Technology and Novartis in the area of continuous manufacturing (i.e., the Novartis MIT Center for Continuous Manufacturing). Their novel platform technology, integrated continuous manufacturing (ICM), allows for end-to-end integration of the entire manufacturing process, from raw materials to final drug product, in a fully automated and seamless production line. Team members leverage their accumulated technical experience and know-how to enable this innovative system. It was noted that ICM can lower costs, reduce stockpiling, shorten development periods, and improve product quality. Tour members believed that adopting advanced manufacturing technologies such as ICM will increase the range of products brought to the market, ultimately improving patient access to high-quality life-saving drugs.

ELI LILLY

The tour's final stop was Eli Lilly's continuous manufacturing facility in Indianapolis. Members observed the operation of the continuous direct compression process and the low-molecular-weight compound production line. The direct compression process is the simplest form of process for tablet manufacturing, and it was noted that such a process makes continuous manufacturing relatively straightforward. Eli Lilly adopts simulation techniques and experimental approaches in evaluating fluctuating factors, and their quality management strategy has been established using process analytical technology (PAT) tools and modeling techniques. Tour members requested information on the type of evaluation techniques to be applied to quality management. Presently in Japan, this issue is also an important matter when pharmaceutical companies consider an approach to quality management. The visit provided a good opportunity for an enhanced understanding of Eli Lilly's approach to quality management.

ISPE Japan Affiliate US Plant Tour Itinerary

Sunday 20 October:
Departed Tokyo for Los Angeles

Monday 21 October:
Takeda (formerly Shire) (a.m.);
Gilead Sciences (p.m.)

Wednesday 23 October:
Continuus Pharmaceuticals, Boston

Friday 25 October:
Eli Lilly, Indianapolis

Sunday 27–30 October:
ISPE Annual Meeting & Expo

CONCLUSION

The Japan Affiliate is deeply grateful to the host plants for their valuable time shared throughout the US tour. It was a remarkable experience for all the traveling Japanese professionals.

As a change of pace, the group enjoyed a final, posttour afternoon of relaxation in Indianapolis, visiting the Indianapolis Motor Speedway and its Hall of Fame Museum. A member of the tour even "kissed the brick" of the Indy 500 finishing line.

The entire week was a period of bonding and establishing special friendships in our industry. To further expand the member network in Japan, the Japan Affiliate holds a reunion every year for all who have participated in the US pharmaceutical plant tour over the many years of its history. Additionally, the Japan Affiliate displayed the tour highlights in poster form at the winter meeting in December in Osaka.

About the authors

Akihiro Matsui is Pharmaceutical and Chemical Plant Construction Division Technology leader at Mitsubishi Chemical Engineering, Co., Ltd. Previous roles at Mitsubishi include Pharmaceutical Plant Constructions Project Manager, and design of pharmaceutical processes (injections and solids).

Michael J. Lucey is the Japan-based Business Development Manager for JGC Group in pharma and energy areas. He has been an ISPE member since 2001.

EFFECTS OF TANK-AGITATED FERMENTATION on Therapeutic mAb Quality

By Anelis Quintana Cantillo, MSc, Wendy Montero Pérez, Azalia de la Caridad Rodríguez Taño, MSc, Olga Lidia Fernandez Saez, Leina Moro Pérez, Alexi Bueno Soler, José Luis Durán, José Arquímides Castro Del Pino, and Tammy Boggiano Ayo, MSc

Regulatory authorities have approved the use of recombinant monoclonal antibodies (mAbs) to treat infectious diseases [1] and chronic conditions such as cancer [2] and inflammatory diseases [3]. Recently, biosimilar antibodies have been developed to increase product availability and lower prices. The production of therapeutic antibodies is mainly carried out in mammalian host cell lines, which include NS0 murine myeloma cells, human PER.C6 cells, and Chinese hamster ovary (CHO) cells [4], due to their ability to synthetize human protein–like molecular structures. The production process for these products must maintain the desired quality while providing manufacturing flexibility and maintaining profitability.

This article describes experiments carried out to evaluate the impact of physical variables of agitated tank fermentation on the process performance and product quality profile of therapeutic mAbs. The aim of these experiments was to develop a consistent fermentation manufacturing process [5] for a therapeutic biosimilar mAb that would maintain the desired quality attributes. Fractional experimental design allows the evaluation of culture media, temperature, airflow, and agitation speed variations on product purity, isoforms composition, secondary and tertiary structure, and ligand binding.

MATERIALS AND METHODS

Fermentation Process

An NS0 cell line clone producing a chimeric IgG1 mAb was grown in 2-liter (L) stirred bioreactors (Applikon, The Netherlands) in perfusion. The bioreactors were seeded at 5×105 cells/mL, and dilution velocity was increased considering a cell-specific perfusion rate of 0.1 nL/cell/day.

Experiments to elucidate the impact of media and fermentation process parameters were carried out as a reduced two-level factorial with two center points. A commercial media formulation (CMF; a commercially available protein-free hybridoma medium [PFHM-II]) and a mix of CMF and a proprietary media formulation (MB02) 50/50 volume per volume (v/v) were assessed. Impellent tip speed ranged from 0.6 to 1.0 m/s, airflow from 0.0075 air volume per medium volume per min (vvm) to 0.0225 vvm, and temperature from 34°C to 37°C (Table 1); pH was set between 6.8 and 7.2, and the dissolved oxygen concentration upper limit was set to 50% ± 5%.

To monitor cell density, viability, and IgG concentration, 30-mL samples were collected daily. Cells were counted in a Neubauer improved hemocytometer; cell concentration and viability were assessed by the trypan blue exclusion method; and IgG concentration was determined by ELISA [6]. Perfusion supernatant was filtered through a 3-mm to 0.2-mm filter tandem prior to the purification process.

To set the key process parameter of fermentation operation, a numerical optimization function was made using Design-Expert 6.0.1 software.

Purification Process

Figure 1 depicts the mAb purification process. The mAb preparation was loaded onto a protein A support equilibrated with 200 mM Tris, 100 mM NaCl, pH 7.4 buffer, and eluted from the protein A support with 100 mM glycine, pH 3.0 buffer. The eluate comprising the mAb was buffer-exchanged on G-25 medium. It was subsequently loaded onto a cation-exchange (CEX) chromatography support equilibrated with 50 mM sodium acetate, pH 5.0 buffer; eluted with 28 mM sodium citrate, 200 mM NaCl, pH 7.6 buffer; and finally filtered through a Sartobind Q filter. The absorbance units were measured at 280 nm.

Table 1: Factorial design runs for four factors applied to the development of the process design space of an mAb.

Condition	Media	Stirring, rpm (m/s)	Airflow, vvm	Temperature, °C
1	CMF	150.00 (0.4)	0.0075	37.00
2	CMF	450.00 (1.2)	0.0225	34.00
3	CMF	150.00 (0.4)	0.0225	37.00
4	CMF	450.00 (1.2)	0.0075	34.00
10	CMF	300.00 (0.8)	0.0150	35.50
5	CMF/MB02	150.00 (0.4)	0.0075	34.00
6	CMF/MB02	450.00 (1.2)	0.0225	37.00
7	CMF/MB02	450.00 (1.2)	0.0075	37.00
8	CMF/MB02	150.00 (0.4)	0.0225	34.00
9	CMF/MB02	300.00 (0.8)	0.0150	35.50

Physicochemical Characterization

SDS-PAGE Under Nonreducing Conditions and Western Blot

Sodium dodecyl sulfate polycrylamide gel electrophoresis (SDS-PAGE) is a common technology for antibody-purity analysis. In this case, purified mAbs were resolved on 7.5% polyacrylamide gels under nonreducing conditions followed by silver nitrate staining.

For western blot analysis, proteins were transferred to a 0.45-mm nitrocellulose membrane (Whatman), blocked with 5% skim milk (Fluka) in Tris-buffered saline and probed with goat anti-human-gamma-chain-specific phosphatase alkaline–conjugated antibodies (Sigma) diluted in phosphate-buffered saline (PBS) with 0.1% TWEEN 20. The western blot was developed with Fast Red detection reagent (Sigma).

Size Exclusion Chromatography (SEC)

Chromatographic analyses were performed on a high-performance liquid chromatography (HPLC) system (Shimadzu, Kyoto, Japan). SEC was performed using a TSKgel G3000SWXL column (Tosoh Bioscience, Stuttgart, Germany). Samples (500 µg) were injected, and UV detection was carried out at 280 nm.

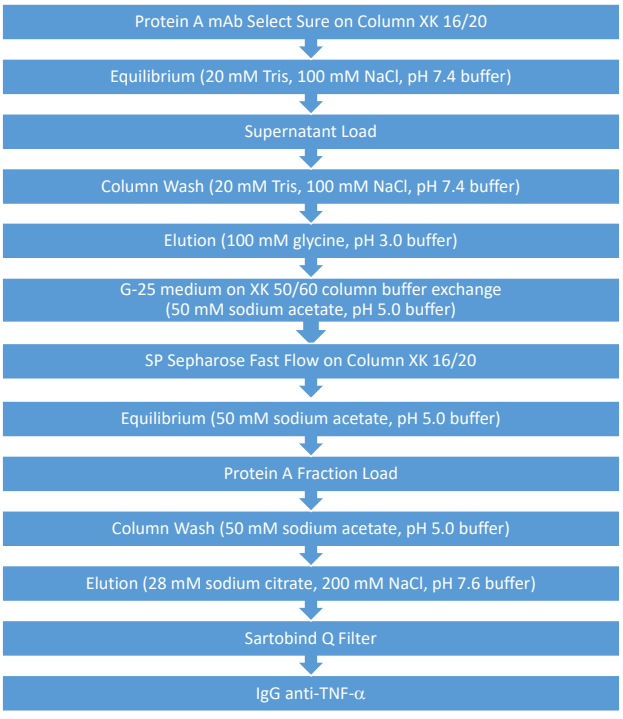
Cation-Exchange (CEX) Chromatography

CEX separation was performed using a weak CEX resin (ProPac WCX-10, 4×250 mm, Dionex, Germering, Germany). The mobile phases used were mobile phase A (0.01 M sodium phosphate buffer, pH 6.6) and mobile phase B (0.01 M sodium phosphate buffer + 0.5 M NaCl, pH 6.6). The elution was performed by an ascending gradient from 4% to 80% eluent B before the eluent composition was returned to the starting condition (100% eluent A). UV detection was carried out at 280 nm.

Circular Dichroism (CD) Spectroscopy

CD experiments were performed using a Jasco J-1500 spectropolarimeter equipped with Jasco PTC-510 Peltier thermostatted cell holders to control temperature and a Jasco MCB-100 mini–water circulation bath (Jasco Corporation, Japan). The far-UV-CD spectra were obtained in the range of 200–250 nm, in quartz cuvettes of 0.1 cm optical path. The spectra were recorded at 0.1-nm intervals, at a constant speed of 100 nm/min with 1-second response time, 1 nm bandwidth, and 15 accumulations. The protein concentration was 0.3 mg/mL for far-UV-CD. The baseline was corrected in all experiments, using as a control the patient solution, 10 mM sodium phosphate buffer. Noise reduction was applied to the baseline-corrected protein spectra using the smoothing option of the device's Spectra Manager II software (Jasco) and the final construction of the graphic in Origin 8.0 software (Origin Lab Corporation, US). The influence of the differences in protein concentration between the batches was minimized by representing the spectra by a scaling factor.

Figure 1: Purification process flowchart.



Fluorescence (FL) Spectroscopy

The fluorescence spectra were recorded on a Jasco J-1500 spectropolarimeter equipped with a Jasco FMO-522 fluorescence monochromator (fluorescence detector Jasco FDT-538), Jasco PTC-510 Peltier temperature controller, and Jasco MCB-100 water circulation mini-bath. The emission spectra of intrinsic fluorescence of proteins were measured in the range of 300–450 nm, every 1 nm, with 1-second response time and 1 accumulation, after excitation at 295 nm, to obtain fluorescence spectra derived from the tryptophan (Trp) residues. Bandwidths of 5 and 10 nm were used for excitation and emission, respectively. The protein concentration

used was 0.15 mg/mL, using quartz cuvettes of 10 mm optical path. The baseline was corrected in all experiments using as a control the patient solution, 10 mM sodium phosphate buffer. Noise reduction was applied to the baseline-corrected protein spectra using the smoothing option of the device's Spectra Manager II software and the final construction of the graphic in Origin 8.0 program.

Determination of Binding Affinity to the Ligand

Binding affinity was carried out through molecular recognition using an ELISA system. The polystyrene microtiter plates (high binding, Costar, 3590) were coated with 100 µL per well of a solution at 1 µg/mL of tumor necrosis factor alpha (TNF-α) in coating buffer (carbonate-bicarbonate 0.01 mol/L, pH 9.8), overnight at 4°C.

The plates were washed with phosphate-buffered solution, 0.5% Tween 20 (PBS-t, pH 7.5), and then the plates were blocked with 200 µL per well of a solution of PBS-t and bovine serum albumin (Sigma 3294) at 1% for 1 hour at RT. The plates were washed with PBS-t. The diluted samples were added in a range of 1,000 ng/mL to 0.1 ng/mL, 100 µL per well, in the blocking solution at RT for 1 hour. The plates were washed with PBS-t, 100 µL per well; then, the secondary antibody, anti-human IgG goat serum conjugated to alkaline phosphatase (Sigma, A3188) at a dilution of 1:4000, was added. The plates were washed with PBS-t, 100 µL per well, and, finally, the substrate p-nitrophenylphosphate (1 mg/mL, Boehringer Mannheim GmbH, 107.905) in diethanolamine buffer (pH 9.8) was added. The data were read at 15 minutes at 405 nm, and the results were processed on a Microsoft Excel spreadsheet designed for that purpose.

RESULTS AND DISCUSSION

Definition of Fermentation Process Key Parameters

The impact of the operation parameters on the stirred tank fermentation process was assessed at 2-L scale with two culture media. Impeller speed, airflow, and temperature were combined in 10 fractional factorial design perfusion runs (Table 1). Significant differences were found for integral viable cell concentration (IVCC) values during the perfusion runs studied (Figure 2). The adjusted model (which has a correlation coefficient of 95.29%) showed as significant input variables the airflow (P = 0.0301), the interaction between agitation and temperature (P = 0.0214), and the interaction between temperature and the airflow (P = 0.0344). Our results showed that IVCC decreased due to the decrease of viable cell concentration in correspondence with the increase of the three studied parameters.

In the case of temperature, the behavior in our experiments was different from that usually reported in the literature; in other reports, decreases in temperature induce slower growth [7] due to the arrest of cells in G1 phase, which can increase the longevity because of prolonged cell viability [8].

In the adjusted model, the growth rate (which has a correlation coefficient of 99.53%) was significantly negatively affected by the cell culture media (P = 0.0111), airflow (P = 0.0036), temperature (P = 0.0132), interaction between culture media and airflow (P = 0.0074), interaction between agitation and temperature (P = 0.0020), and interaction between temperature and airflow (P = 0.0049). The increase in airflow and temperature decreased the cell growth rate. This phenomenon is associated with an increase in hydrodynamic stress in which the growth of cells is restricted by agitation. The stress generated by bursting bubbles could also develop a mediator transcription response for cytoskeleton repair [9].

For the model adjusted for the production rate (which has a correlation coefficient of 89.94%), no process parameters significantly influenced the output variable. However, volumetric productivity (Figure 3) is negatively affected by tip speed (P = 0.044), being more productive in those runs of lower agitation stress. This could be a concern because at low agitation rates, nutrient mixing could be insufficient and cells could settle in the bioreactor.

The resulting data indicated that airflow, temperature, and agitation speed are key parameters for the consistent performance of the fermentation process. Therefore, the optimal conditions of

Figure 2: Comparison of IVCC of 2-L-scale stirred tank perfusion conditions evaluated in the fractional factorial experiment.

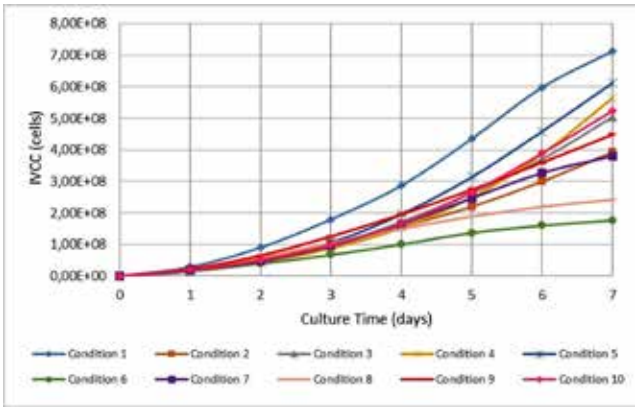


Figure 3: Comparison of volumetric productivity of 2-L-scale stirred tank perfusion conditions evaluated in the fractional factorial experiment.

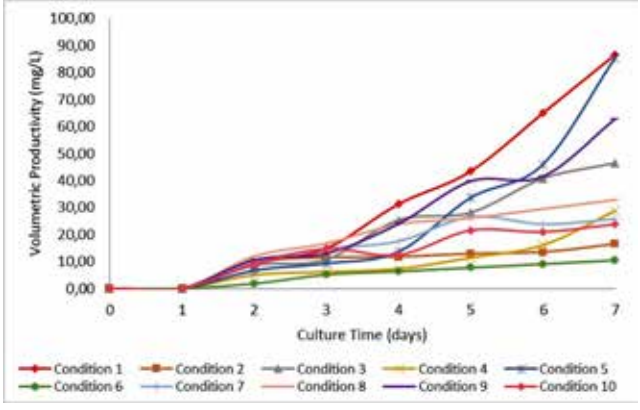
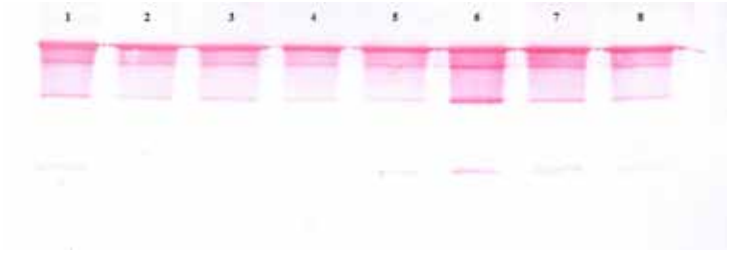


Figure 4: SDS-PAGE under nonreduced conditions of the final purified SP Sepharose Fast Flow. Lane 1: molecular weight marker; lane 2: condition 1; lane 3: condition 2; lane 4: condition 3; lane 5: condition 4; lane 6: condition 5; lane 7: condition 7; lane 8: condition 9; lane 9: condition 10; lane 10: isotype control.

Figure 5: Western blot under nonreduced conditions of the final purified SP Sepharose Fast Flow. Lane 1: condition 1; lane 2: condition 2; lane 3: condition 3; lane 4: condition 4; lane 5: condition 5; lane 6: condition 7; lane 7: condition 9; lane 8: condition 10.



fermentation operation were determined using a numerical optimization function, taking into consideration the culture medium as a single variable because it presented only a significant individual contribution in the growth rate. The equivalent to the range between 0.8 and 1.0 m/s of tip speed (300–400 rpm at 2-L scale) was taken as a range to guarantee the subsequent scaling of the process. With this restriction, the model indicates the possibility of working between 0.008 and 0.014 vvm and with a temperature between 35.6°C and 36.5°C. This range of airflow is similar to others used in the literature (0.004–0.15 vvm) [10] to eliminate the carbon dioxide produced in cellular respiration and guarantee the oxygen consumption of culture.

Physicochemical Characterization

Determination of Purity by SDS-PAGE and Western Blot

Antibody-purity analysis is critical to successful development of mAb biopharmaceuticals. Figure 4 shows the purity pattern of the preparations obtained from the supernatants under different fermentation conditions. In almost all cases, three bands were observed. The first one, which is of greater intensity, corresponds to the intact molecule, and the two lower ones correspond to molecules in which one (or both) of the light chains has been lost [11]. Differences in the intensity of the different molecular variants can be appreciated: the purity for conditions 2, 3, and 4 main bands was greater than 95%, and the purity for all other conditions was below this value; however, statistical differences were not found (P = 0.4737). Those samples with less purity showed bands at lower molecular weights. Some authors have attributed this type of finding to artifacts formed during sample preparation [12]. In our opinion, however, this is not the case because the same processing protocol was used for all samples; therefore, this finding might be related to other operational variables of the production process. However, it should be noted that only the typical antibodies' three bands composed all samples.

All bands observed in SDS-PAGE were identified by western blot (Figure 5), except for a band of much lower molecular weight, which can be seen in the lanes of conditions 1, 5, 7, 9, and 10, and could correspond to a heavy chain band of about 50 kDa. These results confirmed that the preparations obtained are composed of the mAb with a high degree of purity.

Determination of Aggregates

SEC was performed to detect the levels of aggregates, monomers, and fragments. A characteristic HPLC-GF chromatogram of SP Sepharose Fast Flow eluates presented a characteristic peak of the antibody that appeared in a retention time oscillating between 7.51 and 7.87 minutes; the variability between them was 1.57%, which indicates that the majority peak elution behaved similarly in the eight fermentation conditions. In addition, a smaller peak representative of the dimers was observed at values between 6.59 and 6.82 minutes and a variability of 1.32%.

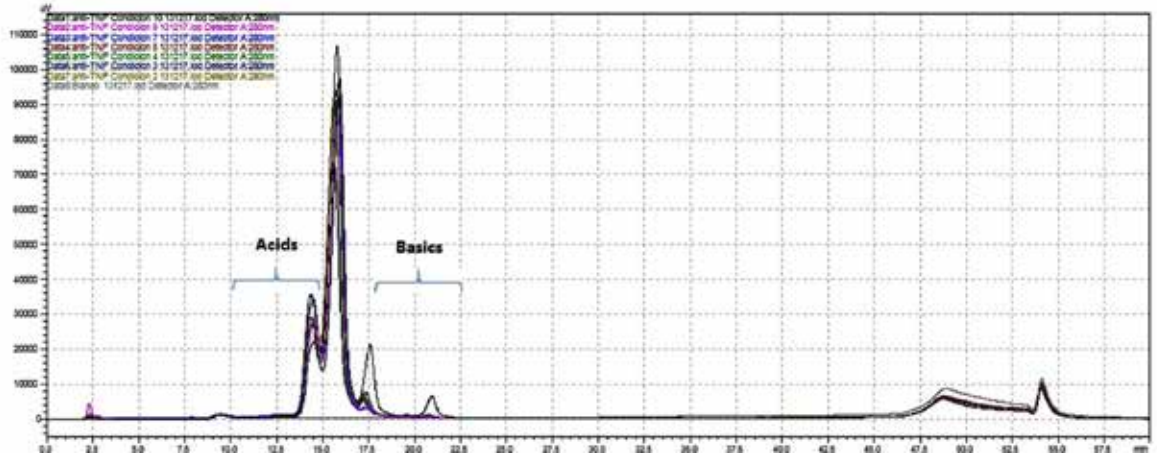
Purity values obtained in the eight fermentation conditions ranged between 99.76% and 99.89%, which indicated a high purity of the molecule obtained in the eight conditions and coincided with other related findings. The variability between the peaks of monomers of the eight purified material was 0.14%; that was below 2%, which is the accepted limit for the accuracy in a single day for this type of test [13].

The statistical analysis performed shows that there were no significant differences in the content of soluble aggregates in the eight conditions evaluated (P = 0.2664).

CEX Chromatography

Monoclonal antibodies show heterogeneity derived from post-translational modifications that include deamidation, glycosylation, oxidation, aggregation, proteolytic degradation, and disulfide bridge formation. Of these modifications, oxidation, deamidation, and proteolytic degradation give rise to charge

Figure 6: Comparison of weak CEX chromatograms of the final purified SP Sepharose Fast Flow. Light green line: condition 2; dark blue line: condition 3; green line: condition 4; maroon line: condition 5; blue line: condition 7; pink line: condition 9; black line: condition 10.



heterogeneity; therefore, weak ion exchange chromatography is used to analyze this variability in therapeutic antibodies [14].

Figure 6 shows the superimposed chromatograms of the samples analyzed. The integration of the chromatograms shows the existence of four peaks, a major peak of neutral isoforms, one peak on the left representing the acid isoforms, and two peaks to the right that correspond to the basic isoforms.

The first peak corresponding to the acid isoforms eluted between 14.33 and 14.57 minutes and represented 12.76% to 20.99% of the area under the curve. The main peak of neutral isoforms represented 53.51% to 58.30% of the isoforms and eluted between 15.61 and 15.91 minutes.

The greatest differences were detected for the peaks of basic isoforms. The first peak eluted between 17.21 and 17.43 minutes and ranged between 0.28% and 3.33% of isoforms detected for all conditions except for condition 10, which represented 11.37% of isoforms detected. The last peak eluted between 20.64 and 20.89 minutes and represented ranges of isoforms detected between 0.03% and 0.28% for most samples; the exception was condition 10, in which the latest peaks represented 14.54% of the isoforms detected. The test showed resolution and reproducibility in the retention times of the peaks because the coefficient of variation ranged between 0.29% and 0.76%.

The presence of lower levels of basic variants has already been reported when comparing biosimilar antibodies such as adalimumab with its original reference product [15]. These basic peaks have been related to the presence of one or two lysines at the C-terminal end of the antibodies, and their absence may be due to a higher activity of a carboxypeptidase enzyme [16].

CD Spectroscopy

CD spectroscopy is a suitable method to quickly determine the type of secondary structure of proteins, and the analysis of a protein's spectra in the far UV directly reveals information about its structural classification [17]. The secondary structure of the eight evaluated conditions of biosimilar antibody was determined from the analysis of the far-UV-CD spectra (Figure 7). As differences in intensity were observed, probably due to an influence of protein concentration, data were transformed using a scale factor [18] and all IgG were shown to overlap indistinguishably.

Spectra were similar in terms of the wavelengths of the positive and negative bands and in the wavelength at zero intensity; they evidenced proteins with a high content of beta sheets, with a positive band around 202 nm and a negative band at approximately 217 nm [19].

Figure 7: CD analysis of mAb samples. The near-UV-CD spectra are presented from condition 1 (black), condition 2 (red), condition 3 (blue), condition 4 (green), condition 5 (pink), condition 7 (olive), condition 9 (dark blue), and condition 10 (maroon). The arrows indicate the positive and negative bands, around 202 and 217 nm, respectively, and the wavelength at zero intensity at approximately 209 nm.

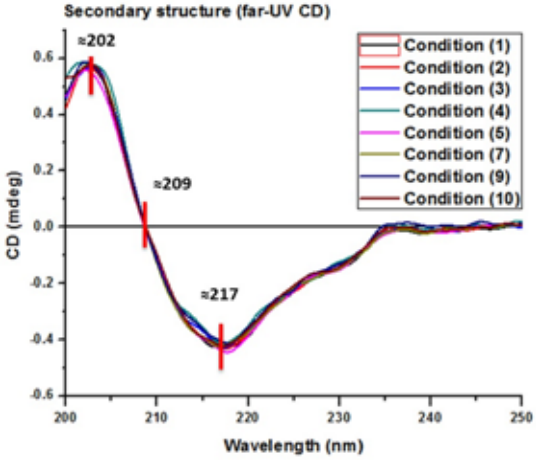
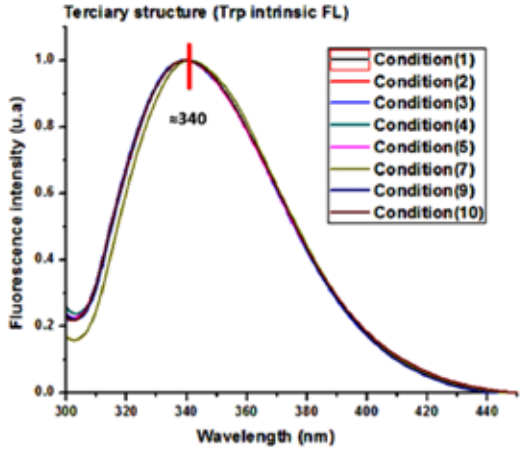


Figure 8: Comparison of intrinsic fluorescence spectra of mAb samples. Spectra are presented from condition 1 (black), condition 2 (red), condition 3 (blue), condition 4 (green), condition 5 (pink), condition 7 (olive), condition 9 (dark blue), and condition 10 (maroon). The arrow indicates the maximum emission of Trp.



Information about the tertiary structure conformational characteristics of the proteins was determined by emission of fluorescence in the range of 300–450 nm, after the selective excitation of the Trp at 295 nm. Figure 8 shows the fluorescence spectra expressed in fluorescence intensity in arbitrary units (u.a.) versus length of wave (nm).

The eight evaluated conditions were also similar in terms of their maximum fluorescence emission of Trp, at approximately 340 nm, which corresponds to the maximum described in the literature for antibodies [20]. The results obtained suggest that the secondary structure and conformational features of the tertiary structure determined by CD and FL of the batches evaluated are similar.

Determination of Binding Affinity to the Ligand

The biological activity of therapeutic antibodies is manifested when they bind to a specific ligand. In this study, the comparison of binding affinity of the purified antibody preparations was performed in a recognition ELISA to determine the binding specificity [21] prior to in vitro neutralization assays using cellular models.

The results obtained indicate that the intensity of ligand binding is dependent on the dose of antibody used (Figure 9), obtaining 100% binding at concentrations of approximately 1,000 ng/mL, and practically no signal exists for concentrations less than 1 ng/mL. This sigmoidal behavior in the studied work range allows the calculation of the EC50 (effective mean dose) as a quantitative parameter to compare the affinity of the molecule for its ligand in the different preparations [22].

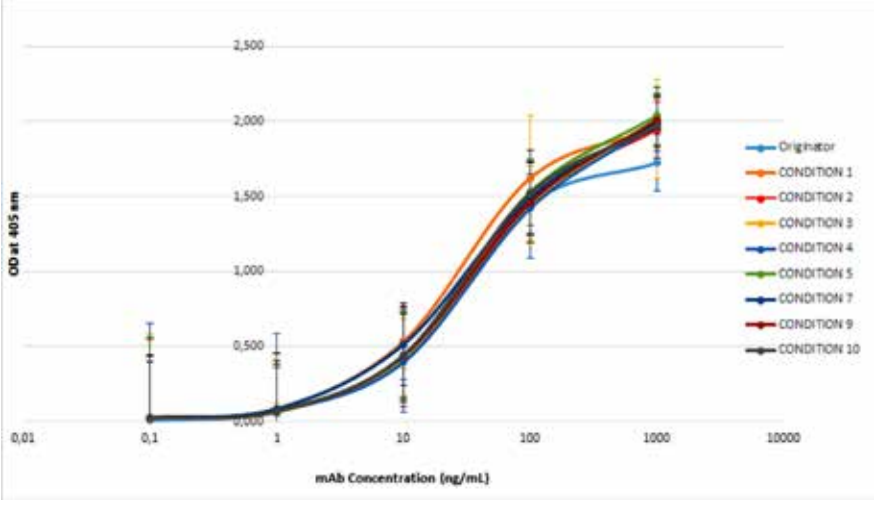
The statistical comparison of the EC50 obtained for the different preparations obtained shows significant differences determined by the temperature variation ($P = 0.0055$), and the interaction between the agitation and the airflow ($P = 0.0099$).

Definition of Critical Process Parameters

Monoclonal antibody products are inherently heterogeneous because of posttranslation modification that often occurs during the fermentation process. The quality evaluation of the molecule obtained in the different fermentation conditions clearly showed that variations on airflow ($P = 0.0045$) and interaction between culture media and airflow ($P = 0.0056$) induced differences in the intensity of the different molecular variants in SDS-PAGE. The higher amounts of H2L2 (complete antibody) were obtained in CMF independently of airflow changes; also, in mixtures with proprietary media formulation, the amounts of H2L and HL variants increased. This could be related to antibody disulfide bond fragmentation related to the presence of free thiols in the supernatant because of diminished concentrations on media mixture of reduction inhibitors for the enzymes involved in the pathway [23]. Diminished airflow also promotes antibody reduction because it maintains a more stable oxygen delivery level, as previously reported [24].

Our study also pointed out that variations on airflow ($P = 0.0280$) and temperature ($P = 0.0162$) influenced distribution of isoforms in isoelectric focusing (data not shown). The increase of both airflow and temperature was related to the apparition of bands of lower isoelectric point; this finding is consistent with reports that demonstrated higher temperature led to a higher level of acidic variant because deamidation or glycation [25] with the low levels of basic

Figure 9: The dose-dependent response of the affinity of the antibody obtained under different fermentation conditions.



The intensity of ligand binding is dependent on the dose of antibody used.

isoforms, detected on WCE chromatograms. The increase in airflow ensures increased oxygen delivery levels, which could lead to an increase on oxidized variants as acidic species because of the generation of negative charges by the Asn (glycans) cleavage to Asp (carboxylic acid).

Our study also showed significant differences in antigen-binding affinity assays, where EC50 of conditions 2, 3, and 7 were 51%–55% higher than the control; therefore, it is possible that product microheterogeneity could potentially generate product variants with decreased functionality. None of the studied parameters was related to biological recognition, so it is possible that potential variations in glycosylation pattern were responsible for antigen-binding affinity modifications. Monoclonal antibody glycosylation is mainly induced by process chemical stress parameters [26]. However, further study analyzing potential causes for the differences in the antigen-binding affinity should be developed.

Optimal conditions were determined for fermentation operation based on the equations obtained using the numerical optimization function of Design-Expert 6.0.1 software. In this context, we assumed that the purified mAb should have more than 95% purity in the H2L2 band in SDS-PAGE, less than 1% aggregation determined by gel filtration HPLC, five peaks in weak cation exchange, and the lowest EC50 dose for ligand binding. As a result, it was determined that in the fermentation process, any of the two culture media could be used. Stirring can be moved in a range between 0.8 and 1 m/s tip speed (between 330 and 450 rpm in the 2-L system); airflow should range between 0.008 and 0.015 vvm, and the temperature should be between 34.04°C and 36.87°C. These results partially coincided with the results of the fermentation process optimization based only on the kinetic parameters of the culture, in which the same ranges of airflow velocity and impeller tip speed were defined, but with a narrower temperature window of between 35.6°C and 36.5°C.

CONCLUSION

Results of this study indicated fractional factorial designs as useful tools for minimizing the number of runs required in the initial screening of potentially influential process parameters of stirred tank fermentation in perfusion. Airflow temperature and agitation speed are key parameters for the good performance of this fermentation process.

Temperature, stirring speed, and airflow were defined as critical operational parameters based on their effects on quality profiles of a therapeutic mAb. Preparations obtained under different fermentation conditions showed differences in purity, whereas the H2L2 molecule ranged from more than 97.52% purity in conditions 2, 3, and 4 to between 78.55% and 92.11% in the other experimental assays. An increase of more than 10% in the amount of basic isoforms was also detected in one of the experimental conditions assayed, and binding affinity to the ligand was more than 50% lower than the control in three conditions.

The statistical model derived from fractional factorial design predicted that in fermentation process scale-up, the operational and design space in terms of stirring and airflow would be the same, but variations in the temperature outside the narrow operational range from 35.6°C to 36.5°C could compromise process yield; however, they would not adversely affect the required quality specifications.

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CHLORINE DIOXIDE GAS DECONTAMINATION

vs. Liquid Disinfection

By Jennifer Longstaff

Manual decontamination procedures are laborious processes and can be costly, requiring significant time and resources to complete. Manual procedures also may need to be repeated if initial efforts do not fully kill pathogens. To reduce failures and potentially reduce cost, chlorine dioxide gas decontamination was investigated as an alternative solution.

The Bausch + Lomb (B&L) Vision Care production facility in Greenville, South Carolina, manufactures contact lens solutions in sterile processing areas within a clean environment. Because the manufactured products either clean contact lenses or are placed directly into a person's eyes, they must be sterile and containers must be filled and sealed in an extremely high-quality environment [1].

Each year, the facility closes for planned maintenance shutdowns. Though necessary, these shutdowns create unsterile environments because foreign equipment, tools, and people enter the clean areas. Therefore, the environment must be cleaned and disinfected before normal production resumes.

MANUAL CLEANING AND DISINFECTION

Historically, manual cleaning and disinfection procedures to prepare the plant for reopening required nearly 100 personnel working in multiple shifts for over six days (three days to clean and then three days to disinfect rooms using mops and buckets). Rooms were cleaned with detergents and/or surfactants and then wiped down with a high-level disinfectant solution. To maintain high quality standards, this cleaning and disinfection process has multiple stages: gross cleaning, followed by fine cleaning, followed by at least three rounds of disinfection. If any posttreatment swabs test positive for contaminants, that particular area might require additional treatment.

In general, manual cleaning and disinfecting activities use physical cleaning motions and disinfectants to kill organisms. Once cleaning is complete, a liquid disinfectant is used to disinfect the area. This cleaning process is considered effective at removing biological contaminants on environmental surfaces.

The disinfectant used is typically applied to a surface, a device surface, or a cloth. Once applied, the disinfectant sits for the contact time prescribed by its manufacturer.

The disinfectant used at the facility is a fast-acting, liquid cold sterilant/disinfectant, filtered through a 0.2-micron filter and specifically formulated for use in the sterilization and disinfection of hard environmental surfaces in pharmaceutical, medical device, biotech, and cosmetic manufacturing facilities. This product is a stabilized blend of peracetic acid, hydrogen peroxide, and acetic acid that provides fast, effective control of microbes, including spores. The disinfecting agent is typically used for a number of reasons: (a) ease of use; (b) consistent dilution because no mixing or activation is required; (c) efficacy—microbial control against bacteria, fungi, viruses, and bacterial spores; (d) safety—the low toxicity profile supports worker safety; (e) convenience—excellent material compatibility allows use on most environmental surfaces; and (f) flexibility and versatility of use—depending on the use concentration, contact time, and application method, the product can be used as a sterilant, sporicide, disinfectant, or sanitizer.

This process is costly and labor-intensive. The manufacturing facility consists of filling rooms, sterile staging areas, gowning areas, and sterile hallways, each with a significant amount of surface area. The filling lines and equipment have many surfaces to treat and thus require large amounts of the disinfectant solution. The company would spend approximately $150,000 to fully disinfect the entire sterile processing facility, and the disinfection process would take about three (24-hour) days and require a crew of nearly 100 people.

Gross Cleaning

Gross cleaning consists of scrubbing all stainless steel equipment with a cleaning solution and using brushes to remove all visible residue. Walls and ceilings are mopped, HEPA filters are wiped with an isopropyl alcohol (IPA)–soaked class 100 wipe, all returns are wiped with disinfectant-soaked lint-free towel, and floors are mopped with a disinfectant.

Fine Cleaning

Fine cleaning occurs after gross cleaning and consists of spraying a cleaning solution on all surfaces except HEPA filters and wiping all stainless steel surfaces and equipment, HVAC return vents, waste containers, curtains, plexiglass, and equipment. Some equipment is uninstalled to facilitate better cleaning. Walls and ceilings are mopped with the cleaning solution and floors are mopped with a disinfectant.

Disinfection

Prior to switching to gas decontamination, there were three rounds of disinfection. In the first round, everything was sprayed with a disinfectant solution, curtains and plexiglass were wiped with a disinfectant-soaked lint-free towel, and all walls and floors were mopped. The second round repeated the first round's cleaning and included wiping the inside of some equipment hoppers as well. In the third round, all surfaces were sprayed and wiped with the disinfectant solution, and then all surfaces were wiped with an IPA-soaked class 100 wipe.

Once the cleaning/disinfection process was complete, the areas were swabbed to confirm the efficacy. If any area tested positive for contaminants, it had to be cleaned and disinfected again, increasing costs and requiring more time and effort.

Given the labor intensiveness, variability, lack of repeatability, and cost of the manual cleaning and disinfection process, B&L sought more efficient, reliable, and cost-effective alternatives. Chlorine dioxide gas was chosen as a test agent because it has been shown effective at decontamination of large-scale facilities [2–4], rooms and suites of rooms [5–9], isolators [10–12], processing vessels and tanks [13, 14], and biological safety cabinets [15, 16]. See Table 1 for a comparison of manual disinfection and decontamination using chlorine dioxide gas.

Table 1: Comparison of manual disinfection and decontamination using chlorine dioxide gas.

	Manual Disinfection	Chlorine Dioxide Gas
Treatment time	3 days (97 people)	2 days (6 people)
Efficacy	Some positive swabs	All biological indicators dead; no positive swabs
Cost	~$150,000* (~$100,000 in disinfectant solution + ~$50,000 in labor)	$97,000 (all inclusive)
Application method	Spray and wipe	Gassing
Method of kill	Oxidation	Oxidation
Level of kill	Sterilant	Sterilant

*Costs could increase if recleaning or re-decontamination were required. (Initial cleaning effort and costs were the same with each method.)

CHLORINE DIOXIDE DECONTAMINATION

Because chlorine dioxide is a true gas at room temperature (boiling point 11°C), its distribution and penetration do not rely on an operator's skill. As a gas, it reaches all areas—including cracks, crevices, and difficult-to-reach surfaces—and provides full coverage, making decontamination more successful than manual disinfection.

As the FDA states, "suitability, efficacy, and limitations of disinfecting agents and procedures should be assessed" [1]. To do this, biological indicators (BIs) were placed throughout the space to test the process and ensure proper decontamination.

Gas Material and Equipment

The following equipment was used to decontaminate the space:

- A 330,000 ft^3 (9,344 m^3) aseptic classified space
- Manual chlorine dioxide gas–generating systems (qty. 14)
- Chlorine gas cylinders (2% chlorine/98% nitrogen) (qty. 28)
- EMS chlorine dioxide gas–monitoring systems (qty. 2)
- Extension cords (100-feet and 25-feet; qty. 10 each)
- Blowers (approximately 1,800 CFM each; qty. 18)
- Small fans (qty. 40)
- Duct tape and plastic
- Spools of ¼-inch red polyethylene tubing (for gas injection; qty. 28)
- Spools of ¼-inch green polyethylene tubing (for gas sampling; qty. 10)
- Rolls of thin 3-mil plastic sheeting (for conveyor sealing; qty. 4)
- Roll of 6-mil plastic sheeting (for large-opening sealing; qty. 1)
- Low-level chlorine dioxide gas safety sensors (qty. 3)
- Pairs of BIs—106 *Geobacillus stearothermophilus* spore strips (qty. 20)
- Prepared culture media: formulated tryptic soy broth modified with pH indicator (qty. 20)

Sterile Processing Facility Decontamination

Gross and fine cleaning of the facility was completed as previously described prior to the chlorine dioxide gassing team's arrival. Once cleaning was completed, decontamination followed in the ensuing steps.

Day 1—Arrival and Initial Setup

The decontamination team of five people arrived onsite in the early afternoon. The listed equipment was brought to the decontamination area, and the manual chlorine dioxide gas generators were set up outside the decontamination space. External windows and doors were taped and sealed to contain the gas during the actual decontamination process.

Day 2—Setup

The decontamination team arrived in the morning and split into smaller teams to continue sealing the space and setting up the decontamination equipment. Sealing began in the packaging transition area, which has small openings in walls where conveyors exit

with finished product in sealed containers. These openings were sealed with a mixture of plastic and duct tape. Because of the nature of the facility, a special duct tape that leaves little to no residue was used. Sealing was performed on the outside surfaces so the sterilant would not miss important internal surfaces.

The HVAC for some areas was turned off, allowing roof units to be sealed. Some HVAC units were left on for workers' comfort and to control humidity in the space.

Some HVAC units had exhaust and supply vents common with areas outside the cleanroom space. When gas enters duct work, it will leak to outside areas unless the vents are sealed. Therefore, common vents outside the space were located and sealed with duct tape and plastic.

At the same time that the area was being sealed off, another team set up the gas generation system by evenly distributing blowers and small fans throughout the space. Blowers and fans were usually placed close to power outlets. Because the fans were used to speed up the diffusion of the gas and were not needed to force the gas into specific areas, where they were placed was not critical.

Red gas injection tubing was run from each generator to multiple locations within the space. Gas generators were located outside the space, ensuring that generators could easily be stopped if necessary for safety. Some gas injections points were combined in one area to minimize the time to place the tubing.

After the gas injection tubing was placed, the green tubing used for sampling gas concentrations was run from the chlorine dioxide gas–monitoring system's gas sensor, which was placed outside the decontamination space, to locations in the space away from the gas injection sites. The monitoring system used a small diaphragm pump to draw in air samples from the different locations (one at a time) through a photometer to read the actual real-time chlorine dioxide concentration. The photometer measures the absorbance of the gas, and the monitoring system converts this absorbance into a chlorine dioxide gas concentration reading in mg/L. The monitoring system uses these readings to determine when the concentration reaches the required dosage.

In some projects, some areas may not come up to concentration as expected, either due to leakage or because gas consumption is greater than expected. If that happens, some generator injection points are moved to the spare injection points. Spare gas injection points were not used on this project.

Once the fans and tubing were set up, and most HVACs sealed, 20 pairs of BIs were placed at 20 locations throughout the facility to test the efficacy of the process. Pairs of BIs were used based on validation studies performed by Luftman and colleagues [15]. In this study, it was decided that if both BIs were positive, the results were positive (growth); if both BIs were negative, results were negative (no growth). On the rare occasion that one BI was positive and one BI was negative, it was assumed, with a 95% confidence level, that there was a 5.7 log reduction of spores. For facility decontamination, these results would be considered successful and significantly more effective than utilizing a liquid disinfectant solution.

Once the BIs were placed, the remaining unsealed HVAC cooling coils were shut off, allowing outside humidity to enter the space and raise humidity in the room to over 70%. The decontamination took place during the summer months, so ambient/outside humidity was naturally high. Once room humidity was verified in all areas to be above 65% for a minimum of 30 minutes, the HVAC was shut down and sealed and then the last entry doorway was sealed.

Day 2—Gassing

At approximately 16:45 (4:45 p.m.), the gas cylinders were opened and gas injection began. Chlorine dioxide gas was generated by passing a low-level chorine gas (2% chlorine/98% nitrogen) through solid sodium chlorite cartridges, which converts the chlorine to a 99.9% pure chlorine dioxide gas. Workers walked around the decontamination space carrying low-level safety sensors to locate any possible leaks in any of the plastic and duct tape sealing. This task was performed periodically to ensure worker safety. Chlorine dioxide gas has a low odor threshold (0.1 ppm), which coincides with the 0.1 ppm, eight-hour personal exposure level.

Gas injection ran continuously from 16:45 to 21:00 (4:45 p.m. to 9:00 p.m.) to accumulate a minimum dosage of 720 ppm-hours to achieve a 6-log reduction of spores (see Figure 1 for concentration readings and Figure 2 for dosages).

All concentrations were at or near the target of 1 mg/L, except for the pre-gown area (see Figure 1). This sample tubing had a leak that diluted the sample reading. The area was verified to be above concentration by visual inspection. A yellow-green color was observed inside the space, signifying the presence of chlorine dioxide gas. This inspection does not inform the user of the concentration; however, if the gas is highly visible, an experienced user knows the concentration is higher than the 1 mg/L target concentration.

After the dosage was reached, a team went up to the roof to unseal the air handling units (AHUs). At approximately 22:00 (10:15 p.m.), all AHUs were unsealed and turned on.

Aeration in the three sterile component staging areas was started at 21:00 (9:00 p.m.). These areas were identified to have no exhaust capabilities; therefore, a supplementary aeration system was set up in this area. This system consisted of four external blowers pulling air from the component staging area and blowing it out the nearest rollup door to the plant exterior. All filling lines aerated in a normal amount of time. Safe levels of chlorine dioxide (0.1 ppm) were attained about 22:30 (10:30 p.m.) in all areas.

Around 23:00 (11:00 p.m.), three people entered the sterile facility and donned gowns following B&L procedures. The team removed the BIs, tubing, blowers, and fans and crated equipment. Then, the team used a low-level safety sensor to verify the gas concentration in all areas was below safe level. Once this was verified, all sealing plastic and tape were removed. The team exited the cleanroom at approximately 0:00 (12:00 a.m.). The remaining equipment was packed into the crates, and the team left the site at approximately 01:30 (1:30 a.m.). Finally, all BIs were incubated for 36 hours in the prepared culture media to test for growth. Table 2 lists the BI results.

Figure 1: Chlorine dioxide gas sample readings (mg/L) charted over time.

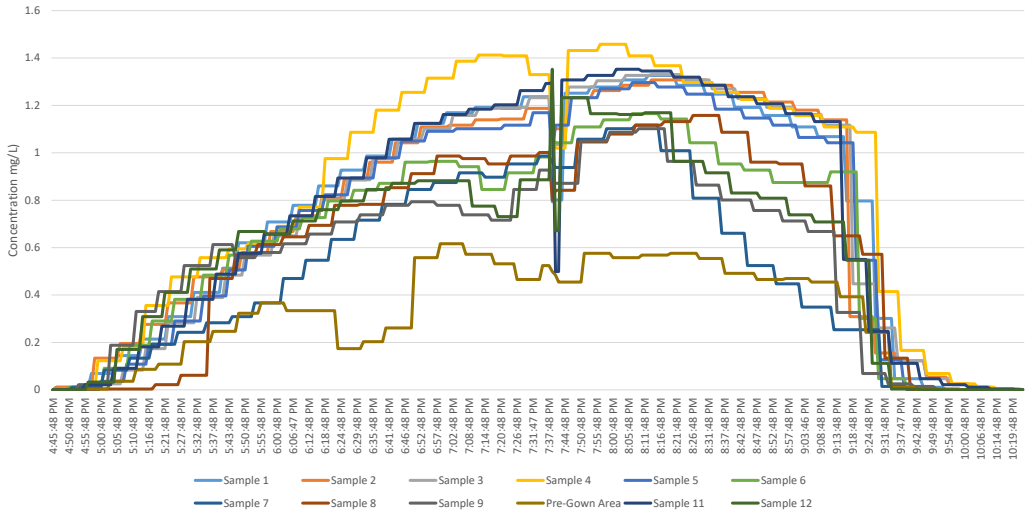
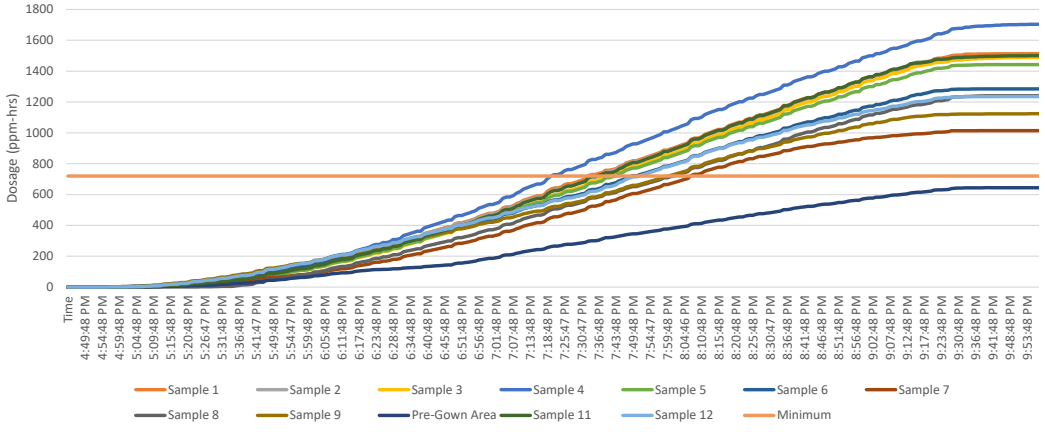


Figure 2: Chlorine dioxide gas dosages charted over time. Dosages were above the minimum dosage of 720 ppm-hours except in the pre-gown area.



DISCUSSION

Many pharmaceutical/biotech companies operate cleanrooms, with some specified as sterile processing areas. This policy is to keep the product microbiologically clean. During the normal course of events in cleanrooms, maintenance occurs. When maintenance occurs, contaminants can enter an area. To combat this, cleaning is performed after the planned service and before production is restarted. In the past, B&L used manual cleaning process (gross and fine) followed by three separate disinfecting steps.

The first part of any decontamination is cleaning to remove excess bioburden. Once this is accomplished, the decontamination step occurs. In the past, this was done at B&L by manually spraying and wiping the high-level disinfectant solution on all surfaces. Manual decontamination is not optimum because it is difficult for workers to spray and wipe every surface and get complete disinfectant coverage in the scratches, cracks, and crevices where organisms hide. When surfaces are sprayed with disinfectant, droplets are deposited onto the surface. If these droplets are larger than the cracks and crevices, they cannot penetrate completely. Even if the liquid disinfectant is fogged or mopped, it still does not reach every nook, crack, and crevice.

In contrast, chlorine dioxide, which is a true gas at room temperature, can penetrate every space due to its extremely small molecule size (0.124 nm [10^{-9}]). Compared to using liquids and a manual disinfection process, the advantages of gas decontamination become apparent.

Table 2: Biological indicator locations and results.

BI #	Location	Result After Incubation
1	FFS, valve lever	Negative
2	Line 7 machine in plastic enclosure	Negative
3	Line 5 valve on machine	Negative
4	Line 2a second door back left machine	Negative
5	Line 1 back round machine	Negative
6	Prep area center rack	Negative
7	CTA right window	Negative
8	Tote unload podium	Negative
9	Central sterile component staging center support	Negative
10	New area square support	Negative
11	Line 7 hallway machine	Negative
12	Line 6 angle beam in plastic enclosure	Negative
13	Line 6 hallway, center door machine	Negative
14	Line 5 hallway, center door machine	Negative
15	Line 4 machine back middle door	Negative
16	Line 2a hallway, machine	Negative
17	Line 1 hallway, machine middle door	Negative
18	Exit sanitization booth rack	Negative
19	Entry sanitization booth yellow bucket	Negative
20	Prep area 2 back right orange container	Negative
Positive control		Positive

CONCLUSION

The completed chlorine dioxide gas decontamination cycle at the B&L sterile processing facility was qualified as successful. All BIs were negative, apart from the positive controls.

The resulting ppm-hour dosage achieved from the decontamination cycle was adequate to provide a 6-log sporicidal reduction on the BIs after 36 hours of incubation. Total ppm-hour exceeded the required 720 ppm-hour for 6-log reductions of spores for all areas.

The decontamination cycle was also a success from an economic point of view: The costs of gassing were approximately 30% less than the traditional spray-and-wipe approach. With this cost saving, better coverage of the decontamination agent, and decreased downtime, this process was considered a complete success. B&L now uses chlorine dioxide gas as the preferred decontamination agent.

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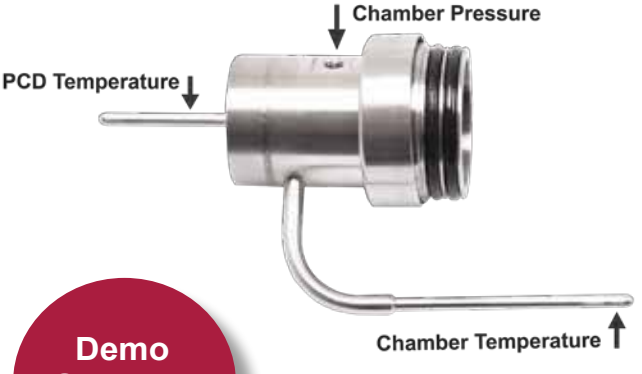

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