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BIOPHARMA MANUFACTURING

Cell and Gene Therapies and Their GMP Requirements

Biopharma's Next Wave

Article of the Year 2018

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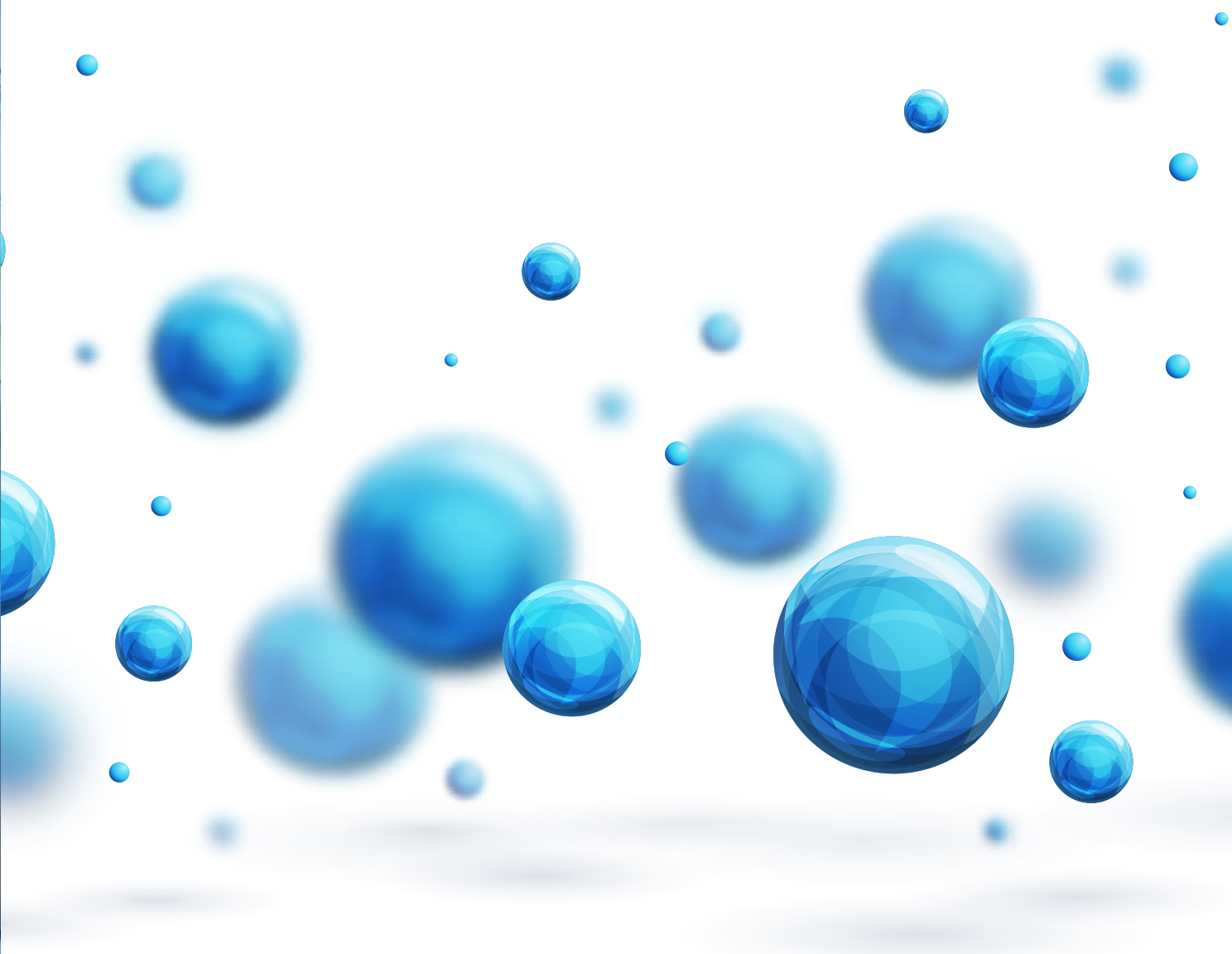

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CELL AND GENE THERAPIES AND THEIR GMP REQUIREMENTS

Cell and gene therapies are the latest revolution in medicine manufacturing. Unlike small molecules or traditional biotech products, these therapies introduce cells and genes into a patient to treat the underlying cause of a disease—they are living medicines. This article provides an overview of key considerations for manufacturers of cell and gene therapies.

ON THE COVER Biopharmaceutical manufacturing's "building block" DNA structure is shown on a scientific background.

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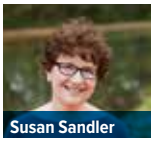
Susan Sandler

The November-December issue of *Pharmaceutical Engineering* is published in the months of the Thanksgiving holiday in the US and the year-end holidays celebrated around the world, so it seems appropriate to note the many changes to the magazine this year and give thanks to those who have contributed to and supported those changes.

PE ONLINE

PE Online launched in November 2018. The site features content from current and recent print issues of PE as well as the iSpeak blog, and it is easily searchable for faster access to the content that interests you most. PE Online also publishes content not found anywhere else, such as sponsored content and white papers from various ISPE partners. These offer additional analysis and industry information that enhances PE's technical and feature articles. Watch for more new developments on the site next year!

The development, launch, and maintenance of PE Online has been overseen by the website team at ISPE, headed by Jessica Bleess, Manager, Digital Strategy and Web. Their contributions to creating and maintaining the site allow us to provide a quality online magazine that you can access anywhere you go, and we are thankful for their work in support of the magazine.

THE PRINT MAGAZINE

In 2019, PE published more than 50 features and technical articles, plus columns, member profiles, and other content, in the print magazine. Much of this content was developed, sourced, and/or reviewed by members of the *Pharmaceutical Engineering* Committee (PEC), led by Ferdinando Aspesi, Chair. The PEC provided additional support through an extensive overhaul of internal editorial and production processes this year. Thank you to the PEC for your support and your continued commitment to providing quality content to ISPE members.

Two freelance editorial consultants, Heather Saunders (Just The Write Type) and Elizabeth Nishiura, provide exceptional editorial and operations support to the magazine. The "look" of the magazine continues to evolve with design work by THOR Design Studio that helps define our brand and ties in with the PE Online site. These invaluable members of our team enhance the quality of PE.

PE AUTHORS

Finally, thanks to all the authors who contributed content to this year's issues of PE. Your expertise and knowledge support the important and life-saving work of ISPE members. The expanded coverage of critical topics such as biopharmaceutical manufacturing—this issue's theme—helps inform the industry about changing trends and the role that ISPE members play in bringing new trends to life. The reviewers who provided subject-matter expertise must also be recognized for their contributions that help the authors to fine tune their articles.

On page 36, we recognize the outstanding finalists and winner of the 2018 Roger F. Sherwood Article of the Year award. Congratulations to the authors of the "best of the best" articles during 2018. We look forward to assessing articles published in 2019 for next year's award and anticipate with excitement all future submissions.

Best wishes for a joyous and peaceful holiday season, and for a happy new year.

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

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LeAnna Pearson Marcum

LEADING AT ALL LEVELS OF YOUR CAREER

I was recently meeting with one of the individuals I am lucky enough to call a mentor and friend. During our dinner, we talked about various topics from general life items to questions about work. One of the questions she asked that inspired me to write this article was, "If leaders are people with experience and wisdom, how can I be seen as a leader when I am just starting my career?"

I think this is a question that is asked often. I know I have asked myself this when starting new roles or at new companies. Many students and young professionals (YPs) ask me this. There is no easy answer to this question, and there are lots of options, but any option will take you putting in the work and effort—this is the hard part for some to hear.

I recently read a book by Brené Brown called *Rising Strong: How the Ability to Reset Transforms the Way We Live, Love, Parent, and Lead*. One of the quotes from it that I now have at my desk is "You can choose courage, or you can choose comfort, but you cannot choose both." This resonated with me from a career and professional growth perspective. I realized after speaking with my mentor that I have made both choices throughout my career. Each time I have raised my hand to lead a committee or be on a task team, I have been choosing courage. In most of these situations, I had some background in the role; however, in many cases, I was raising my hand because I didn't have that experience and I wanted it, and sometimes this was terrifying. During those times when I felt like I jumped into the deep end, I utilized my mentors and colleagues to help guide me. I truly believe that the bravest thing we can do is reach out when we need help.

TAKE THE NEXT LEADERSHIP STEP

So, how can you lead at all levels in your career?

- Volunteering in a professional organization is one of the biggest ways I was given a leadership opportunity before I ever became a leader within my organization. This does not mean that you have to run a committee or jump straight to the board of directors—just take on some micro-volunteering positions.
- Read books on leadership (see the sidebar for some of my favorites).
- Ask your company if they offer any leadership courses.
- Reach out to a leader and ask them questions on how they have chosen courage over comfort.

MICRO-VOLUNTEER

What exactly is a micro-volunteering position? It is an opportunity that allows you to lead a specific task or special event. This should take less time than leading a volunteer program or committee.

- Look for a position that has a component that pushes you and displays your leadership skills.
- Ask the chair or leader of a task group or team how you can help; trust me, they always need help!

Expand Your Leadership Library

- *Dare to Lead: Brave Work. Tough Conversations. Whole Hearts.* by Brené Brown
- *StrengthsFinder 2.0* by Tom Rath
- *You're It: Crisis, Change, and How to Lead When It Matters Most* by Leonard J. Marcus, Eric J. McNulty, Joseph M. Henderson, and Barry C. Dorn
- *Daring Greatly: How the Courage to Be Vulnerable Transforms the Way We Live, Love, Parent, and Lead* by Brené Brown
- *True North: Discover Your Authentic Leadership* by Bill George
- *Emotional Intelligence 2.0* by Travis Bradberry and Jean Greaves
- *Permission to Screw Up: How I Learned to Lead by Doing (Almost) Everything Wrong* by Kristen Hadeed

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LEAD A GROUP

Leading a group can be done at the local or international level.

- Before you decide to do this, make sure you understand the time commitment and expectations. (See my editorial in the March-April 2019 issue of *Pharmaceutical Engineering* on managing expectations to help you with this.)
- Identify someone who previously had this role and ask them to be a mentor to you in the role, or just bounce ideas off them.
- Set goals for yourself to achieve, and ask the team to hold you accountable to these goals.

ISPE VOLUNTEER OPPORTUNITIES

There are several groups within ISPE looking for volunteers in both leadership and micro-volunteer roles.

- YP Community of Practice: Email LPearson@bluebirdbio.com to learn more.
- PE magazine: ispe.org/pharmaceutical-engineering
- Women in Pharma®: ispe.org/women-pharma
- ISPE Communities of Practice: ispe.org/membership/communities-practice
- Planning committee for various ISPE conferences: Email mbock@ispe.org for more information.

> During those times when I felt like I had jumped into the deep end, I utilized my mentors and colleagues to help guide me.

- Local Affiliate and Chapter committees: Reach out to your local Affiliate or Chapter for more information.

Moving outside of your comfort zone can yield tremendous results in the long run. Take the first step and stay courageous.

LeAnna Pearson Marcum is a QAV Manager with bluebird bio in Durham, North Carolina, and the 2019–2020 ISPE International Young Professionals Chair. She has been an ISPE member since 2009.

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CELL AND GENE THERAPIES AND THEIR GMP REQUIREMENTS

By Kasia Averall

Cell and gene therapies are the latest revolution in medicine manufacturing. Unlike small molecules or traditional biotech products, these therapies introduce cells and genes into a patient to treat the underlying cause of a disease—they are living medicines.

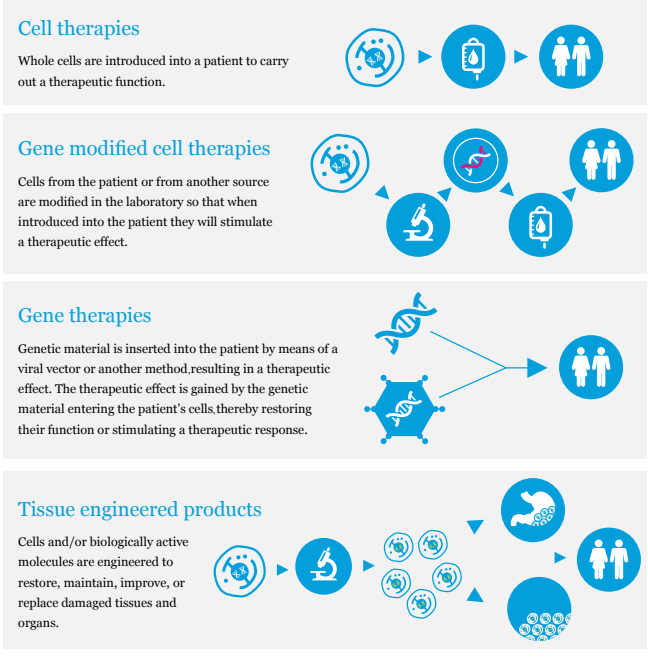
This article provides an overview of key considerations for manufacturers of cell and gene therapies. It is primarily relevant to manufacturing in the UK and Europe, but has leveraged worldwide references where possible.

A GROWING FIELD

Broadly, this field has four types of therapies: cell therapies, gene-modified cell therapies, gene therapies, and tissue-engineered products (Figure 1) [1]. The term "cell and gene therapies" has been used throughout this article to collectively refer to these four types, also known as regenerative medicines or, in the European Union (EU), advanced therapy medicinal products (ATMPs).

Autologous therapies are manufactured using cells taken from a patient, which are then readministered to the same patient. Therefore, each batch is unique and irreplaceable. Allogenic

Figure 1: The four types of cell and gene therapies. Reprinted with permission from reference 1: "What Is the Potential of Cell and Gene Therapies?" ©2019 Catapult.



products are those where batches are manufactured using material from a single donor and administered to different patients (Figure 2).

The cell and gene therapy field is expanding worldwide. Data from the Alliance of Regenerative Medicine show there are now more than 906 regenerative companies worldwide, conducting more than 1,000 clinical trials [2]. Total global financing stands at $13.3 billion, a 73% increase from 2017 [2].

Some of the biggest developments for cell and gene therapies have been in oncology. One of the most advanced areas in terms of clinical development and regulatory approvals is chimeric antigen receptor T cell (CAR-T) therapy. Here, T cells (a type of immune cell) are collected from a patient and modified by adding a chimeric antigen receptor—a membrane-bound protein that recognizes cancer cells—so the CAR-T cells can more effectively distinguish cancerous cells from noncancerous cells. These modified T cells are infused back into the patient to begin attacking cancer cells [1].

Cell and gene therapies are progressing from clinical trials to approved products. In 2018, the first CAR-T therapies were approved in the EU, Australia, and Canada, following US approvals in 2017 (Table 1) [2].

Payment and reimbursement strategies are being worked out as well. The UK National Health Service offers CAR-T therapies for children and young people with B cell acute lymphoblastic leukemia, and the UK National Institute for Health and Care Excellence recommends CAR-T therapy for adults with diffuse large B cell lymphoma and primary mediastinal B cell lymphoma [3]. There is a demonstrated market demand for these products.

If current trends are realized, the number of cell and gene therapy patients in the UK is estimated to grow from approximately 200 in 2018 to around 100,000 in 2028 [4]. This dramatic growth will be underpinned by supporting systems in manufacturing, logistics, and patient treatment.

To support this expansion, robust manufacturing processes and collaboration with an end-to-end supply chain—including therapy, clinical administration, and follow-up—are required. In the EU, cell and gene therapies are medicinal products governed by medicinal product regulatory frameworks; therefore, cell and gene therapy product manufacturing must comply with GMP principles.

Figure 2: The manufacturing of autologous and allogenic therapies. Reprinted with permission from reference 1: "What Is the Potential of Cell and Gene Therapies?" ©2019 Catapult.

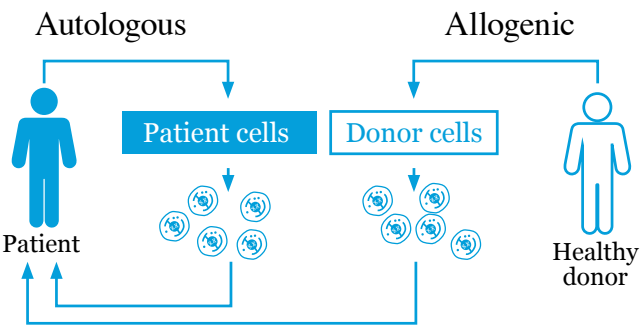
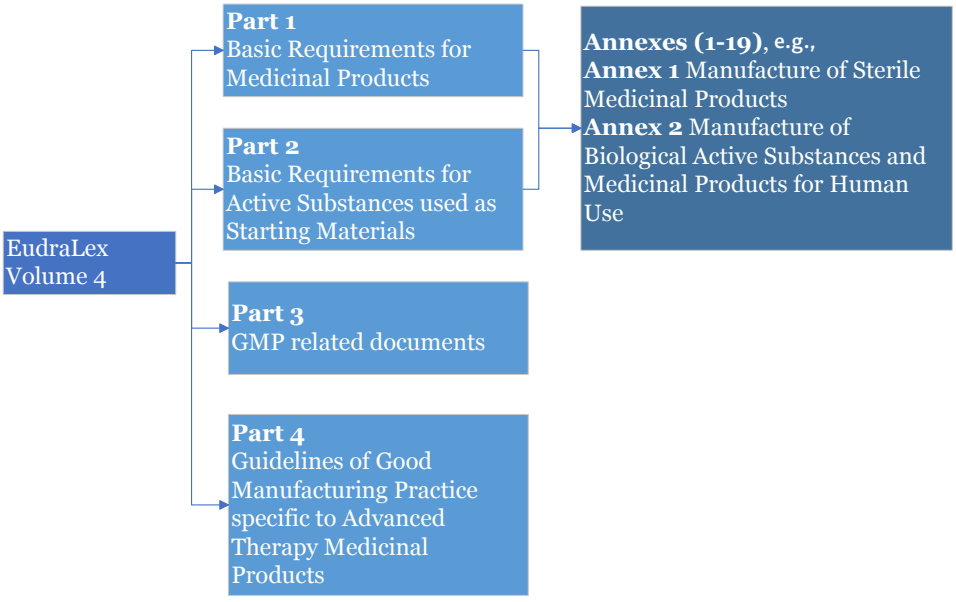


Table 1: Recently approved cell and gene therapy products [2].

Name	Company	Type	Indication	Approval Status
Kymriah	Novartis	CAR-T therapy	Oncology (acute lymphoblastic leukemia [ALL], chronic lymphoid leukemia, and diffuse large B cell lymphoma)	US Food and Drug Administration (FDA) approval August 2017 (additional indication approved May 2018) European Medicines Agency (EMA) approval August 2018 Health Canada approval September 2018 Japan approval (for ALL treatment) February 2019
Yescarta	Kite Pharma/Gilead	CAR-T therapy	Oncology (B cell malignancies [e.g., non-Hodgkin lymphoma])	US FDA approval October 2017 EMA approval August 2018 Health Canada approval February 2019
Luxturna	Spark Therapeutics	Adeno-associated viral vector gene therapy	Retinal dystrophies	US FDA approval December 2017
Alofisel	TiGenix/Takeda Pharma	Allogenic stem-cell therapy	Complex perianal fistulas in patients with Crohn's disease	EMA approval March 2018

Figure 3: EudraLex Volume 4 structure (source: Kasia Averall).



REGULATORY FRAMEWORK

As with all EU-manufactured or supplied medicinal products, cell and gene therapies are governed by EU Directive 2001/83/EC, specifically as amended by Regulation 1394/2007 on ATMPs [5]. However, there are notable differences between the regulatory structure governing cell and gene therapy products—ATMPs in the EU—and that governing other medicinal products.

In the EU, GMP guidelines for medicinal product manufacture are detailed in EudraLex Volume 4 [6], which is split into parts and annexes (Figure 3). As of May 2018, cell and gene therapy manufacturers based in or supplying the EU must comply with the newly issued Part 4, Guidelines of GMP specific to ATMPs [7]. Prior to the release of the Part 4 guidelines, manufacturers were required to comply with existing GMP guidance given elsewhere in Volume 4, specifically Parts 1, 2, and 3 and the annexes. The new guidance is a stand-alone document designed to allow cell and gene therapy manufacturers to make full use of new technologies; it is prefaced with text confirming that GMP guidance given in the rest of Volume 4 does not apply. For example, when Part 4 was introduced, Annex 2, "Manufacture of Biological Active Substances and Medicinal Products for Human Use," was revised to exclude ATMPs [8]. Therefore, manufacturers of both cell and gene therapy products and other medicinal products should ensure that their pharmaceutical quality system (PQS) satisfies the requirements of all relevant EudraLex parts.

Other regulatory requirements arise from the use of human cells. Upstream of the manufacturing process, before GMP manufacturing begins, the EU's donation, procurement, and testing requirements for human cells are governed by the EU Tissues and Cells Directive (EUTCD), 2004/23/EC [9]. Once ready for manufacture, the subsequent processing, storage, and distribution of these cells comes under the remit of GMP, as detailed in Part 4 of EudraLex Volume 4.

In the UK, the competent authority for the EUTCD is the Human Tissue Authority (HTA), while the competent authority for GMP manufacturing is the manufacturer's relevant member state authority. Manufacturers must engage with both competent authorities and understand which oversees the different parts of their processes. Depending on the activities taking place on site, two authorizations may be required. To facilitate this, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) Innovation Office offers a one-stop shop—a single point of contact for all regulators involved in regenerative medicines, including the Human Fertilisation and Embryology Authority, the Health Research Authority, the MHRA, and the HTA.

The manufacture of cell and gene therapy products may include genetically modified organisms (GMOs), in which case manufacturers must also comply with relevant health and safety regulations. In the UK, this is covered by the Genetically Modified Organisms (Contained Use) Regulations 2014 [10]. Unlike GMP guidance, which seeks to ensure the therapy quality, health and safety regulations ensure that risks to the health of the manufacturing operatives and the environment have been fully assessed. These regulations mandate a containment strategy to prevent release of GMOs into the environment. Similarly, any discharge of waste streams down the drain may require local trade effluent permission.

Other regulations that apply to other medicinal products apply equally to cell and gene therapies, such as the guidelines issued by

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the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) [11]. ICH Q9 provides the principles of quality risk management, which are helpful for cell and gene therapy manufacturers required to comply with the risk-based approach mandated by EudraLex Volume 4, Part 4. Another example is pharmacopoeias; Part 4 specifically references European Pharmacopoeia 5.2.12, "Raw Materials of Biological Origin," meaning manufacturers must consider these requirements for the raw materials they are using in cell and gene therapy manufacturing.

MANUFACTURING CHALLENGES

With the cell and gene therapy field expanding so quickly, manufacturing processes need to deliver reproducible and safe processes at an achievable price. This section outlines some challenges facing cell and gene therapy manufacturers.

Manufacturing Processes

Cell and gene therapy manufacturing processes range in complexity. Although some processes do not require substantial manipulation of cells, others include more detailed cell cultivation or manipulation steps, such as gene modification. None of these processes are risk-free, and all pose challenges to the manufacturer. To meet these challenges and provide guidance for a range of manufacturing processes in a rapidly developing field, EudraLex Volume 4, Part 4 describes the risk-based approach that applies equally to all ATMPs in all settings.

When making, designing, and implementing cell and gene therapy manufacturing processes, manufacturers need a process to identify the specific risks associated with the product and manufacturing process and implement appropriate controls. These risk assessments should consider the specific risks posed by autologous or allogenic therapies. For autologous products, where each batch is unique and irreplaceable, the manufacturer must implement enough controls to ensure that each batch is of an appropriate quality despite the limited batch sizes, inherent variability of starting material, and manufacturing process constraints. For allogenic therapies, batch sizes and patient populations can be much larger.

Supply Chain Complexity

Managing supply chain complexity is not a new issue for the pharmaceutical industry. Every manufacturing process requires starting materials, raw materials, and consumables to yield product, samples, and waste. Cell and gene therapies are no different, and many existing supply chains are based on those used by traditional biotech or blood products. Additional challenges are posed by autologous product manufacturing, where vein-to-vein traceability is required. Traceability must begin before batch manufacturing, with the collection of the patient cells, and continue after manufacturing, as the therapy is administered to the patient, with the manufacturer observing all post-marketing pharmacovigilance requirements.

Storage and Equipment

Once they are on site, human cells and the raw materials required for manufacturing must be carefully stored to maintain them. Cell and gene therapy manufacturing sites contain vapor-phase liquid nitrogen storage, –80°C storage, as well as controlled ambient, 2°C–8°C, and –20°C storage. When assessing risk in these storage areas and implementing controls to prevent failure, manufacturers must consider that patient material is irreplaceable and loss of cell culture ingredients, such as labile cytokines or growth factors, may prevent batch manufacturing from occurring within the time frame required by the patient.

Although magnified by autologous product manufacturing, these considerations are shared by allogenic product manufacturing processes. Both manufacturing processes tend to use single-use manufacturing equipment—which must also be traceable throughout batch manufacturing—such as tubing sets, bags, and filters. While some types of single-use equipment come from large biotechnology manufacturers as off-the-shelf items, many more need to be custom designed by the manufacturer, which increases the risk of loss. A humidity excursion in the warehouse may not impact these products directly, but it can damage the packaging seals, rendering them nonsterile. Although there are advantages to single-use consumables, the plastics and resins used in their construction or the methods used to sterilize them may adversely impact GMP manufacturing processes, such as cell differentiation. Cell and gene therapy manufacturers should work closely with suppliers to ensure control over plastics and resins used in the manufacture of these items—a task made more difficult by the relatively small scale of manufacturing processes. Cell and gene therapy manufacturers are small-scale customers to most suppliers, at least for the moment.

Variability Control

As manufacturing processes work with biological material, there is a high degree of variability in both the starting and raw materials and the finished products. Starting materials received from individuals vary from person to person, and with the collection method. Raw materials, such as cytokines, can have a significant impact on cell behavior and batch quality. Cell and gene therapy manufacturers must understand the impact that each batch component can have on the quality of their finished therapy and implement controls accordingly. Depending on the phase of manufacturing, issues to be addressed will include specification setting, supplier management, or working with suppliers to supply pharmaceutical-grade materials in place of research-grade materials. Suppliers of raw materials suitable for small-scale research batches may not be suitable for or able to supply large-scale GMP manufacturing processes. In addition, there are a limited number of companies supplying the materials required for cell and gene therapy manufacturing processes. The challenges of a large-scale biotechnology supply chain are only enhanced for newer, cutting-edge, smaller-scale cell and gene therapy processes.

Sterilization

Cell and gene therapies are generally administered intravenously and, therefore, must be sterile. However, as living products, they cannot be sterilized by heat or irradiation. In addition, because human cells are larger than a 0.2-µm sterilizing filter, cell and gene therapy products cannot be sterilized by filtration. Therefore, cell and gene therapies require aseptic manufacturing processes; additionally, all batch inputs, including any viral vectors used, also must be sterile.

Open Processing

Most cell and gene therapy manufacturing processes were developed in academia and consequently begin as open processing, taking place in a biosafety cabinet with an EU Grade B background (roughly analogous to an ISO 14644-1 Class 5 or Class 6/US FDA Class 100 or 1,000 background). Manufacturers of traditional sterile products will be familiar with the complexities and cost of running cleanrooms for this class. Open processing comes with an increased risk of product contamination from the environment or operators, and, once contaminated, irreplaceable patient material may not be recoverable. There are higher risks—and costs—associated with the increased gowning, environmental monitoring, and cleaning regimens required to support an EU Grade B environment. Therefore, where possible, manufacturers are increasingly working to close their manufacturing processes or conduct the open steps in an isolator, allowing them to take advantage of an EU Grade C or Grade D background (approximately equivalent to an ISO 14644-1 Class 7 or 8/US FDA Class 10,000 or 100,000 background). Manufacturers must consider, however, that many components in living medicines cannot be sterilized with hydrogen peroxide vapor, requiring manual transfer into the isolator.

Cell and gene therapy manufacturers cannot perform concurrent open manufacturing of different products or batches in the same area due to the risk of batch cross contamination, especially when different viral vectors are being processed. However, each patient sample represents a unique batch—especially for autologous products—meaning manufacturers produce a large number of individual, small batches. Another advantage of closing the manufacturing process is that it opens the possibility of concurrent batch manufacture, which is necessary to deliver the throughputs required to supply predicted clinical demand. Multiple closed systems processing different batches can be used in the same area when supported by control measures to prevent cross contamination.

Waste Stream Management

Waste streams produced by cell and gene therapy manufacturing may range from small scale for autologous cell therapy processes to much larger volumes (e.g., thousands of liters) for viral vector manufacturing. Viral vector manufacturing produces large volumes of waste because of low production yields.

In addition, if GMOs have been used in the manufacturing process, they need to be inactivated before disposal. There are two main reasons for this. First, inactivation of waste may be mandated by the GMO class of the organism. In the UK, the Genetically Modified Organisms (Contained Use) Regulations 2014 [10] have different requirements for waste inactivation based on the GMP class, with increasing stringency (e.g., autoclaving in place) required for higher-classification organisms. However, for GMO Class 1 and 2 organisms, which are more frequently used in manufacturing processes, inactivation can take place outside the cleanroom using chemical methods. The second reason to inactivate waste in situ is to prevent cross contamination in multiproduct facilities or prevent contamination of clean cell processing steps.

If inactivation using an autoclave cannot be achieved inside a cleanroom, chemical waste inactivation may be required. When selecting and qualifying the inactivation agent, the manufacturer must account for the matrix within which the agent will work. This will include a background of human cells, any potential bacterial or fungal contaminants, and the environmental conditions such as pH and temperature representative of the process.

CROSS CONTAMINATION

Manufacturing sites may be multiproduct, requiring control measures in place to prevent batch contamination. For autologous gene therapy products, where each patient sample represents a unique batch, different products can be manufactured using different viral vectors. Most of the cross-contamination measures described in this section are based on measures in place at the Cell and Gene Therapy Catapult Manufacturing Centre in the UK, where viral vector manufacturing occurs under the same roof as cell therapy manufacturing.

For these types of multiproduct manufacturing facilities, cross-containment measures start with facility design. The requirement for segregated areas can be achieved by dedicated air-handling units in each area. If the HVAC systems serving manufacturing areas provide 100% fresh air with no recirculation, different batches can be processed within isolators concurrently as long as they are supported by a robust risk assessment with appropriate control measures in place. Pressure cascades should be used to maintain cleanroom grade and containment. The latter can be achieved through either pressure sinks or bubbles.

When making this decision, manufacturers must assess the activities occurring in each area (e.g., ensuring mitigating controls are in place to prevent particulate contamination generated from gowning activities being pushed into cleanroom manufacturing areas). Complex HVAC systems are at increased risk for failure; therefore, manufacturers must understand airflows in the event of HVAC failures and design processes accordingly. If the pressure cascade does not fail-safe and maintain containment, even a brief HVAC failure can spread contamination through an entire manufacturing facility.

Operational measures should be determined by risk assessment and be based on the types of organisms handled on site. Manufacturers must understand the risk associated with their specific materials. Factors to include in this risk assessment include the GMO class or containment level required, results of

mycoplasma or sterility testing, any microorganisms (e.g., adventitious agents) that could be transferred to the manufacturing process (for cell lines), or if any viral vectors used are capable of replicating (i.e., replication competence). Donor material should also be screened for infectious agents.

The risk of cross contamination can be further reduced by implementing segregated material, people, and waste flows; adopting a gowning regimen that prevents movement from areas where viral vectors are handled (i.e., virus-positive areas) to areas where they are not; decontaminating items leaving virus-positive areas; and closing manufacturing processes where possible. The probability of spills can be reduced by using multiple layers of packaging and using trays and totes to move materials around the facility. For selecting waste inactivation agents, cleaning agent selection should include verification with representative challenge viruses to ensure that any spills can be effectively decontaminated. Large-scale spill procedures are required for viral vector manufacturing.

QUALITY CONTROL, PERSONNEL, AND PQS

Cell and gene therapy manufacturing processes require an underpinning PQS and quality control (QC) laboratory, and all aspects of cell and gene therapy manufacturing require trained personnel.

Quality Control

QC tests for living therapies are complex and often lengthy, requiring specialist knowledge by analysts. With short-shelf-life batches and urgent patient need, release QC testing may require more time or material than the manufacturing process can readily support. For autologous product processes, in which each patient sample is a single batch, there is insufficient time or material to perform pharmacopoeial sterility testing; therefore, rapid sterility methods are frequently used instead. This requires enough validation and data collection to satisfy regulators, and, because these products are novel, there is a lack of data for comparability. Given the potential short shelf life of such products, manufacturers may need to adopt a two-stage release process, where sterility, mycoplasma, and environmental monitoring results are certified after the therapy has been shipped. Robust recall procedures are required to either intercept shipments or notify clinicians in the event of a specification breach.

Manufacturers need to reduce turnaround times and the amount of material that QC testing processes require. Long-term industry efforts are focusing on process analytical technology and adaptive control strategies where critical process parameters are linked to critical quality attributes. However, the therapies are still novel and supporting data sets are small.

Contract laboratories can offer solutions to start up cell and gene therapy manufacturing and remove the initial financial outlay. However, a low level of standardization in cell and gene therapy QC testing means that expertise in different tests often resides only with the manufacturer or developer of the therapy. Additionally, transporting samples to contract laboratories may adversely impact delicate samples, and turnaround times are extended.

Personnel

To support QC needs, trained specialist personnel with an understanding of specific requirements of cell and gene therapy manufacturing is required. There is a shortage of skilled personnel, and often the scientists with the strongest understanding of the manufacturing process do not have a GMP background and have little or no experience in a GMP facility. Manufacturers need to implement robust recruitment, onboarding, and training processes to ensure their staff understands GMP requirements. In addition, as manufacturers drive toward more enclosed, automated, and predictable processes, experienced GMP staff can be recruited from outside the cell and gene therapy technology world. The requirement for trained specialist personnel is not restricted to the QC lab; manufacturing, warehousing, waste stream management, and cross-contamination prevention measures require trained personnel as well.

PQS

Underpinning everything in this article is the requirement for a good PQS. For cell and gene therapy manufacturers, the PQS design should be specific for onsite activities. A strong quality risk management process is required to implement the risk-based approach detailed in EudraLex Volume 4, Part 4. Especially in multiproduct facilities or those handling viruses, cross-contamination strategies based on risk must be implemented and followed. As process knowledge increases through operational experience, review of deviations, and changes to product-testing data, these strategies should be continually reviewed and updated. Therefore, interrogation and trend analysis of PQS events is critical.

The complexities of cell and gene therapies necessitate a strong supplier management and supply chain strategy based on the impact of each item on finished batch quality. When timelines are short, quality processes need to be simple and flexible with rapid escalation pathways to ensure batch certification decisions are made in a timely manner and based on correct information.

Finally, to deliver these therapies to patients, manufacturers cannot work in isolation; success depends on building direct, collaborative relationships with clinics that administer these pharmaceutical products. Cell and gene therapies can have very short shelf lives, and manufacturing must be tied to patient treatment dates, especially in the case of autologous products. Manufacturers need to carefully schedule manufacturing slots and material availability with QC testing, qualified person certification, and courier availability to ensure a patient sample is successfully delivered as a life-saving therapy.

CONCLUSION

Cell and gene therapies are regulated as medicinal products within the EU (and elsewhere) and are required to comply with GMP requirements. However, as a new form of medical intervention, cell and gene therapies face manufacturing-related challenges unlike those associated with traditional small molecule or biopharmaceutical products. These challenges arise from the use of human cells or viral vectors, biological variability in the process,

and the relative newness of the field. Many processing component or supply chain solutions are taken from existing pharmaceutical manufacturing. Cell and gene therapy manufacturers require robust PQSs and risk management strategies to maintain product quality while working in an innovative field.

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About the author

Kasia Averall joined Cell and Gene Therapy Catapult in November 2016, tasked with establishing the pharmaceutical quality system for the new multiproduct, multi-collaborator ATMP manufacturing center in Stevenage, UK. The facility was successfully licensed by the UK MHRA in August 2018, and Kasia now leads the quality assurance team supporting a variety of cell and gene therapy manufacturers. Before joining Cell and Gene Therapy Catapult, Kasia worked in both quality assurance and regulatory affairs over a range of dosage forms. She has a degree in natural sciences (biological) from the University of Cambridge.

2019 ISPE Biopharmaceutical Manufacturing Conference:

THE NEXT WAVE IN BIOPHARMA MANUFACTURING

By Susan Sandler

Innovations in production methods and technologies that enable a competitive and sustainable biopharmaceutical product supply were the focus of presentations at the 2019 ISPE Biopharmaceutical Manufacturing Conference in Boston, Massachusetts, 18–20 June. Future directions for the biopharma manufacturing industry were well represented by speakers from a range of environments.

The fast-moving biopharma industry is reaching the point where therapies will be available to more patients, and presentations at ISPE's fourth annual Biopharmaceutical Manufacturing Conference provided ample insights into the "next wave." Keeping the patient in mind is most important for the industry, noted conference chair Andre Walker, CPIP, Principal, Walker BioPharm Consulting.

More than 300 attendees from 168 companies and 15 countries attended to learn about innovation and the latest developments in biopharmaceutical manufacturing.

ADDRESSING CHALLENGES

Steve Bagshaw, CEng, FIChemE, Chief Operating Officer of Fujifilm Diosynth Biotechnologies, presented on "Advancing Tomorrow's Medicines—Overcoming the Manufacturing Challenges Today."

Great progress is being made, Bagshaw said. One example is AveXis's recent FDA approval for Zolgensma, a gene therapy for pediatric patients with spinal muscular atrophy (SMA). In the US, 400 to 500 babies each year are born with SMA, and Zolgensma is a cure. AveXis has about 1 million square feet of manufacturing space in four sites, the most potential capacity of any gene therapy company, and plans to have 1,000 employees in highly skilled manufacturing roles by the end of 2019.

The dose cost for Zolgensma is $2.125 million—so the challenge of affordability remains. However, there is good news for gene therapy market growth, with steep increases projected for revenues as the number of drugs increases. Today, biotech drugs represent 25% of global pharmaceutical sales. Revenues for gene therapies are projected to climb from $10 billion in 2025 to over $20 billion by 2030. In 2019, there are 734 gene therapies; the number is projected to grow to 1,202, 2,415, and 5,476 by 2021, 2023, and 2025, respectively.

Faster growth is needed to develop and move these products forward to reach patients, Bagshaw said. Clinical trial design is changing, including flexibility in areas such as mobile cleanrooms, small bioreactors, and enclosed fill-finish units.

Production "is very handmade at the moment," he said. "Our challenge is how to turn this into an industry that you can scale up." The challenge of what he termed "Biotechnology 4.0" is in scale-up; for example, in many cases, we don't yet know how to get to 2,000 liters, he said. For patient groups that work with the industry, it is "devastating" to know a cure has been developed but they can't obtain it. "Our challenge: keep up with the science and work out how to make these products in a way that we can get them to the patient."

According to Bagshaw, viral vector manufacturing using viruses to deliver gene therapy presents its own challenges, including a highly manual manufacturing process, scale-up issues, product characterization and analytics, IT and data management, downstream processes, and upstream process issues involving tools, equipment, and technologies. Analytics needs more attention, he said, and resources and energy are being devoted to the contract world to better understand processes. Flexibility in contract development and manufacturing organizations will be key.

Needs include product platform establishment. "We're looking for that elusive product platform that works for multiple companies," Bagshaw said. "Getting 10 times improvement

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requires us to understand what we are doing," not just what is being manufactured.

Companies are already collaborating on driving up both process and stage yield. Shorter timelines—perhaps just three or four years—are necessary, but the challenge is how to shorten them. The answer may lie with simplifying and automating processes. "One hundred times is where we need to be—not 10 times," he said.

Bagshaw believes that major manufacturers should focus more on training a highly skilled workforce that can support the anticipated growth surge. For example, Fujifilm is partnering with Blinn College for training.

Also, collaborative initiatives with government (such as the United Kingdom's Catapult initiative) are needed. Advanced therapies manufacturing action plans, such as the one set up in the UK, are "a really important part of the ecosystem that is part of advanced therapies," he said, noting that the Centre for Commercialization of Regenerative Medicine in Canada is another example of this type of initiative.

Regulatory activity includes the US FDA bringing in gene therapy expertise and expanding clinical reviewer hiring to meet the anticipated needs for at least 200 investigational new drug applications each year, which are predicted to bring 10–20 cell and gene therapy approvals each year by 2025.

This activity is taking place against the backdrop of the expectation of sustainability of industry and its businesses—which is a new challenge, Bagshaw said.

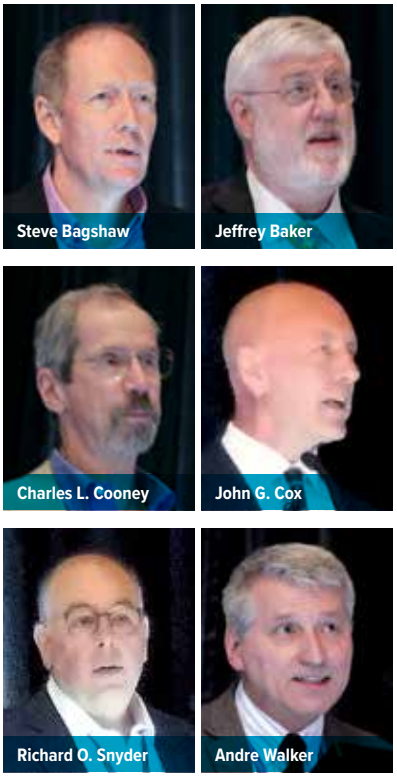
NEXT-WAVE INNOVATION

Jeffrey Baker, PhD, Deputy Director, Office of Biotechnology Products, Center for Drug Evaluation and Research, FDA, spoke about the impact of innovation and technology changes on biopharma manufacturing. In his presentation, "Pace and Sequence, Why and Why Not: Implementation of New Technology in Real-World Biopharmaceutical Manufacturing," Baker noted that product development, assay development, and some supply chain management—rather than on-the-floor manufacturing—are to innovation and change like ripples in the water after a stone is dropped in.

Baker's suggested the following to manage the uncertainty inherent in the biopharma field:

- Accept that uncertainty is neither good nor bad; it is merely another attribute to be understood.
- Differentiate between data analysis and knowledge management.
- Differentiate statistical thinking and statistical calculation.
- Make relevance central to risk assessment.
- Value understanding over specification.
- Optimize value rather than cost.

As an example of the uncertainty in the biopharmaceutical industry, Baker described some feedback to an "active listening session" in May 2019 with the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL), a public-private partnership with more than 90 members, including 11 major pharmaceutical companies. In this discussion, NIIMBL posed the question, "With respect to the regulatory landscape, what changes would you like to see implemented that would enable your company to deploy innovative technology for manufacturing or continuous improvement?"



Baker said the key conclusion of the session was that there is rarely a business case for implementing new technologies in biopharmaceutical manufacturing. Other observations included the fact that prior to launch, new technologies pose a risk to timelines; postlaunch global change management, including maintaining separate processes for different markets, is a hurdle; and companies are generally averse to being the first to deploy a new technology in manufacturing because they believe that a sponsor may face overly burdensome hurdles during a regulatory filing.

Managing uncertainty and risk are a way of life in the biopharma industry. "It's not about technology for the sake of technology," Baker said. "Use technology to solve meaningful problems. You need to understand that technology is like capital—don't expect a fast return. Don't be fearful—but if you are, recognize it, acknowledge it, and move ahead. Brave people are scared, but they don't let fear drive their decisions."

PLATFORMS FOR THE FUTURE

Charles L. Cooney, PhD, Robert T. Haslam (1911) Professor of Chemical Engineering, Emeritus, Department of Chemical Engineering, Massachusetts Institute of Technology, presented on "Developing Platforms for NexGen Biotherapeutics."

The goal of pharmaceutical manufacturing is the sustained delivery of a quality (safe and efficacious) product to the patient. Achieving this objective involves both delivery to the patient and sustaining the business. Think about new platforms through the lens of technology, regulation, and business, Cooney said. The industry needs to "manage the business case without losing sight of the goal."

Platforms serve this goal because they remove the uncertainty of technology development, permit continuous improvement,

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Biopharma Growth Trends:

More Innovation on the Way


Eric S. Langer

Innovation has been and continues to be a driver for the strides being made in biopharma development and manufacturing, noted Eric S. Langer, President and Managing Partner, BioPlan Associates, Inc., who addressed "Innovation in Transformative Medicine: What's Changing the Bioprocessing Landscape." He shared some results of research conducted by his company on biomanufacturing growth trends.

Since 2014, respondents have chosen manufacturing productivity/efficiency as the single most important trend, and it has grown more popular every year, Langer reported.

Continued increases in outsourcing should be expected, he said, with contract manufacturing organizations (CMOs) anticipated to grow by more than 12%. Today, cell and gene therapy developers use legacy research market supplies, but supply by CMOs is likely to expand to a $2–$3 billion market, depending how the industry builds out capacity. In 8 to 10 years, Langer said, supplies could be a new industry sector, which could rival recombinant proteins/mAb in more than 10 years.

Many new technologies and product classes are being developed, including cell and gene therapies and antibody–drug conjugates. Industry respondents expect increased activity from China and other Asian countries: 86% of China biopharma manufacturers expect to produce products for export to the US and EU, compared to just 25% today, and China is a likely outsourcing market for US manufacturers. Langer noted that cell therapy manufacturing may require dozens of facilities worldwide to fulfill patient needs.

Better cell or virus/vector analytic tests and more CMO options for R&D and clinical production were the top-cited "most needed cell and gene therapy manufacturing improvements, systems, platforms, and infrastructure."

Other trends noted from the research:

- Average titers were 3.03 g/L, up 50x over time.
- Downstream process remains a problem, although there are many approaches to address the challenge.
- Facility constraints were reported by half of research respondents; it was the top-cited constraint in the past 10 years.
- Continuous digital signal processing (downstream) is expected, and 42% of respondents hope it will address constraints.

Data on efforts to reduce manufacturing costs included:

- The average cost for recombinant proteins now is $307 per gram.
- A target cost is $100 per gram.
- Fifty-three percent of respondents have implemented programs to reduce operating costs.
- Reduced bioprocessing costs have become the norm.
- Some companies pay bonuses for options to reduce costs.

Hiring for biomanufacturing remains a challenge. Downstream process development staff is the biggest pain point, followed by upstream process development staff. Cell and gene therapy staff are also in short supply.

Capacity also affects CMO growth. Langer's firm has assessed biopharma companies and developed a ranking for each country to identify regional concentration. "Where the staff is, that's where the need is going to be, not just where the capacity is," Langer said. The research identified 1,500 global facilities; of these, two-third are in late-stage clinical/commercial capacity, and over a third are in commercial capacity. One-third of marketed products are made by 540 CMOs.

CMOs will play an increasingly important role in biopharma, Langer said. CMOs are adding single-use bioreactors that are now becoming the norm. He noted that single-use technology is becoming very reliable, and that the percentage of stainless capacity should decrease as new single-use products "graduate" to commercial scale. However, single-use product manufacturing still faces challenges; his company's research identifies bag breakage and loss of production material, leachables and extractables, the high cost of disposables, and material incompatibility with process fluids as problem areas.

Substantial testing of continuous manufacturing is underway, but it has yet to move forward because vendor solutions are lacking, he said. The industry still sees perfusion as a problem versus batch-fed manufacturing.

—Susan Sandler

provide a framework to manage across the product life cycle, and ensure security and integrity of supply.

Cooney noted that extending a platform for delivery of differentiated products to the patient is something the industry knows how to do and continues to do better. For example, biopharma companies are delivering monoclonal antibodies (mAb) for fusion proteins, biospecific mAb, and antibody–drug conjugates, as well as for biosimilars and biobetters. A platform built around recombinant DNA products made through genetic engineering of bacteria morphed into an extended platform for animal cells, and is now becoming the foundation for next-generation biotherapeutics.

The lessons learned from building mAb platforms should be applied to new therapeutic modalities, such as gene therapy and cell therapy. In gene therapy, these lessons are relevant to replacement and repair therapy through gene knockdown, regulation, and editing; immune regulation; gene editing; RNA therapeutics (siRNA, mRNA); and microbiome. In cell therapy, the lessons may apply to replacement or repair and regenerative medicine. "We can do it in the lab, can establish proof of concept—but can we manage repeating ourselves," which the industry can do with mAb?

Cooney described what is needed to enable, grow, and sustain a platform, including integration into a business model, analytical methods supporting performance metrics, standards supported by a large body of published literature, regulatory guidelines across global markets, a network of technology providers, and a network of users.

He suggested these core principles in a vision for advanced manufacturing:

- Manufacturing is on a critical path between science and the patient.
- Markets will be smaller volume with uncertain demand.
- Supply must be adequate by indication and geography.
- Regulatory guidelines provide the grammar and vocabulary for communication across the value chain.
- Safety and efficacy, also known as quality, are sacrosanct.
- Profit from product sales must support business continuity and future product development.

VIRAL VECTORS AND MORE

Richard O. Snyder PhD, Vice President, Science and Technology, Pharma Services, Thermo Fisher Scientific, presented on "Viral Vectors for Cell and Gene Therapies: From Research to Commercial Production." He described the viral vector's role in in vivo gene therapy and gave some background about progress with this technology as well as the work that Thermo Fisher is doing.

The gene therapy landscape is maturing rapidly, Snyder said. Many participants are joining, and both regulatory expectations and industry practices to meet

those expectations are advancing. The sector is unique, he said, for several reasons related to speed, bespoke facilities, and market dynamics.

Speed

- The first-in-human to biologics license application (BLA) occurred in less than four years.
- Early process lock is driving high-volume demand.
- Regulators are highly engaged, with the potential for one-and-done treatment.
- Manufacturing is increasingly important due to cost and complexity.

Bespoke Facilities

- Such facilities can't use vast biologics capacity.
- Instead, they have dedicated suites with platform processes (change transgene).
- They are also complex facilities with regard to vector type and manufacturing platform.
- They reflect the desire of manufacturers to secure preapproval commercial capacity.

Market Dynamics

- Existing biologics innovators are switching to gene therapy.
- Large biopharma companies are outsourcing multiple technologies.
- High pricing reflects reimbursement and ramp-up uncertainty.
- The industry faces a new supply chain paradigm (high product demand in early years and high incidence rate in later years).

Snyder discussed the recombinant viral gene transfer vectors and their progress, including the retroviral/lentiviral vectors that debuted in 2016–2017 (Strimvelis, Kymriah, Yescarta, and Zynteglo) and recombinant adeno-associated viral vectors developed between 2012 and 2019 (Glybera, Luxturna, and Zolgensma).

He talked about manufacturing strategy considerations for large-scale versus small-scale lot sizes. These included (a) the manufacturing platform choice and the frequency of production, (b) rapid proof of concept in humans using a quick, small-scale approach that is followed by new process establishment and product comparability at later phases, (c) upfront commercial-destined process development and establishment for an uninterrupted path to commercial launch, and (d) considerations related to owning and/or licensing manufacturing reagents (for portability versus reliance on another provider), including choice of cell lines and starting materials.

TRANSFORMATION AHEAD

John G. Cox, Executive Chairman, Torque Therapeutics, spoke about "The Transformation of Bioprocessing—Past, Present, and Future." Cell and gene therapies present a whole new set of challenges for bioprocessing engineers, Cox said. "We've got to figure out how to make those modalities have the impact on mankind that monoclonals [and others] have had," he said. The biotechnology industry's creation involved a first revolution (molecular and cellular biology) and second revolution (genomics). The next revolution has begun with the "explosion" of new biologic therapeutic modalities, including gene therapy; gene editing; cellular therapy; recombinant proteins, mAb, and fusion proteins; RNAi, mRNA, and oligonucleotides; nanobodies; and novel delivery models such as nanoparticles.

Engineering's role in the first two revolutions has been in biotechnical engineering to transform yields, process engineering to transform throughput, and "dominant design" for robust scale-up. "There used to be a dominant design: stainless steel, great engineering, pretty much the same plant layout," Cox noted. However, manufacturing is changing with the developments in the third revolution. Since 2015, the industry has started to see shared capacity; in 2015, Biogen had multiple plants with bioreactor capacity of about 200,000 liters.

In the third revolution, bioprocessing is being transformed. While yield has been a factor in the first, second, and third revolutions, the supply shortages of the first two revolutions are giving way to supply integration with treatment centers. Where scale-up robustness was a feature of the first and second revolutions, scale-down is an aspect of the third. The first and second revolutions had large centralized capital investments, whereas the third revolution features miniaturization/point-of-care distribution. Throughput was key in the first and second revolutions; processing speed is crucial in the third. Quality remains a constant, but the emphasis on the cost of goods in the first and second revolutions is giving way to a focus on the cost of treatment in the third.

"The industry is being changed by these new therapeutic modalities, and the diversity of these is challenging." Nevertheless, the third revolution provides exciting opportunities. "Instead of slowing disease progression, now we are talking about curing diseases!" The challenge remains to make these therapies cost-effective and affordable.

Disclaimer

This article includes an abridged, unofficial summary of an FDA regulator's presentation. It has not been vetted by the agency. The article offers an informal and brief synopsis of the FDA regulator's views and does not represent official guidance or policy of the FDA.

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About the author

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

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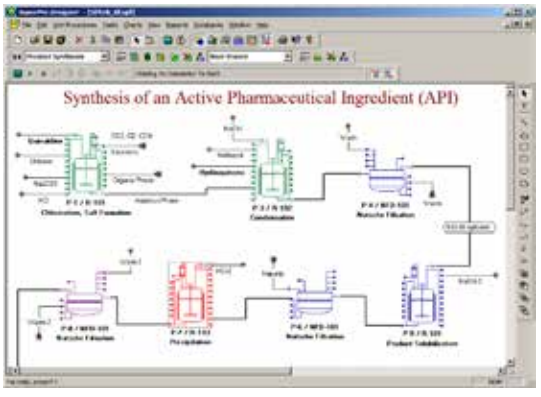

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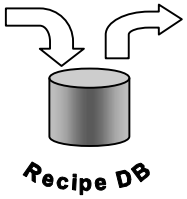

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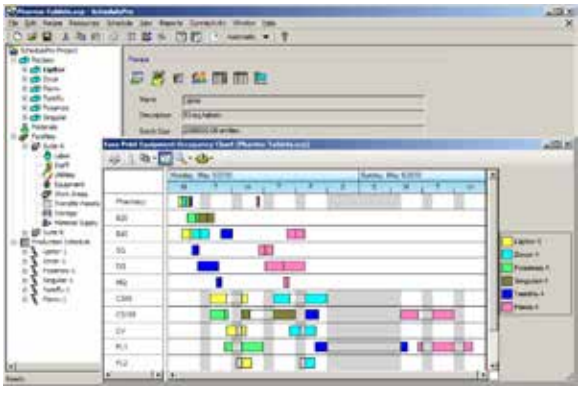

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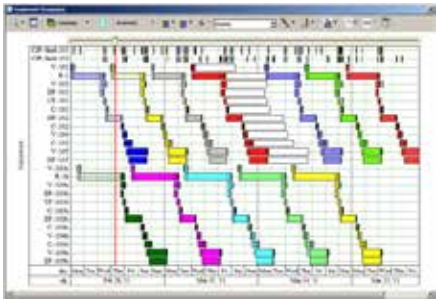

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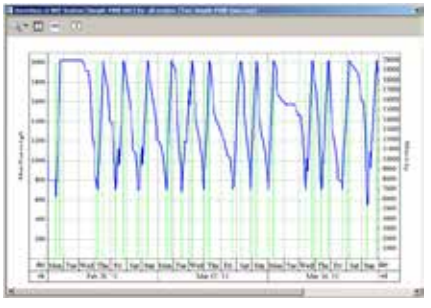

Managing inventories for input, intermediate, and output materials

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

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2019 ISPE Biopharmaceutical Manufacturing Conference:

PRACTICAL REGULATORY AND INDUSTRY ISSUES

By Susan Sandler

Presenters and a panel of FDA regulators and industry experts discussed key regulatory and industry issues during the closing plenary of the 2019 ISPE Biopharmaceutical Manufacturing Conference.

ADVANCED THERAPY MEDICINAL PRODUCTS

Peter Marks, MD, PhD, Director, Center for Biologics Evaluation and Research (CBER), FDA, spoke on "The Critical Role of Manufacturing for Advanced Therapy Medicinal Products" (ATMPs). These products include gene therapies and xenotransplantation products, as well as human cells, tissues, and cellular and tissue-based products (HCT/Ps) requiring licensure. A controlled manufacturing process and an understanding of critical quality attributes for these products provide clinical benefit, he noted.

The ATMP market is growing, as indicated by the rise in investigational new drug (IND) applications to the FDA, Marks said. These new drugs present regulatory challenges because the scientific basis underlying the drugs' efficacy is not always clear, it's challenging to ensure adequate control of the manufacturing process without being excessive, and there's a lack of extensive regulatory precedent in some areas (such as 3D cell printing).

ATMPs present clinical market development challenges as well, he said. These challenges include products intended for use in very small populations, target populations dispersed geographically from the manufacturing site of personalized therapies, and the potential need for long-term safety and efficacy data.

Manufacturing challenges for ATMPs include that these products are often made from living organisms and may not be easily characterized; also, they are frequently temperature sensitive and susceptible to microbial contamination, and their complexity for manufacturing facilities and processes is relatively high.

The FDA is helping advance the development of cell and gene therapy by providing guidance documents and reducing administrative burdens. The FDA also supports clinical development initiatives, standards, and manufacturing initiatives. Draft guidance on cell and gene therapy from July 2018 is available at https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances

Expedited programs for FDA consideration are also helpful. Marks described the regenerative medicine advanced therapy (RMAT) designation to expedite product development and review. It applies to certain cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products, including genetically modified cell therapies and gene therapies producing durable effects. To obtain RMAT status, products must be intended for serious or life-threatening diseases or conditions, and preliminary clinical evidence must indicate the product's potential to address unmet medical needs. The FDA replies to RMAT designation requests within 60 days, and designated products are eligible for priority review and accelerated approval as appropriate.

Sponsors can fulfill postapproval requirements by submitting clinical evidence and studies, patient registries, or other sources of real-world evidence such as electronic health records, an agreed-upon collection of larger confirmatory datasets, or

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postapproval monitoring of all patients treated with said therapy prior to therapy approval.

As of 1 May 2019, 34 products out of 100 requests have been granted RMAT status, Marks said. Most are cellular therapy or cell-based gene therapy products.

The INitial Targeted Engagement for Regulatory Advice on CBER ProduCTs (INTERACT) program further encourages early interaction between regulators and sponsors and replaces the pre-pre-IND meeting process regarding preclinical, manufacturing, and clinical development plans.

Closed manufacturing systems are a possible solution on the horizon, Marks said. They could facilitate more efficient technology transfer, which in turn could streamline preclinical evaluation required for first-in-human trials, make technology more accessible to academic innovators, and increase the value of the asset to investigators and industry. Potential challenges include agreement on vectors, prework needed to develop vectors and protocols, and vector and protocol distribution.

CHANGES TO BIOLOGICS LICENSE APPLICATIONS

Keith Webber, PhD, Vice President, Biotechnology, Lachman Consultant Services, Inc., spoke on "Navigating Your Way from Route 361 to Route 351." The title refers to the transition from Public Health Service Act (PHSA) Section 361, which was established to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the US or among its states, to PHSA Section 351, which specifically addresses biologic drug regulation.

The introduction of new modalities raised questions about whether they are regulated under Section 361 only, or if additional licensing is required. HCT/Ps that don't meet all Section 361 criteria are not regulated solely under that law. A valid biologics license is needed to market a drug that is also a biological product.

Guidance issued by the FDA on 17 November 2017 provides regulatory discretion for three years, until 17 November 2020. After that date, an IND or an approved biologics license application (BLA) will be required to distribute products designated as drugs.

Section 361 compliance touches on a host of activities, which Webber outlined, including site registration, listing products, evaluating facility design, potency assays, and establishing test methods and acceptance criteria for incoming components, in-process controls, and lot release. CBER's INTERACT program can provide advice through the process.

PANEL DISCUSSION

The Industry and Regulatory Panel discussion closed out the conference. Participants were:

- Jeffrey Baker, PhD, Deputy Director, Office of Biotechnology Products, Center for Drug Evaluation and Research (CDER), FDA
- Peter Marks, MD, PhD, Director, CBER, FDA
- John McShane, Managing Partner, Validant
- Richard O. Snyder, PhD, Vice President, Science and Technology, Pharma Services, Thermo Fisher Scientific


Peter Marks


Keith Webber


The Industry and Regulatory Panel

- Keith Webber, PhD, Vice President, Biotechnology, Lachman Consultant Services, Inc.
- David Doleski, Compliance Head, Biologics Quality Operations, Sanofi (moderator)

A number of products are coming. What plans does the FDA have to handle the dramatic increase in the number of applications?

Marks: "We are staffing up. It's a little bit of challenge since everyone is looking to staff up at the same time. To have somebody truly able to give feedback, they need to be at the agency for several years, and trained. Even independently reviewing takes a year or two. As new meeting types come like INTERACT Tech Team meeting (which is also new and similar to CDER critical path meetings), they are useful; but if we don't have enough staff, it takes a long time to schedule. We will do our best and hope the industry will be sympathetic."

One slide [RMAT applications] showed a relatively significant number of applicants were declined: 56%? Comment to general reasons.

The declined applications fall into two major categories, Marks replied. "We sometimes get people who are very excited and want the designation based on very little evidence. If you have very little evidence but it is consistent and clear, we've given the designation based on a handful of patients." However, without consistency, the designation will not be given. If sponsors come back with more data, their applications may be approved.

The second, less-common reason that applications are denied is that "people submit clinical data about a product they intend to make in the future, like a product made in Europe. If you are not making the product, we don't know you will get same results as they got in Europe. Data must be from the product you intend to use. Importing the European product is not a problem. It is not too different from breakthrough therapy designations."

SPECIFYING GAS TRANSFER

ZETA
EVOLUTION OF TECHNOLOGY

"A crucial parameter for production of sufficient biomass levels is oxygen. Therefore, the **transfer of oxygen from gas to the liquid phase** is a limiting step in the bioreactor system and is expressed by the $k_L a$ value. The liquid layer around a gas bubble should be as thin as possible in order to improve the oxygen transfer rate (OTR) enabling cells to take up oxygen efficiently and to keep them alive and productive. We know one thing for sure: **the quality of a product is already shaped in the upstream process** and that sophisticated bioreactor design thus has a major impact on product quality and safety!

With my Team we have developed a **new methodology to measure the $k_L a$ value** for a better understanding of the different bioreactor systems! Every parameter you can measure inside a bioreactor is an advantage. Knowing the specific performance indicators of the bioreactor system allows a **target oriented scale-up of the lab or pilot system.** ZETA's CFD simulation is able to support the engineering work around scaling and retrofitting of bioreactor systems keeping in mind that only experimentally validated models can **create added value** and additional benefits."

Thomas Maischberger
Process Engineer &
Product Development
thomas.maischberger@zeta.com

www.zeta.com/**kLa**

Why measuring $k_L a$ value?

- ensure adequate supply of oxygen
- optimize process control variables
- better process understanding
- optimize scale-up and scale-down models
- improved bioreactor design

get more infos on $k_L a$ value at PE WHITE PAPER Section

"We often see clients who immediately want to get to market space but really struggle because of legacy platforms and analytics."

Application of data analytics on AI [artificial intelligence]: What is the FDA stance, especially on control strategies, testing, tech transfer, scale-up, and validation? Are guidelines coming from the FDA on AI?

AI "is real and it's here," Baker said. "It is not science fiction. One challenge is that with a sort of bleeding edge technology, frequently there is proprietary material, so it is difficult to have a lot of shared learning." However, Baker shared good news: Global regulatory agencies are becoming more comfortable using model systems. "Very effective models make really good predictions." For example, nested models can make predictions in an information space. "Conceptually, we're comfy with that. The challenge [is to] demonstrate that the model does in fact make informed decisions."

Another challenge with AI involves quality management (QM) systems, which are often set up as pass/fail, Baker added; however, this is not an FDA issue. "What are you going to use the system for?" he asked. "Process control? Reproducible and anticipated outcomes? If you use it for continuous improvement and platform development, how do you sequester through the QM system? It's a tool to make decisions. What kinds of decisions are we making? High-quality decisions come from high-quality information. It's emerging tech."

Marks added that the FDA met recently with Friends of Cancer Research to address chimeric antigen receptor T cell immune therapies, discussing critical quality attributes and hypothesizing outcomes if AI were used to identify those attributes. They are working to establish an agreement that encourages manufacturers to provide data, but information about critical quality attributes tends to be closely guarded in manufacturing. He noted two perspectives within the FDA. Some believe, "AI may be such a big mess that no one will figure it out." Some take the opposite view. "Others say AI is pretty powerful, so something can be figured out."

How to make the leap from a very small patient population, developing clinical materials, to commercial manufacturing?

McShane, who works with small firms on this challenge, replied: "When they get breakthrough designation or RMAT, the pace picks up incredibly. A lot of firms may not even have a head of quality at that point! Yet they know they need a quality system that will be commercial in less than 18 months. For a lot of my clients, quality is behind and it's really tough to catch up. You do not want to be the company that can't come to market because you have data integrity problems, or are not following ICH guidelines, or can't get investigations or change control done. I suggest that everyone have a developmental plan. I urge you to have a quality plan to think about your quality system and when is the right time to put in certain segments. You'll be way ahead going forward."

Snyder added, "That's where working with a CDMO [contract development and manufacturing organization] with a track record can be a benefit. A challenge we often see is clients who have gone in and licensed a technology out of a university, have proof of concept, and then immediately want to get to market space but really struggle because of legacy platforms and analytics; the cost to switch is extreme."

Webber agreed. "Moving from earlier R&D culture to earlier manufacturing of drugs culture: it is a huge challenge to have a QM system. It is a long-term challenge, scaling out to manage a number of patients in the future." Development of standards was talked about at this conference, he noted, and that area will contribute substantially to development over the long term.

Magnitude of conversion to BLA: How many products are eligible/need to be converted? What progress has been made?

Baker did not have numbers to share. However, he noted, "The number is not so large as the scope of the challenge. Transition products have been on the market for a long time by companies committed to continuous improvement and stabilization with modern analytics—an administration exercise is what it will be."

He also said, "The scope is broader than you might think—products and technical stewardship, and the commitment to technical stewardship shown over the last 20 to 25 years. We're not in the business of whopping people over the head with a BLA stick." On the other hand, sponsors should "stay current, appreciate that 21st-century technologies are an expectation." He continued, "The team is working very hard on this [conversion to BLA]. I have been a little surprised. I expected a lot of industry engagement; I have not seen as much of that as I thought. Maybe this is because the requirement was part of the Affordable Care Act [ACA], so maybe people were waiting to see what would happen."

In response to a follow-up question asking for an explanation of the transition process, Baker said, "When biotech was smaller, many products we call 'biotech' today were approved as NDAs [new drug applications], and many were approved as BLAs. The field was being invented."

Then, an ACA provision amended the definition of a biologic, stating that proteins are biologics. The FDA subsequently provided

statutory interpretation of the definition of a protein. Under this interpretation, "protein products approved as NDAs will be deemed BLAs," Baker noted. These are the transition products. "Insulins are a classic example, but many others are affected." Today, he explained, it's easier to tell what is under CDER's purview and what is overseen by CBER. There are differences in the two approaches: one involves approval of a molecule; the other involves licensing a manufacturing capability.

Doleski said CDER regulates some biologics; many others are under CBER's authority. As the transition concludes, organizational responsibility within the FDA for these products will presumably change.

Baker explained, "We're migrating all those transition products from the small molecule side of CDER for review—supplements, inspections, continuous improvement opportunities. Those have already been moved into the Office of Biotechnology Products. We've identified all reviewers. Many companies were given opportunities for informal meetings with new reviewers and to visit some sites; there have been many positive, informative meetings and discussions outside the context of specific decisions. There have been very different types of discussions around things like biopotency and facility issues. It's been positive. I do not anticipate an enormous flash."

Can you discuss going into process performance qualification (PPQ) batches with only one engineering run?

Baker said, "A BLA submission and process validation program are exercises in advocacy, not forensics. Any groups that approach them as forensics are well intentioned but not working within the current paradigm. You're advocating for a large molecule biotech product and claiming you are capable of maintaining a reliable, consistent drug supply for the patient. Engineering runs mean different things at different companies and may have occurred outside quality management or off protocol. They can be supportive evidence, assuming a QM system is live and does what it is supposed to do." He explained that the number of engineering runs, process verification (PV) runs, and the scope of continuing validation are all part of making that argument. Professional scientists and engineers are responsible for making the case that the site is going to be ready to run. "Great development, tech transfer, PPQ, maintenance of validated state—all make the case," he said.

McShane added that, per FDA 2011 Validation Guidance, PV begins with development, which can include engineering runs and PPQ batch completion, and continues through a continuous process verification (CPV) program.

Baker noted, "Then you are in protocol, not experiment. Protocol says, 'This is what success looks like.' If you're going to run experiments to see how process works, that's development. If you have validated process, you are providing high-level assurance that it will meet predetermined expectations in a way that impacts the patient."

McShane continued, "FDA guidance says use statistics. After PPQ batches, start continued process verification and run it forever. Many have struggled getting CPV up and running." Ultimately, he explained, reliability over the manufacturing life of that product is what counts, and CPV supports that.

Disclaimer

This is an abridged, unofficial summary of FDA regulators' presentations and discussion during a panel dialogue. It has not been vetted by the agency. This article offers an informal and brief synopsis of the FDA regulators' views and does not represent official guidance or policy of the FDA.

Acknowledgment

Thanks to Andre Walker for assistance with articles about the 2019 ISPE Biopharmaceutical Manufacturing Conference.

About the author

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

2019 ISPE Biopharmaceutical Manufacturing Conference:

INDUSTRIALIZING NEW PLATFORMS

By Susan Sandler

Juan Andres, Moderna, Inc.

Moving platforms from development to the delivery of more biopharmaceuticals to more patients is reality, not just a concept, for Moderna, Inc. Juan Andres, the company's Chief Technical Operations and Quality Officer, presented on "mRNA Medicines—Industrializing a New Platform" at the 2019 ISPE Biopharmaceutical Manufacturing Conference, sharing information about groundbreaking work underway at Moderna.

Andres likened scale-up processes, development, and commercializing production to preparing a meal for a large group. "Preparing dinner for four is not like preparing dinner for 200," he said. The challenges in producing biopharmaceutical drugs on a larger scale—especially with new technology—are "super challenging."

LEARN FROM THE PAST

Andres advises the industry to "look to the past in anticipating the future"; history can offer ideas on how to face new challenges. He traced key developments in the industry, starting with antibiotics in the 1930s, moving to what he called a second medical revolution in the 1980s, then on to biologics. "These cycles can predict what we are living now," he noted. In the moments of revolution, or new cycles, chemistry, manufacturing, and controls (CMC) are all sources of variability. Between cycles, however, this is not the case; manufacturing is the source of variability as the platform becomes established.

Since 2010, the industry has been in another manufacturing revolution, with multiple different platforms starting to emerge and bringing variability with them. "There are many unknowns with cell and gene therapy and some of the other technologies that are coming," Andres said.

He provided some background about Moderna's platform, messenger RNA (mRNA), which instructs a patient's cells to produce proteins that could prevent, treat, or cure disease. According to Andres, "We make mRNA and use the body as a natural 'bioreactor.'"

Moderna has over 20 products in development, 12 in clinical trials. The company started with prophylactic vaccines and moved into other areas little by little, with modalities including cancer vaccines, intratumoral immuno-oncology, localized regenerative therapeutics, systemic secreted therapeutics, and systemic intracellular therapeutics. Rare diseases are the newest area for Moderna. Taking a platform approach enables fast learning, Andres said.

The ability to build learning into CMC is key to industrializing mRNA technology. The ability to scale the platform while learning continues is a central issue, and Andres shared highlights from Moderna's approach.

KEEP CONTROL OF WHAT YOU ARE LEARNING

Moderna has a year-old facility in Norwood, Massachusetts, and a GMP manufacturing strategy. Prior to constructing the facility, Moderna used outsourcers, but the company saw a centralized approach as more efficacious than working with multiple outsourcers. Moderna also decided to have its own manufacturing site to enable increased speed in learning and implementation: the Norwood facility is the primary facility, with a CMO network as contingency. This decision enabled Moderna to optimize processes and increase mRNA output by four times.

Moderna leadership recognized that the company would need "a lot of supplies and a common platform where things are done the same, product by product," Andres explained. "We knew we would have to scale." That was a tough challenge, but having the Norwood facility allowed the scale needed: by 2020 to 2022, Moderna is aiming for 100g. Cost is improving, he noted, with expenditures falling 45% to 55% between 2015–2016 and 2017–2019.

The Norwood facility was built and operationalized in just 22 months; it includes preclinical, clinical, and personalized cancer vaccine production, and plasmid and buffers (including mRNA).

LEARN AND IMPLEMENT FAST

Moderna focused on digital enhancements and quality from the start. Digital integration was seen as a "must" for operations such as engineering runs, toxicology runs, tech transfer, manufacturing, testing and receiving raw materials, and product testing, release, shipment, and administration.

For example, all equipment is integrated in the cloud, almost no paper is used, and Moderna uses electronic batch records.

Moving from paper to electronic batch records cut documentation errors by over 85% and reduced overall cycle time and variability. Review time fell from three days to just three hours. Logbooks are integrated digitally, and the facility uses the internet of things on the shop floor for functions such as push-button consumable replenishment, which eliminates manual entry of material orders and lets operators focus on execution. Material requests are batched to optimize delivery.

Learning is captured with advanced analytics and artificial intelligence. Analytics driving operations include suite view (operators see and respond to alarm conditions); KanbanFlow software (visual boards drive materials, sample, and production flows); daily huddles (teams review schedules and real-time plant status to plan work); train segregation (digital fences monitor and segregate trains within a ballroom); and operational excellence (ability to analyze personnel and materials flows to drive continuous improvement).

SIMPLE THINGS CAN MAKE YOU TRIP

Filling product, paying vendors, making orders: such so-called mundane activities are hard to do. It is not just science that is needed, Andres noted.

Know the basics and do them well, he said. Having a people strategy is important to this. Even in operations that would not be considered novel, a company like Moderna needs people with industry experience to help it move forward.

INSPIRE COLLABORATION

Collaboration improves research and development, platform technology and development, and CMC, Andres said. It's essential that clinical development and manufacturing, quality, and supply chain interface. "We are learning as we go," he said. "We wanted a very open environment that inspires collaboration." For that reason, the Norwood facility has an open design.

Collaboration goes beyond the walls of the facility, he noted, and is a strategic issue. "Involve health authorities early—this is essential! We have great collaborations with the FDA, Europe authorities, and big pharma companies we are partnering with. Bring them in!"

"We are not gene therapy, not large molecules, not small molecules—so what are we? We need to partner and involve them early. These could be a new class of medicines. Let's not wait until we know everything."

Moderna's Norwood facility is the Facility of the Future category winner in ISPE's 2019 Facilities of the Year competition. A full profile is available at https://ispe.org/pharmaceutical-engineering/ispeak/meet-moderna-inc-2019-facility-future-category-winner

About the author

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

Article of the Year 2018 Winner:

CONTINUOUS MANUFACTURING IN BIOTECH PROCESSES

The winner of the 2018 Roger F. Sherwood Article of the Year award is "Continuous Manufacturing in Biotech Processes: Challenges for Implementation" by Robert Dream, PE, CPIP Christoph Herwig, PhD; and Emilie Pelletier. The article can be viewed at https://ispe.org/pharmaceutical-engineering/november-december-2018/continuous-manufacturing-biotech-processes

The article explores the promise and challenges of continuous manufacturing (CM) for biotechnology. CM in biotech offers the potential for greater product quality while reducing costs and shortening time to market. Challenges to be overcome include research and development efforts to characterize certificates of pharmaceutical products on single-unit operations and integrate them into the process; integrated control strategies for operations; technology available on the market; approaches to validation and quality; and regulatory compliance.

The article "clearly confirms that efforts are underway to have continuous manufacturing in biotechnology, but not all the process steps are ready for a CM implementation," said Ferdinando Aspesi, Senior Partner, Bridge Associates International, and Chair of the *Pharmaceutical Engineering* Committee (PEC). "The authors describe well the challenges and the work ahead that we have to undertake in the industry. The article deserves the award because it is encouraging readers to invest time, science, and technology to achieve continuous manufacturing in biotechnology."

FINALISTS

The 2018 Roger F. Sherwood Article of the Year award finalists are:

- "Heat Recovery Regulations and HVAC Energy Consumption" (May–June 2018), by Jim Heemer, BS, MSE, and Hugh Reynolds: https://ispe.org/pharmaceutical-engineering/may-june-2018/pharma-facilities-equipment-heat-recovery-regulations-hvac
- "The Rise of Biopharmaceutical Manufacturing in Asia" (May–June 2018), by Scott Fotheringham, PhD: https://ispe.org/pharmaceutical-engineering/may-june-2018/rise-biopharmaceutical-manufacturing-asia
- "Transitioning to Multicolumn Chromatography: Real-World Challenges and Results" (May–June 2018) , by Lindsay Arnold, PhD: https://ispe.org/pharmaceutical-engineering/may-june-2018/challenges-results-moving-multicolumn-chromatography
- "Pharma 4.0: Hype or Reality?" (July–August 2018), by Lorenz Binggeli, Hans Heesakkers, Christian Wölbeling, and Thomas Zimmer, PhD: https://ispe.org/pharmaceutical-engineering/july-august-2018/pharma-40-hype-or-reality
- "Getting Ready for Pharma 4.0: Data Integrity in Cloud and Big Data Applications" (September–October 2018), by Toni Manzano and Gilad Langer, PhD: https://ispe.org/pharmaceutical-engineering/september-october-2018/getting-ready-pharma-40
- "Continuous Manufacturing In Biotech Processes: Challenges for Implementation" (November–December 2018)—**2018 Winner**, by Robert Dream, PE, CPIP, Christoph Herwig, PhD, and Emilie Pelletier: https://ispe.org/pharmaceutical-engineering/november-december-2018/continuous-manufacturing-biotech-processes

ABOUT THE AWARD

The Roger F. Sherwood Article of the Year award was established in 1993 to increase article submissions and improve the quality of those received. The award has been refreshed in recent years to showcase the best content in *Pharmaceutical Engineering*, increase industry recognition, highlight ISPE's reputation as a global knowledge leader, and bolster magazine content quality. More information about the Article of the Year and past winners is available at https://ispe.org/pharmaceutical-engineering/about/article-year-award

For the 2018 award, a subcommittee of the PEC served as judges. They reviewed 37 feature and technical articles published in *Pharmaceutical Engineering* during calendar year 2018 (volume 38). The PEC subcommittee was headed by Michelle Gonzalez.

The judges used the following criteria to assess articles: usefulness to ISPE readers; how the articles improve the knowledge of key topics; and clarity/ease of reading. The Article of the Year award winner was selected from the six finalists.

WHY ISPE GAMP® SUPPORTS THE FDA CDRH Case for Quality Program

By Siôn Wyn, Christopher John Reid, Chris Clark, Michael L. Rutherford, Heather Watson, Lorrie Vuolo-Schuessler, and Arthur D. Perez, PhD

The US FDA Center for Devices and Radiological Health (CDRH) Case for Quality program promotes a risk-based, product quality–focused, and patient-centric approach to computerized systems. This approach encourages critical thinking based on product and process knowledge and quality risk management over prescriptive documentation-driven approaches.

ISPE GAMP® global leadership strongly supports this risk- and quality-based approach to the assurance of computerized systems and believes that current ISPE GAMP® guidance is already fully aligned and consistent with such an approach, including new guidance coming this year from the CDRH.

The FDA CDRH launched the Case for Quality program [1] following a review of data and feedback from both the FDA and industry stakeholders. The FDA's analysis identified widespread or common manufacturing risks that impact product quality. One of the core program components is the Focus on Quality initiative. Although the FDA usually evaluates a manufacturer's compliance with regulations governing design and production of devices, the Focus on Quality initiative goes beyond this by treating compliance attainment as the baseline and looking for the inclusion of critical-to-quality practices that result in higher-quality outcomes.

The program's focus on computerized systems has increased in recent public statements related to the Case for Quality, and the CDRH has recently indicated their plan to release guidance on the topic of computer system assurance.

One element is a risk-based approach to computerized systems that focuses on product quality and patient safety. This approach encourages critical thinking based on product and process knowledge as well as quality risk management over prescriptive documentation-driven approaches. One of the prioritized medical device guidance documents that the FDA intends to publish in FY 2019 is a draft titled "Computer Software Assurance for Manufacturing, Operations, and Quality System Software" [2]. These activities are of great industry significance and are aligned with the GAMP® risk-based approach as well as with ISPE's broader patient-centric position and focus on cultural excellence.

An ISPE GAMP® concept paper is being developed to explore more fully the implications and opportunities in the field of computerized systems compliance and demonstrate how the GAMP® risk-based framework can fully support the objectives of the Case for Quality program.

ISPE GAMP® global leadership strongly supports the program's value-based, patient-centric, and risk-based approach to the assurance of computerized systems and believes that current GAMP® guidance is already fully aligned and consistent with such an approach. GAMP® leadership believes that an understanding of the supported process and associated data flow is fundamental to determining system requirements. Product and process understanding is the basis for making science- and risk-based decisions to ensure that the system is fit for its intended use and that quality and data integrity–related requirements are met.

GAMP® leadership believes that such an approach is appropriate throughout the regulated life science industries, including pharmaceutical, biological, and medical devices, and throughout the complete product life cycle, regardless of the specific applicable

predicate regulation. GAMP® strongly supports the adoption of new and innovative computerized technologies and approaches throughout the product life cycle to support product quality, patient safety, and public health.

BACKGROUND

As stated on the FDA's website, "Top-quality medical devices help the FDA better protect and promote public health. And one of the top priorities for FDA's medical devices center is a focus on quality" [1].

In a 2011 report on medical device quality [3], the FDA described how an excessive focus on compliance may divert resources and management attention away from investments in quality and toward compliance activities like documentation, which do not directly lead to improved quality outcomes.

Industry focus was seen to be on meeting regulatory compliance requirements rather than adopting best quality practices. This trend was related to a low investment in automation and digital technologies, which could greatly assist in quality improvements and process control.

IMPLICATIONS FOR COMPUTERIZED SYSTEMS

FDA CDRH has discussed the Case for Quality program implications, conclusions, and actions related to the use and assurance of computerized systems in various reports and presentations, which are summarized in various sources [4–6].

As stated by the FDA Commissioner, the FDA intends for the program to:

> *encourage device manufacturers to make investments to re-tool their manufacturing processes in ways that can facilitate manufacturing innovation, encourage investment in new production methods and materials, and lead to better medical products… such as through intelligent, automated processes that monitor and record manufacturing quality metrics, incorporating features and technological characteristics that can contribute to better options and higher quality that achieves their clinical purpose [7].*

One of the reasons manufacturers were not seeking quality improvements by adopting automation and new digital technologies was the perceived compliance burden and regulatory risk. The validation of computerized systems was seen as a barrier to the adoption of new technologies, with the cost of validation in some cases being reported as twice the cost of the basic system.

The FDA has observed that a compliance-centric approach has not only hampered innovation in manufacturing and product development practices, but also resulted in quality issues. As noted [4], the perceived regulatory burden has contributed to outdated compliance practices; to counter this, the FDA advocates critical thinking and risk-based Agile approaches rather than a focus on documentation or regulatory compliance.

Cisco Vicenty, FDA CDRH Case for Quality Program Manager, noted the FDA has suggested a move away from an approach primarily based on formal validation, verification, and documentation and a move toward approaches that meet needs and ensure system fitness for intended use, especially with regard to product quality and safety and quality system integrity [4]. Low-risk systems require less effort for validation and documentation, and the selected approach should be the least burdensome possible. Supplier activities and information and other existing information should be leveraged wherever possible.

Vicenty emphasized that current regulations already allow such a value- and risk-based approach [4]. The FDA will focus regulatory activity on inspection and review of systems that impact quality or safety. The FDA does not intend to focus regulatory resources on inspection and review of assurance activities related to systems with little or no direct impact on product quality and safety. The use of computerized system validation and other tools is also encouraged, and these will not be the focus of FDA inspection.

The approach described is based on clearly defining the intended use of the system and determining a risk-based approach based on the system's impact on device safety and quality. Appropriate methods and activities can be selected, including leveraging existing activities and supplier data, automated tools and data capture, and use of Agile testing methods and unscripted testing as appropriate. The least burdensome approach of recording assurance activities should be applied, and any records produced should be of value to the organization.

GAMP® SUPPORT FOR THE CASE FOR QUALITY APPROACH

This section illustrates how current GAMP® guidance, including ISPE *GAMP® 5 Guide: Compliant GxP Regulated Systems* [8] and ISPE *GAMP® Guide: Records & Data Integrity* [9], is fully aligned with and supports the FDA's position. All information is from the *GAMP® 5 Guide* unless otherwise noted.

The main objective of *GAMP® 5* is the effective achievement of patient safety, product quality, and data integrity. The guide applies a life-cycle approach based on intended use and product and process understanding. The application of quality risk management enables effort to be focused on critical aspects of a computerized system and risks to be effectively managed. Supplier activities and documentation should be leveraged wherever possible, and unnecessary duplication and unnecessary activities should be avoided. The key concepts underlying *GAMP® 5* are shown in Figure 1.

GAMP® 5 notes the need to avoid duplication of activities (e.g., by fully integrating engineering and computer system activities so they are only performed once); to scale all life-cycle activities and associated documentation according to risk, complexity, and novelty; and to leverage supplier activities wherever possible.

GAMP® 5 also notes that most computerized systems are now based on configurable packages and acknowledges that traditional linear or waterfall development models are not the most appropriate in all cases. *GAMP® 5* uses various diagrams to represent the system life cycle from the regulated company's perspective. These diagrams often present relationships in a linear representation,

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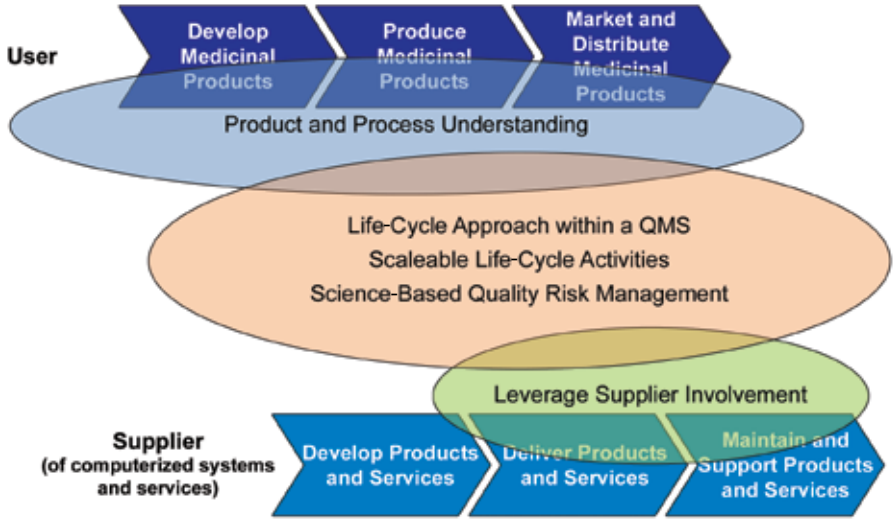
Figure 1: *GAMP® 5* Key Concepts [8].



which is reflective of the case for most standard systems and systems based on configurable packages. This use of linear representations is not intended to constrain the choice of software development methods and models. Suppliers or developers should use the most appropriate software development methods and models, which may include rapid-application development or prototyping techniques and incremental or iterative approaches, including Agile.

GAMP® 5 does not advocate any specific or special software development models or methods. Instead, it encourages the application of current cross-industry software development best practices and tools within the context of an appropriate quality management system (QMS) to provide sufficient documentation and assurance (based on risk, and primarily through the use of effective supporting tools) of fitness for intended use, and to allow effective software maintenance throughout the life cycle.

GAMP® 5 guidance strongly supports the use of effective tools, technology, and systems to support and manage the GxP computerized systems life cycle. Appropriate tools reflecting current technology and good practice are always preferred to paper-based solutions. Such tools are considered part of the infrastructure and are not subject to validation. The use of normal IT good-practice approaches, such as ITIL [10], to the delivery management and support of systems, services, and infrastructure is strongly encouraged.

Testing approaches should focus on achieving systems that are fit for the intended use and focus on identification of defects. Achieving working effective software with as few defects as possible (and no critical defects impacting patient safety) is the main objective. Actual test content, strategy, and effectiveness are the priority, rather than production of documentation. A flexible approach to testing evidence based on risk, complexity, novelty, and the nature of the software function and intended use is encouraged. Records and information supporting the management and life cycle of GxP computerized systems should be of value to the regulated organization, and not maintained for the benefit of third parties.

Based on the nature of the components and the likelihood of defects and level of risk, *GAMP® 5* advocates that effort should be concentrated as follows:

Custom > Configured > Nonconfigured > Infrastructure

Critical thinking should be applied to achieve effective and efficient approaches to the life cycle and management of computerized systems [9]. The concepts of cultural excellence and maturity assessment are well embedded in GAMP® and ISPE in general [9, 11, 12].

CURRENT INDUSTRY CHALLENGES

GAMP® global leadership is aware that regulated companies continue to focus excessively on compliance and unnecessary computerized system validation activities and documentation, diverting resources and management attention away from investments in quality and toward compliance activities that do not directly lead to improved quality outcomes.

Examples of common problems include:

- Risk assessments that are regarded as tick-the-box documentation exercises, rather than as truly driving life-cycle activities that identif y required controls and provide valuable input to verification strategies

- Supplier assessments that do not influence the life-cycle approach, do not truly assess supplier suitability or quality in any meaningful way, or do not add to the management of quality or lessen business risk to the customer
- Application of GxP requirements, concepts, and documentation to technical areas where application of current best IT practices, including the use of tools and automation, would be more appropriate and effective and would improve quality
- Overreliance on complex and prescriptive document templates rather than guidance on necessary and value-added content
- Inappropriate and often unnecessary reviewers and approvers of documents
- Unnecessary duplication between documents, and unnecessary complexity or content in documents, leading to increased compliance and quality risk
- Lack of critical thinking driven by perceived and unwarranted fear of regulatory inflexibility

The root causes of these problems may include lack of appropriate subject matter expert input, lack of awareness of the distinction between quality risk and compliance risk, and intolerance of risk driven by a focus on internal compliance audits, coupled with a general misunderstanding and overinterpretation of regulations and guidance.

CONCLUSION

GAMP® strongly supports a pragmatic quality-focused approach as promoted by the Case for Quality program and advocates a risk-based approach to computerized systems that is focused on intended use as well as product quality and patient safety, as defined in current GAMP® guidance.

The objective of GAMP® guidance is the effective achievement of patient safety, product quality, and data integrity. *GAMP® 5* applies a life-cycle approach based on intended use and product and process understanding, while the application of quality risk management enables effort to be focused on critical aspects of a computerized system.

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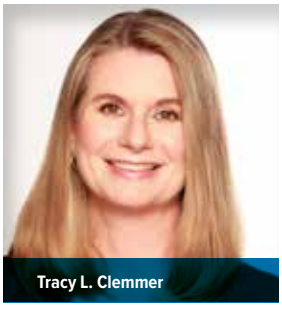
Member Profile

MULTIPLE ISPE ROLES
Lead to Unlocking Potential

By Paul J. Cumbo, MS, MLitt


Tracy L. Clemmer

Tracy L. Clemmer's experience has spanned the globe, and she has an impressive list of ISPE roles on her résumé. In addition to being a past President and Chair of the Training and Education Committee of the ISPE Singapore Affiliate, she was a Board Member and Chair of the Training and Education Committee of the ISPE China Affiliate and now serves on the ISPE Australasia Affiliate's Board of Directors. She was also the recipient of the 2010 ISPE's Max Seales Yonker Member of the Year Award.

Currently an independent consultant, Clemmer works with a worldwide range of clients in the pharmaceutical and biopharmaceutical industries, where she has more than 25 years of experience. She specializes in validation, manufacturing, project management, training, auditing, organizational development, and pharmaceutical sales. Across these many contexts, she said that "the people I've met are what I cherish most about my professional journey."

Unlocking human potential is her strongest motivation. "What drives me is helping people realize the best of their capabilities and making systems work better." With a BS in industrial engineering and an MBA, Clemmer couples her knowledge and experience with a genuine desire to improve organizations and their systems. "I found that implementing sustainable solutions is difficult in organizations with a rigid, 'we know how to do it' culture. The first step is to bring awareness and acceptance that change is needed." She credits ISPE with bolstering her skills in support of these goals. "ISPE has provided me opportunities to develop and strengthen my leadership capabilities."

PHARMA ROOTS

One might say Clemmer's career trajectory was oriented toward the pharmaceutical industry by default. "I grew up in 'Pharmaceutical Row' near Philadelphia. It was a neighborhood thing—everybody worked for 'Big Pharma.' It wasn't initially a passion; rather, it was just something I grew into." Eventually, though, Clemmer developed a very personal interest in the industry. "My brother was diagnosed with cystic fibrosis at 4 months. We were told his life expectancy was to be 9 years. He lived to be 27, which I credit in no small part to the pharmaceutical products that enabled him to live the best quality of life he could. I know that pharmaceuticals are providing better quality of life for people around the world."

Clemmer's disposition toward service and helping others has been strengthened by the travels she has undertaken. Travel "creates an experience of cultural immersion." Last year she traveled to Nepal with a nonprofit organization that supports a school for underprivileged girls in Upper Mustang, an isolated district in northern Nepal. She noted, "I had the opportunity during my visit to meet the child I sponsor. It was a very humbling experience."

Clemmer has worked in the United States, the United Kingdom, Singapore, Sweden, Korea, Thailand, China, Taiwan, Hong Kong, Malaysia, Japan, and Australia. She described the move from Singapore to China as "sensory overload." "I couldn't speak the language. I was in the ethnic minority. Everything was so different. All five senses were heightened. The intensity was refreshing, especially after Singapore, where everything is very organized." This range of experience has broadened Clemmer's appreciation for the diversity of the world—a perspective that informs her work as an independent consultant.

This independence is important because Clemmer sees herself operating generally outside the competitive aspect of the market; her aim is to focus on improving any organization with which she works. "I spent two years away from manufacturing and worked in sales. It was the first and only time in my career where I felt competitive with the other pharma companies. It wasn't very appealing to me because I'm all about the betterment of people. That's why I got into consulting—I wanted to bring best practices to everyone." She credits the experience in sales for adding to her understanding of the industry.

> "Don't ever stop learning. Be open-minded and positive, and remember the power of your network."

HELPING THROUGH CONSULTING

Clemmer understands that her work as an independent consultant is as much about the "soft" elements of workplace culture and organizational systems as it is about the "hard" aspects, such as specific deliverables and results. "For many companies, the use of technology is a challenge and an opportunity. Many are trying to implement technical solutions before understanding their own work practices. This results in overcomplicated business processes, which they then try to bypass."

Clemmer is particularly satisfied with her work to help companies look beyond their own usual assumptions and ways of working. "Sometimes, within a company culture, it's hard to think outside the box." Clemmer knows this firsthand: "When I left Merck in 2002 to join a consulting firm, I recognized that there was a broader world out there." That's when she got involved with ISPE. "ISPE helped me attain a view across the industry and see how different companies did things. ISPE brings together industry players to share collective knowledge and wisdom and improve the industry across the board."

Asked for her advice to young professionals in the industry, Clemmer replied, "Don't ever stop learning. Be open-minded and positive, and remember the power of your network." Clemmer demonstrates how a person with an experienced, open mind and an adventurous, willing spirit can bridge wide gaps—even between the disparate worlds of Big Pharma and a remote village in the Nepalese Himalayas.

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.

ISPE BRIEFS

ISPE Special Interest Group Formed for Artificial Intelligence

ISPE's newest Special Interest Group (SIG) will work on the emerging areas of artificial intelligence (AI) and machine learning (ML). The AI SIG was formed under GAMP®. A conversation with Eric Staib, Vice President of Compliance and PVAI Compliance Officer with Genpact, who heads the new SIG, provides details.

Why has this SIG been formed?
The industry is increasingly relying on software to automate many functions previously performed by humans. As our computer systems become more integrated and data sets become more robust, computer science is advancing our ability to learn from data and draw conclusions about what may or should happen next.

We are now reaching a point where algorithms are sophisticated enough to begin making decisions on our behalf. This is the field of AI, and we need guidance on how to use this technology in a GxP-compliant manner.

What are the key drivers/objectives of the SIG?
We are exploring the impact of AI on our regulated processes and possible use cases of these technologies within the life sciences industry.

We want to educate ISPE members and the industry on what these technologies are, and what they can do. We are also considering how they impact regulated processes/systems and decisions, and identifying risks and potential approaches to control these risks in a regulated environment.

What regions are represented by SIG members?
The team includes owner companies, industry suppliers, service organizations, and regulators from the US, Europe, and Asia.

What are the hot topics being addressed?
Robotic process automation, AI/ML, and how to validate and maintain these technologies in a compliant manner consistent with regulatory expectations.

What are the main challenges with these topics?
We have to first acknowledge the wide range of impact that these technologies will have across the breadth of our industry, embrace their adoption, and ultimately accept how patients may benefit from their implementation.

What is the expected output of the SIG, and what is the time frame?
Our first-year output will include ISPE education sessions (at events such as the Annual Meeting and local ISPE Chapter and Affiliate meetings) as well as developing ideas/concepts for articles, papers, and presentations. The SIG is established, and the plan is to define terms, technology boundaries, and formulate an initial set of risks and controls. We shall then test and share these definitions, risks, and controls with a wider audience.

—Anthony Margetts

ISPE Czech Republic and Slovakia Affiliate Launches Women in Pharma® Initiative

The ISPE Czech Republic and Slovakia affiliate launched its Women in Pharma® initiative with a workshop 30 May 2019. Up to 20 attendees were initially anticipated, but registration soared. Ultimately, 40 women and 5 men attended the workshop, and the session could not accommodate all who expressed interest in participating.

More workshops are planned, said Jiří Moninec, Managing Director, G.M. Project, Ltd., in the Czech Republic. The great interest indicates that women are seeking more technical and engineering knowledge, and Moninec was very pleased with the positive reaction to the program.

We'd like to feature your Chapter, Affiliate, CoP, or other ISPE group in an upcoming ISPE Briefs. Share highlights from training programs, conferences, social events, or other activities in an article of 250 to 400 words. We welcome photos (300 dpi or >1 MB). Send submissions to Susan Sandler, Senior Director, Editorial, at ssandler@ispe.org

REGULATING ONLINE PHARMACIES

and Medicinal Product E-Commerce

By Sia Chong Hock, Mervyn Ming Xuan Lee, and Lai Wah Chan

The internet has led to an increase in e-commerce of prescription and over-the-counter (OTC) medicinal products; one in four adults has purchased medicines online [1, 2]. This expansion of e-commerce in pharmaceuticals has greatly improved many companies' bottom lines. For example, in 2017, the Chinese company Ali Health reported a 739% rise in its revenue driven by e-commerce of OTC medicinal products alone [3]. For consumers, online pharmacies offer many advantages, including lower costs, convenience, privacy, and a wider range of choices [4]. For businesses, using online platforms and removing the need for physical storefronts translates into the multiplication of stock-keeping units and increased price competitiveness.

Although e-commerce of medicinal products has many benefits for patients and the pharmaceutical industry, it remains a concern for regulatory authorities (RAs) worldwide. RAs must safeguard the public from potential harm posed by illegitimate online pharmacies. Existing laws may need to be amended, and enforcement approaches changed, to address the transnational nature of e-commerce of medicines.

Note: In this article, "e-commerce" refers to the commercial transaction of buying and selling goods and services over the internet [5]. "Medicinal products" refers to prescription and OTC medicines, and excludes nutritional supplements. "Controlled substances" refers to substances likely to cause dependence when abused, such as amphetamines, morphine, and codeine [6]. "Counterfeit medicines" refers to medicinal products that are substandard or falsified, with fraudulent misrepresentation of their identity, content, or source [7].

SAFETY CONCERNS

According to a 2016 report published by the Center for Safe Internet Pharmacies, 96% of online pharmacies worldwide do not comply with the relevant laws of countries within which they operate [8]. In addition, some online pharmacies have sold counterfeit medicines, defrauded consumers, and stolen customer credentials and credit card information [9, 10].

Despite rigorous educational efforts, many consumers remain unaware of the safety risks posed by counterfeit medicines [10, 11]. Prescription-only medicines (POMs) can be easily purchased from online pharmacies and popular consumer-to-consumer e-commerce platforms, such as Lazada and Carousell, due to the lack of regulations from RAs [12, 13]. The availability of POMs from online pharmacies, whether legitimate or not, is a serious public health concern, especially as more consumers use the internet to self-diagnose and self-treat [14]. The unsupervised use and potential misuse of POMs can lead to severe adverse effects and even death [15].

CURRENT EFFORTS TO PROTECT CONSUMER SAFETY

At present, RAs rely on a collection of legal regulations, international law enforcement operations, and accreditation programs to address safety concerns related to the e-commerce of medicinal products.

US Legal Restrictions on Online Sales

Laws regulating the online sales of medicinal products vary from country to country. In the US, the Ryan Haight Online Pharmacy Consumer Protection Act of 2008 strictly restricts consumers' online access to controlled substances [16]. Online pharmacies dealing with controlled substances must register with the US Drug Enforcement Administration (DEA). Consumers must also complete an in-person medical examination by a qualified practitioner to obtain a valid prescription before they can purchase controlled substances. Hefty penalties serve as a deterrent to individuals who intend to engage in unauthorized sales of controlled substances [17]. Laws regulating online sales of medicinal products in other countries are reviewed later in this article, in the Regulatory and Enforcement Challenges section.

Laws Against Counterfeit Medicines

The Drug Supply Chain Security Act and the Falsified Medicines Directive (FMD) are legislative tools used by the US and the European Union, respectively, to address the dangers of counterfeit medicines. By creating an interoperable electronic track-and-trace system, RAs aim to prevent counterfeit medicines from entering the legitimate supply chain [18, 19]. To ensure that the supply chain is secure, key supply chain stakeholders such as manufacturers, repackagers, distributors, and pharmacies must ensure the authenticity of products at the point of receipt before handing them over to the next party in line [18, 19].

Under FMD, EU-based online pharmacies must obtain a common logo from the national RA to display on their website [20]. Clicking the logo directs the consumer to the pharmacy's entry on the RA's online list of authorized/registered pharmacies, thus verifying that the pharmacy site is legitimate.

International Law

The MEDICRIME Convention, an initiative of the Council of Europe, is the first international treaty to criminalize online sales of counterfeit medicinal products [21]. Individuals engaged in such sales will be prosecuted regardless of the country where the act was committed. For greater effectiveness, more RAs worldwide should ratify the MEDICRIME Convention and enact domestic laws to criminalize online sales of counterfeit medicinal products.

Launched in 2008, Operation Pangea is the leading international collaborative enforcement effort to eradicate illegal online sales of medicinal products. For example, in 2017, law enforcement agencies such as customs, police forces, and RAs successfully seized US$25 million worth of illicit and counterfeit medicines [22], illustrating the effectiveness of collaborative efforts among different agencies when dealing with transnational crimes.

Nonetheless, illegal online sales of medicines are still prevalent [22]. RAs may need to reevaluate Operation Pangea, expand its scope, and develop new approaches to address illegitimate online pharmacies, involving major pharmaceutical companies in their efforts where necessary.

Accreditation Systems

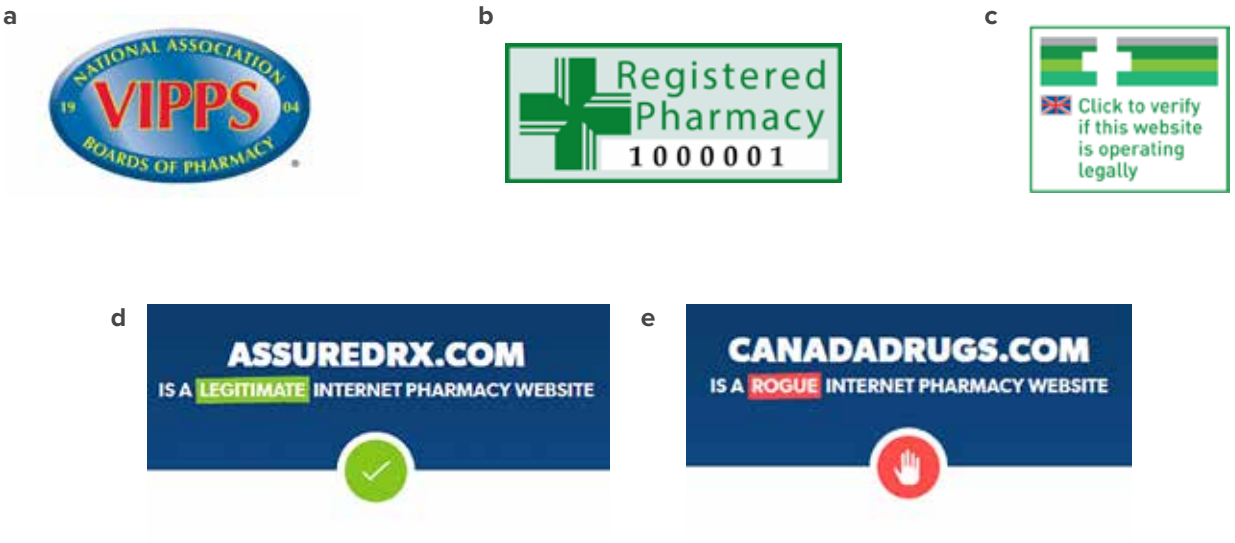
Accreditation systems can help improve information asymmetry and offer safety assurance to consumers [23]. For example, these systems provide tools such as accreditation seals or website checkers that verify the legitimacy of online pharmacies. However, many consumers are unaware of the existence and purpose of accreditation systems [24], and some illegitimate online pharmacies have used fake accreditation seals on their websites to deceive unsuspecting consumers [25]. Table 1 reviews selected accreditation organizations for online pharmacies [20, 26–31], and Figure 1 displays selected accreditation seals.

The lack of standardized criteria and other lapses in compliance checks have led to inadvertent accreditation of illegitimate online pharmacies, thereby threatening patient safety [26]. Hence, RAs need to apply standardized criteria for accreditation systems. They also must educate consumers on safer practices for purchasing medicines online, such as how to differentiate between authentic and inauthentic accreditation seals.

Table 1: Accreditation organizations for online pharmacies.

Accreditation Organization	Countries of Operation	Comments
National Association of Boards of Pharmacy (NABP)	US and Canada	• Operates an FDA-endorsed voluntary accreditation program, i.e., Verified Internet Pharmacy Practice Sites (VIPPS) [27] (Figure 1a). To earn VIPPS accreditation, online pharmacies must comply with US laws, be physically located in the US, and meet listed criteria to ensure quality standards. • Launched the ".pharmacy" domain initiative in 2014 to provide consumers worldwide with a way to identify safe, legal, and ethical online pharmacies [27, 28].
General Pharmaceutical Council (GPhC)	Great Britain	• Operates a voluntary accreditation scheme for online pharmacies to help assure Great Britain consumers when purchasing medicines online [29] (Figure 1b). • Issues the common EU logo (Figure 1c) to legitimate online pharmacies operating in Great Britain.
RAs of EU member states	EU member states	• Under FMD, EU-based online pharmacies must display the common EU logo (Figure 1c) on their websites [20]. • Online pharmacies must register with their respective national RA and comply with relevant laws to obtain the common EU logo. By clicking the national flag under the logo, consumers are directed to the RA website to verify the company's identity.
LegitScript	International	• Third-party certification service helps consumers verify the legitimacy of online pharmacies (Figures 1d and 1e). • Certification is recognized by many RAs worldwide, including those of Japan and Italy [30].
PharmacyChecker	International	• Offers PharmacyChecker Verification Program to verify the legitimacy of online pharmacies. • Provides miscellaneous services like price comparison of medicines among different online pharmacies [31].

Figure 1: Accreditation organizations' systems to show online pharmacy legitimacy: (a) VIPPS accreditation seal from NABP, (b) GPhC voluntary online pharmacy logo, (c) EU common logo for UK online pharmacies, (d) screenshot from LegitScript website indicating that online pharmacy is legitimate, and (e) screenshot from LegitScript website indicating that online pharmacy is illegitimate.



The ".pharmacy" Domain

The ".pharmacy" domain scheme complements national accreditation systems to verify the legitimacy of online pharmacies. It was launched by NABP in 2014 to provide consumers worldwide with a way to identify safe, legitimate, and ethical online pharmacies [27, 28]. As the owner of the ".pharmacy" domain, NABP determines which pharmacies to host on the domain and requires that they demonstrate legitimacy. RAs may audit NABP periodically to ensure its reliability and fairness in implementing this scheme.

REGULATORY AND ENFORCEMENT CHALLENGES

To ensure the safety of medicinal product e-commerce, RAs need relevant legislation as well as adequate resources to find and prosecute criminals. However, in many countries, laws are insufficient to regulate the sales of medicinal products. Moreover, jurisdictional and resource limitations often allow criminals to escape prosecution.

Lack of Strong National Laws Worldwide

Unfortunately, 66% of countries worldwide do not have laws that explicitly regulate or prohibit online sales of medicinal products [32]. POMs and OTC medicinal products can therefore be sold on e-commerce platforms by anyone. As a result, RAs in these countries are only able to employ the "buyers beware" approach and hope that consumers will remain vigilant when buying medicinal products online.

Without legislation, RAs cannot stipulate legal responsibilities for online pharmacies or mandate that they take on quality assurance responsibilities or undergo periodic inspections. In contrast, relevant legislation empowers RAs to implement well-defined frameworks to safeguard public health (Table 2) [28–30, 33–44]. RAs that allow POM online sales can use an official accreditation system and online registries to direct consumers to legitimate sites [29], whereas RAs that prohibit POM online sales make it clear that no one is allowed to sell them via e-commerce [33]. Additional restrictions may be imposed. For example, although China allows online sale of OTC medicines, it prohibits their sales on third-party e-commerce platforms, including its very own Tmall.com [44].

Jurisdictional Limitations and the Transnational Nature of Online Pharmacies

When individuals involved in illegitimate online pharmacies are based outside of an RA's jurisdiction, prosecution can be a challenge [45, 46]. Although most countries criminalize such acts on the basis of counterfeiting and deception with intent to harm, existing legal frameworks are fundamentally bound by territorial boundaries [47].

To extend jurisdiction beyond their borders or request extradition to prosecute a suspect, RAs need a harmonized set of international agreements, such as treaties or conventions [48]. Even then,

Table 2: Approaches of RAs worldwide to control medicinal product online sales.

Country	Legislation Allows Online Sale of Medicines?	Comments
US	Yes: POMs and OTC medicines	State-licensed online pharmacies can sell medicinal products online [30].
Canada	Yes: POMs and OTC medicines	Licensed brick-and-mortar pharmacies can sell medicinal products online [28].
Germany	Yes: POMs and OTC medicines	Licensed brick-and-mortar pharmacies must register with the relevant RA, obtain a mail order permit, and display the EU common logo to sell medicinal products online [34].
Great Britain	Yes: POMs and OTC medicines	Online pharmacies must register with GPhC and have a physical location in Great Britain to sell POMs [29].
The Netherlands	Yes: POMs and OTC medicines	Online pharmacies must register with the relevant RA and display the common EU logo issued by the RA to sell medicinal products online [35].
Australia	Yes: POMs and OTC medicines	Brick-and-mortar pharmacies operating in Australia can sell medicinal products online as long as they adhere to all applicable laws and practice standards [36].
China	Yes: OTC medicines only	A bill to allow the sale of POM via online pharmacies has been delayed due to safety considerations [37]. The sale of OTC medicinal products on third-party e-commerce platforms is prohibited due to safety considerations [44].
Japan	Yes: specific OTC medicines only	The online sale of specific OTC medicines such as fexofenadine and loratadine is prohibited [38]. Other OTC medicinal products can be sold online.
South Korea	No: online sale of POMs and OTC medicines is prohibited	Medicinal products can only be sold at physical stores registered with the RA [33].
Russia	Yes: OTC medicines only	Online sale of any medicinal products was prohibited in Russia [39]. However, since December 2017, a draft law allows online sale of OTC medicinal products [40].
India	Law is unclear	Although the RA bans the online sale of medicinal products, the prohibition is not legislated [41].
Singapore	Yes: specific OTC medicines only	The RA employs a "buyers beware" approach to warn consumers of the risk involved in purchasing medicinal products online [42].
Malaysia	Yes: OTC medicines only	The RA employs a "buyers beware" approach to warn consumers of the risk involved in purchasing medicinal products online [43].
Indonesia	Law is unclear	Legal status of online pharmacies is unclear [30].

transnational jurisdictional claims are often met with controversies, and extradition may be difficult. Culprits may escape to countries with weak enforcement systems to avoid prosecution.

Limited Enforcement Resources

Customs agencies generally lack sufficient resources to inspect all incoming parcels. As a result, packages containing counterfeit medicines from illegitimate sources based in other countries can reach consumers, exposing them to potential harm. It is also challenging for law enforcement agencies to track down individuals involved in illegitimate online pharmacies on their own. Hence, RAs need to reevaluate their current strategies and develop international collaborative initiatives to increase the efficiency of resources spent.

Inadequacy of Cooperation by Private Organizations

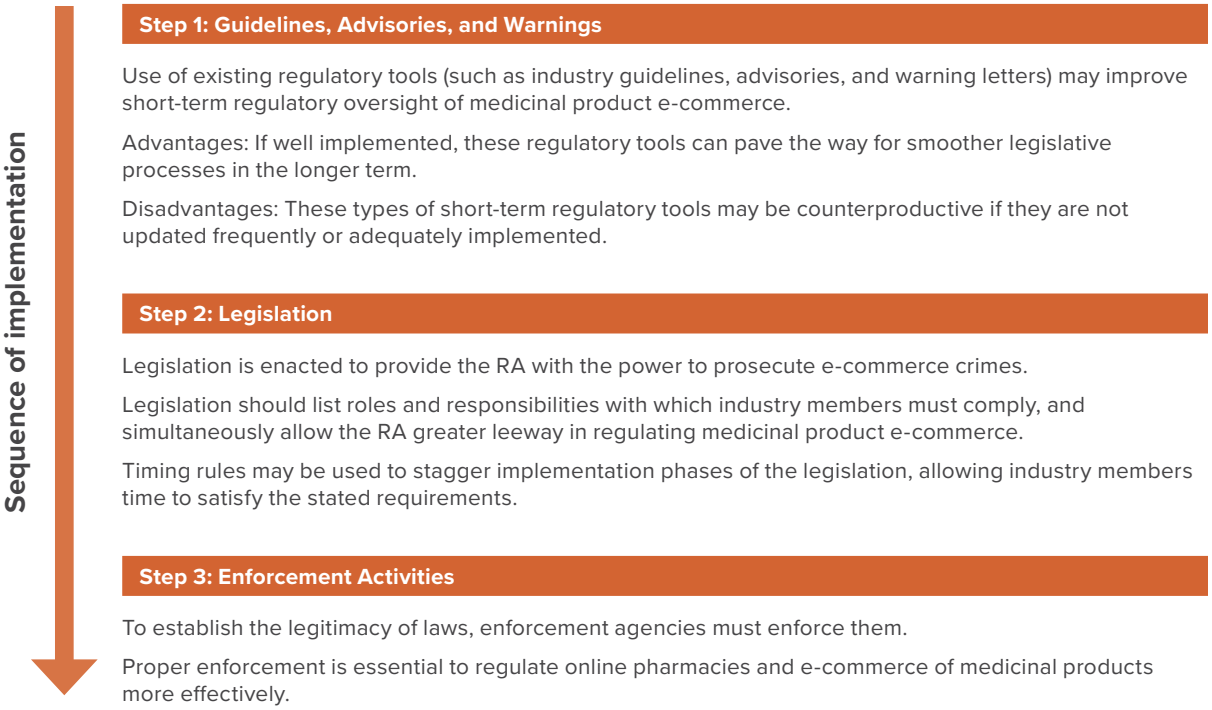
Under existing laws, RAs often must rely on private companies such as delivery couriers, financial service providers, and internet companies to help enforce e-commerce regulations, and the agencies have limited options if those companies do not cooperate. For example, in 2012, delivery courier FedEx withdrew from the collaborative enforcement efforts to protest the US DEA's decision to investigate its role in facilitating activities of illegitimate online pharmacies. In 2016, the federal charges against FedEx were dropped, and FedEx publicly criticized the US government's decision to file charges against the company [49]. RAs must have effective legislation to mandate the involvement of private companies in eradicating illegal e-commerce, with due consideration for hold-harmless provisions.

A STRATEGIC AND HOLISTIC APPROACH TO REGULATE MEDICINAL PRODUCT E-COMMERCE

A strategic and holistic approach may help RAs more effectively regulate online pharmacies and e-commerce of medicinal products. This proposed strategic approach involves a stepwise implementation of a framework that comprises (a) guidelines, advisories, and warnings; (b) legislation; and (c) enforcement activities (Figure 2). Stepwise implementation grants companies buffer time to modify their in-house policies to align with directions set by the RA with oversight power. The success of the approach lies in the collaboration of the authorities (domestic and international) with various organizations (accreditation organizations, Interpol, and private companies).

In countries that currently lack laws to effectively govern e-commerce of medicinal products, the domestic RA should initiate a national licensure system for all online pharmacies operating

Figure 2: **Stepwise implementation framework to regulate medicinal product e-commerce.**



under their jurisdiction to allow for regulatory oversight. A mandatory inspection or accreditation framework may be included in the licensing requirement to ensure that the online pharmacies meet internationally recognized quality system standards.

Pharmaceutical companies may assist RAs to expedite the inspection process by reconciliation with their respective supply chain partners to confirm that medicinal products sold by the individual online pharmacies originate from a legitimate source. Upon satisfactory inspection, online pharmacies will be given country-specific accreditation seals for their websites and added to the online pharmacy registry found on the RA's website.

Ultimately, the online pharmacies licensed by the RA should be hosted on the ".pharmacy" domain operated by NABP, regardless of the countries in which they operate. This initiative will mold the ".pharmacy" domain into the standardized domain and international benchmark for legitimate online pharmacies worldwide, helping consumers verify a pharmacy's legitimacy from its web address. To address challenges beyond the scope of NABP and ensure neutrality of the accreditation system, ownership of the ".pharmacy" domain may be transferred to a neutral international nongovernmental organization such as the World Health Organization or an appropriate United Nations agency.

In addition to creating a safe e-commerce environment for medicinal products, it is vital for RAs to educate consumers on how to access and use the secure e-commerce environment for medicinal products. RAs may consider collaborating with search engine providers such as Google to use online advertisements to spread educational messages; another option might be to employ behavioral advertising techniques, like retargeting, to direct educational messages selectively to consumers at risk of engaging in unsafe e-commerce practices [50].

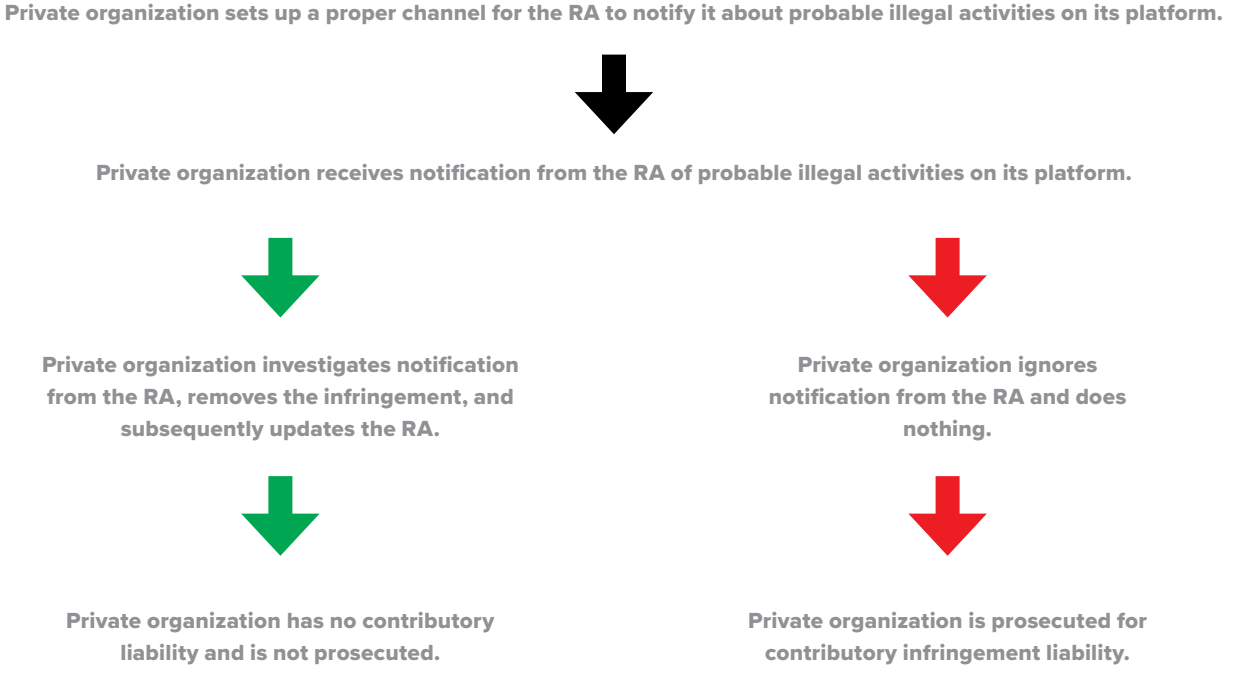
Moving forward, RAs should consider working in partnership with private companies such as delivery couriers, search engine providers, domain name registrars, financial service providers, and online platform owners in the overall regulation of online pharmacies (Table 3 and Figure 3). These private organizations should have self-regulation guidelines or policies to curb the proliferation of illegitimate online pharmacies. The self-regulation guidelines, which should be agreeable to the RA, should contain reasonable precautions that private organizations could adopt to prevent individuals from exploiting their services, regardless of whether they are online or offline [51].

Subsequently, RAs should consider enacting legislation with adequate regulatory bite to mandate that private organizations implement reasonable precautions. RAs can also incorporate safe harbor procedures (Figure 3) into the new or amended legislation to incentivize private organizations to collaborate to stop illegal acts, to proactively investigate any illicit activity at their end, and

Table 3: Reasonable precautions private organizations can implement to prevent illegitimate online pharmacies from conducting illicit activities.

Type of Organization	Reasonable Precautions
Delivery courier	Prohibit individuals from sending parcels containing illegal medicinal products. Verify parcel contents at point of acceptance to ensure that the parcel does not contain illegal medicinal products. Warn individuals who are caught attempting to send illegal medicinal products, and report to the RA when individuals are suspected to be involved in operating illegitimate online pharmacies.
Search engine provider	Verify the accreditation status of online pharmacies to ensure their authenticity before allowing them to advertise sponsored links. Develop smart algorithms to filter out illegitimate online pharmacies from search results.
Domain name registrar	Implement and enforce policies to prohibit the sale of illegal medicinal products. Actively monitor registries and remove websites engaged in illegitimate online pharmacy operations.
Financial service provider	Have a program to identify merchant accounts of illegitimate online pharmacies. Carry out investigations and disable merchant accounts if they are found to be linked to illegitimate online pharmacies.
Online platform owner	Prohibit sales of illegal medicinal products on their online platforms. Implement an active monitoring system to track listings and ensure illegal medicinal products are not sold via their online platforms.

Figure 3: Safe harbor procedures private organizations must comply with to be immune to contributory liabilities from facilitating operations of illegitimate online pharmacies.



> "It is crucial for regulatory authorities to work together to step up international enforcement efforts against illegal sales of medicinal products online."

to avoid any legal contravention [52]. The regulator and regulated should share a common understanding, with due consideration for hold-harmless provisions, to avoid any liability issues.

Concurrently, it is crucial for RAs to work together and with Interpol to step up international enforcement efforts against illegal sales of medicinal products online [53]. This will allow prosecution of suspects involved in illegal online sales of medicinal products, regardless of where the crime was committed. Penalties should be raised proportionately to provide deterrence.

Interpol needs to take on the central policing role of illegitimate online pharmacies and establish an independent international task force to conduct investigations at the global level. This task force would facilitate essential intelligence exchanges among RAs and lead a collaborative investigation with national law enforcement agencies to track down suspects [54]. Such international collaboration can vastly improve the efficiency of investigations and help authorities conserve resources.

CONCLUSION

E-commerce of medicinal products is expected to become an integral part of healthcare systems in the future. Increased e-commerce of medicinal products can bring about advantages such as lower cost, convenience, and consumer privacy. However, the shift from physical stores to online platforms also presents health risks.

Many RAs lack legislation to properly regulate online pharmacies. Jurisdictional and resource limitations have allowed criminals to escape prosecution. The lack of legislation to mandate private organizations' cooperation in investigations also impacts enforcement efforts negatively.

Going forward, a proposed strategic and holistic approach may help RAs regulate e-commerce of medicinal products more effectively. This strategic approach—which incorporates a stepwise implementation of industry guidelines, advisories, and warnings; legislation; and associated enforcement activities—can address the current risks associated with illegitimate online pharmacies and illegal medicinal product e-commerce. Although compliance costs may increase with tighter e-commerce regulation of medicinal products, safeguarding public health should ultimately be the overriding concern of all RAs and stakeholders in general.

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AIRFLOW REDUCTION IN CLEANROOMS AFTER CLOSING HOURS

By Allan Hart, MSc

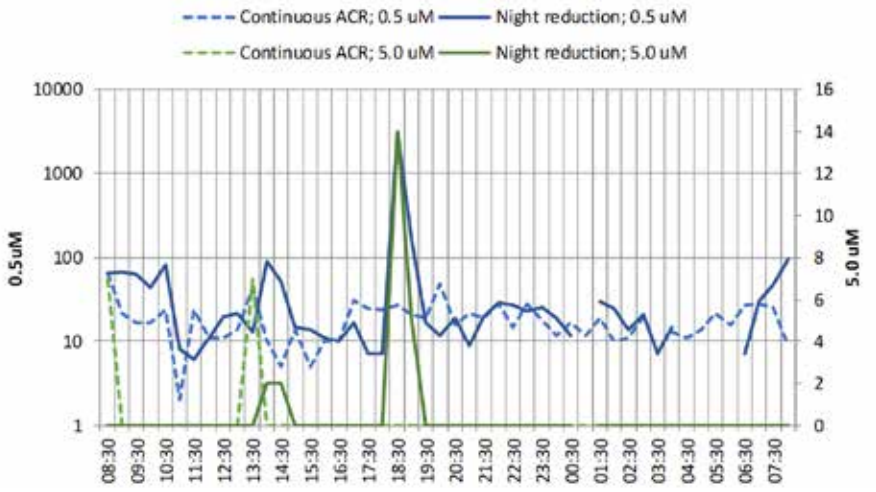
Cleanrooms and laboratories can save a significant amount of energy by reducing airflow of air handling units (AHUs) after closing hours. Although challenging, airflow reduction is a successful energy reduction measure and has been implemented within the energy reduction program of Janssen Vaccines & Prevention B.V. in Leiden, the Netherlands.

In laboratories with clean-air requirements (i.e., cleanrooms), air must be filtered to reduce the number of particles. Airflow, which is measured in air change rates (ACRs), is typically 10 times higher in cleanrooms than in offices. Humans and human activities are the main sources of particles, and our program has found that the cleanroom ACR can be safely reduced after closing hours, when fewer staff members are present. This innovation not only reduces electricity consumption but also saves on district heating, cooling energy, and steam for humidification. In this case study, the HVAC system has variable air volume (VAV)–controlled air valves (active pressure control), and typical ACRs are in the range of 10 to 30. Figure 1 shows the program's after-hours electricity savings due to ACR reduction.

Within GMP-classified cleanrooms [1], areas are pressure-controlled and the amount of supply flow is determined by the specified ACR. The ACR is defined in accordance with the specified cleanroom class; in this case, the cleanrooms are in classes C and D (≈ISO class 7 and 8, respectively). Most cleanrooms are kept at an overpressure (e.g., +15 Pa) to prevent outside particles from entering them. Some clean areas are kept at underpressure (e.g., –15 Pa) due to biological safety requirements and/or cleanroom requirements. Reducing airflow for these types of pressurized cleanroom systems while in operation was previously regarded as impossible due to pressure, particle (GMP, ISO 14644) [2], temperature, recovery time, and biosafety requirements. However, the energy reduction program has met all criteria, and the system is currently operating satisfactorily. Within the energy reduction program, several energy-saving measures have been implemented, such as hydraulic optimization, optimized airflow recirculation [3], and temperature and humidity controls.

Figure 1: Comparison of electricity consumption at the main distribution board, including all electricity use (equipment, HVAC, etc.), before and after ACR reduction. Each series of 5 peaks represents 5 working days (peak hours), followed by 2 weekend days (off-peak hours); total time span for measurements is 2 months.

Figure 2: Continuous measurement (24 hours) of particle concentration for a GMP class C cleanroom. Dotted lines show concentrations when ACR was 100% around the clock; solid lines show concentrations when ACR was reduced by 50% during after-hours operations (23:00 to 7:00). All measured values are more than 10,000 times lower than the at-rest concentration limits.



HUMAN ACTIVITY'S EFFECT ON CLEANROOM NONVIABLE PARTICLE CONCENTRATION

For cleanrooms, air is filtered by HEPA filters and ACRs are high to limit the number of particles. Before implementing our program, we validated the following argument:

> *During after-hours operations, in absence of personnel, the ACR can be reduced because the main sources of particles are humans and human activities.*

An initial step to assess this proposition was to continuously measure the particle concentration inside the cleanroom over a period of 24 hours during a typical production day and night. This demonstrates the effect of the presence of staff members.

Figure 2 depicts particle concentrations for a GMP class C cleanroom before and after implementation of 50% lower airflow during after-hours operations. After closing, from 23:00 to 7:00 (11 p.m. to 7 a.m.), the measured concentrations of particles were generally lower than during working hours. The spikes at 9:00, 14:00, and 19:00 were caused by staff members entering the cleanroom. Notably, the measured concentrations for the 24-hour period were over 10,000 times lower than the allowable limits. Similar results were found for other cleanrooms—with one exception, which is described next.

UNDERPRESSURE EFFECT ON CONTINUOUS PARTICLE MEASUREMENT

Cleanrooms with biological safety requirements operate at underpressure (e.g., –15 Pa) to prevent the escape of air from the cleanroom. This means that air from surrounding areas flows in due to the underpressurized air. By design (bubble type [4]), adjacent areas are also cleanrooms to limit the influx of particles.

Figure 3 presents particle concentrations in a GMP class D cleanroom at underpressure. Notably, the measured concentrations were higher after hours than during working hours. This finding was unexpected and unlike measurements from the other cleanrooms.

While investigating possible reasons for the unexpected results, we found significant air leakage from the media panels and wall sockets, which are in contact with technical areas. Technical areas are not cleanrooms, and thus this leakage introduced a significant number of particles. The lower particle concentration during the day can be explained by the air mixing with more clean air from adjacent areas when doors are frequently opened. When the doors remained closed during the night, the particle concentration built up to higher levels than during the day.

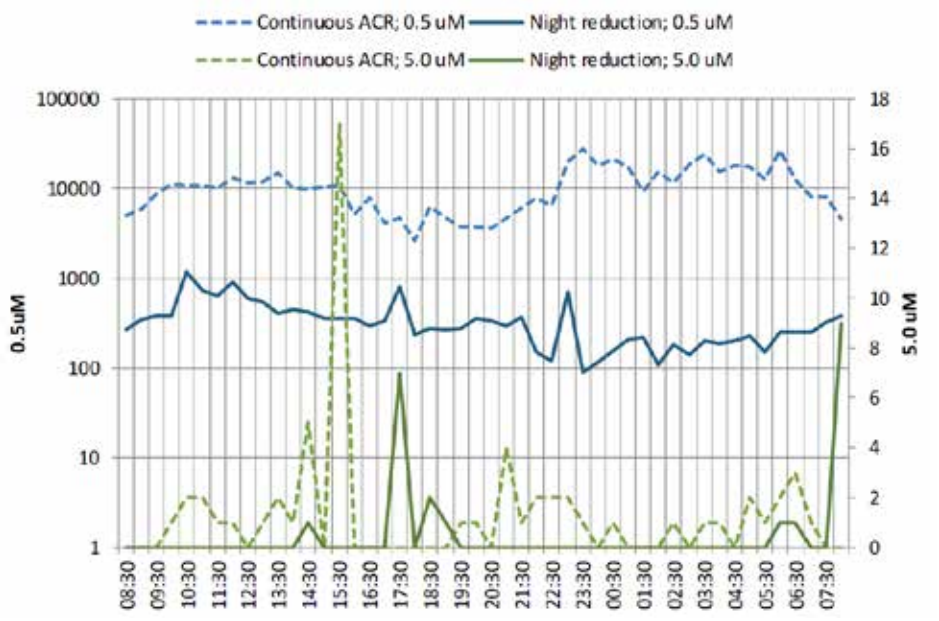
During the program's implementation period, the wall sockets and media panels were sealed off as a corrective action. Particle concentrations for both continuous and reduced airflow were measured again, and they were significantly lower than in the initial measurement. This discovery and the subsequent improvement of cleanroom air quality may be considered (what energy consultants call) a nonenergetic benefit.

INCREASING AFTER-HOURS AIRFLOW IN STAFF'S PRESENCE

During risk assessments, it has been agreed that airflow in a cleanroom may only be reduced when no staff is present. Therefore, airflow must automatically increase before staff enters the clean space.

To address this issue, our program uses the following mechanisms (Figure 4): When someone enters the gowning area outside

Figure 3: Continuous measurement (24 h) of particle concentration in a GMP class D cleanroom at underpressure (–15 Pa). Dotted lines show concentrations when ACR was 100% around the clock; solid lines show concentrations when ACR was reduced by 50% during after-hours operations (23:00 to 7:00). All measured values are 1,000 times lower than the at-rest concentration limits.



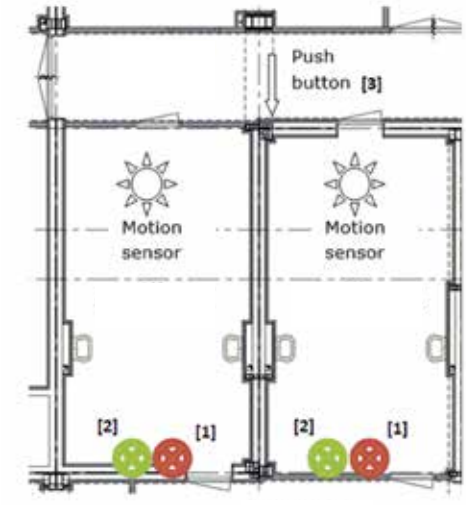
of working hours, a motion detector is triggered. This trigger signals the HVAC to return airflow to normal. Airflow via the HVAC installation is directly related to the fan power. Once the motion detection sensor is activated, HVAC fans rev up and are restored to the original flow. During the ACR transition stage, a red indicator light flashes in the gowning area. Within 5 minutes, airflow is restored to normal; this activates the green light, indicating that staff may enter the cleanroom. Because the gowning procedure normally takes approximately 5 minutes, this waiting period does not affect staff workflow. The ACR can be restored to reduced airflow outside of working hours by using a manual switch (indicated in Figure 4 by the push button), with the last person leaving the cleanroom responsible for the switch.

AIRFLOW AND PARTICLE RECOVERY TIMES

According to ISO 14644 [2], the time required for airflow to recover to the original 100% flow should be demonstrated. Figure 5 depicts airflow recovery and shows that airflow is restored to the original 100% setting within 2–3 minutes.

In addition, in this case study, the particle recovery time for the cleanrooms was measured at reduced airflow. To determine the particle recovery time, particles are introduced in the cleanroom and the time it takes for the particles to be removed is measured. These measurements provide information on flow effectiveness and presence of dead zones in the cleanroom airflow. The particle recovery time at reduced flow is hardly affected and is still well within specified limits. One of the contributing factors is that the HEPA filters operate more effectively at lower airflow.

Figure 4: Plan view of gowning area, including motion detection sensors, lights to signal whether the cleanroom airflow has been restored to 100%, and a button to manually reset after-hours airflow to the reduced ACR.



PRESSURE RECOVERY DURING AIRFLOW TRANSITIONS

To prevent cross contamination between areas, pressure cascades between critical areas should be maintained during the transition from reduced to 100% airflow. During normal operation, pressure values are continuously monitored, and alarms go off when deviations occur.

Figure 5: Airflow recovery time (fan speed) during transition from reduced flow to full flow within 2–3 minutes. The vertical axis represents the percentage of the maximum fan speed (i.e., volume flow).

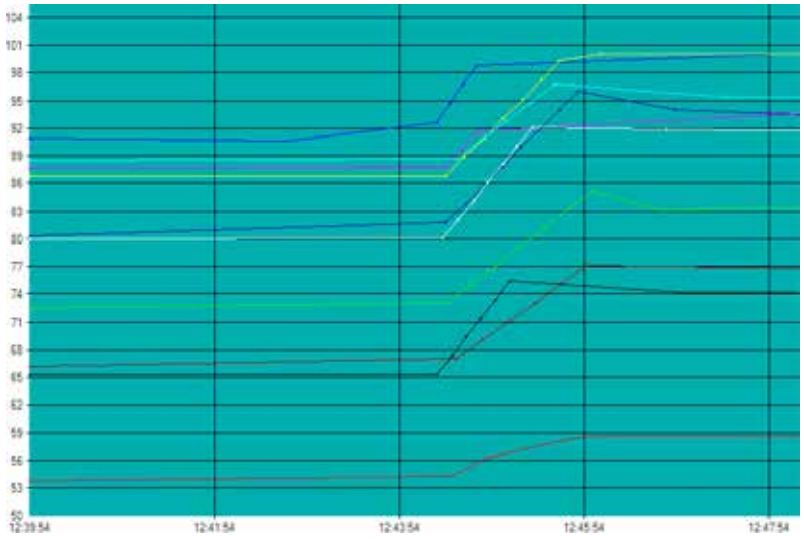
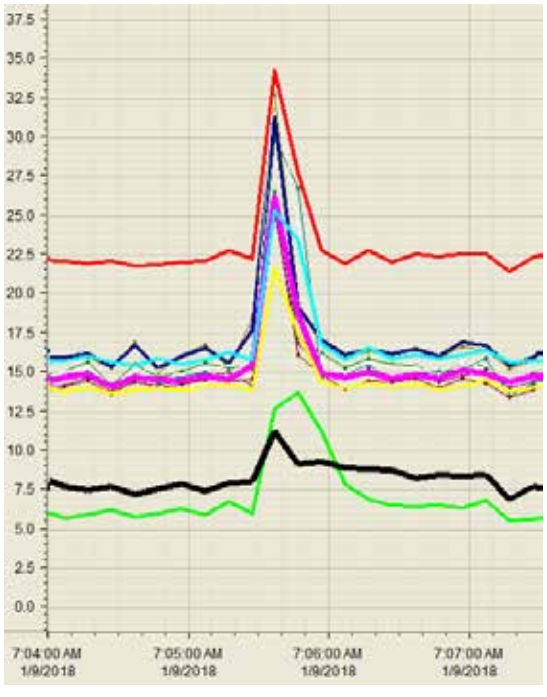


Figure 6: Pressure recovery during transition from reduced to 100% airflow. The spikes are caused when air supply flow adjusts immediately but adjustment of pressure control (return valve) is delayed.



When we activated ACR reduction, the pressure for several areas fluctuated considerably. For these specific areas, airflow was therefore increased or restored to the original 100% flow. This effect reduced the achieved energy reduction by 10%–20%. However, if the transition time is extended, the pressure fluctuation will decrease. This is one of the lessons learned from this project: to reduce the pressure fluctuation, one must smoothly adjust the set-point values and thereby gradually change the valve positions.

Figure 6 shows that pressure is the same for both reduced and full airflow (before and after the spike). During an airflow transition, the pressure spikes but the pressure cascade is maintained for adjacent areas.

TEMPERATURE STABILITY DURING REDUCED AIRFLOW

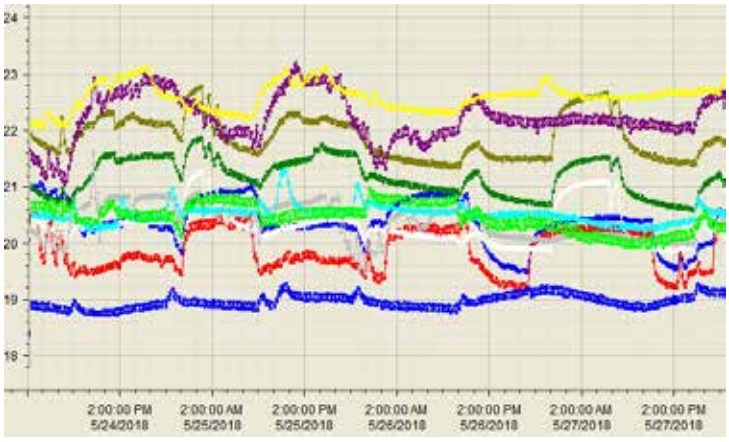
The cleanroom temperatures remain stable during operation at reduced airflow. After closing hours, the equipment load reduces substantially, and there is little to no presence of staff members. As a result, the internal thermal load and thus the required cooling load are reduced. The daily variation is shown in Figure 1 by the difference between peak and base values.

The temperature monitoring system has indicated no significant change in after-hours cleanroom temperatures. For example, over a period of 7 hot summer days in 2018, the cleanroom temperatures were generally lower during after-hours periods of reduced airflow than during operating hours when airflow was 100% (see Figure 7).

FLOW ADJUSTMENT OF VAV VALVES

In our building management system (BMS), air volume flow of the VAV valves is a setting in the software and can be adjusted to include an after-hours operation setting. The software modification should be uploaded to the system while the system is shut down; this is specifically recommended for the brand of BMS software and hardware used for our HVAC system. The upload

Figure 7: Measured cleanroom temperatures for 10 critical areas over a period of 7 hot summer days in 2018. May 26 and 27 were weekend days. Despite reduced airflow, after-hours temperatures are mostly lower than temperatures during normal weekday operations.



procedure is not supposed to take longer than 1 hour. However, in our case, the upload created a significant risk because the system could not be restarted for 2 days due to a hardware/software error.

Anticipating this type of risk is another lesson learned. Implementation during shutdown is strongly advised to minimize issues associated with software modifications.

In our control software, the output signal of the BMS system to the controllers of the VAV unit also had to be adjusted. This meant that all output signals to the VAV controller and VAV controller limit values needed to be checked and/or adjusted individually. This was a time-consuming process, requiring several days of labor for 5,000 m² of cleanroom area.

FAN PRESSURE SET-POINTS

The fan pressure set-point was not initially adjusted for operation at reduced airflow. Two set-points, one for daytime operation and another for nighttime, were not included in the updated control program (software). This was discovered when the HVAC fans resonated during first tests of the system. The pressure set-point of the fans had not been adjusted, but the volume flow had been reduced; this caused the fans to resonate. Resonating of the fans may lead to catastrophic failure of the HVAC system. By reducing the pressure set-point, the resonance issue was resolved.

The lesson learned was that the additional pressure set-point for the fans should be included in the software. The software adjustment planned for this year is to include an additional reduced pressure set-point for the HVAC fans after closing hours, which will significantly reduce HVAC fan electricity consumption in addition to the current energy savings.

CONCLUSION

Project implementation required a few days while the cleanrooms were shut down. Measurements were taken before and after shutdown and during the normal startup procedure. No increase in particles was found, and all parameters (particles, temperature, etc.) remained within their specified limits. Also, during after-hours operation, particle concentration did not increase.

Potentially, the airflow reduction could reduce HVAC energy consumption by 20%–30%. Field results show a total electricity consumption reduction of 10%. Notably, the HVACs account for about 50% of the overall energy use.

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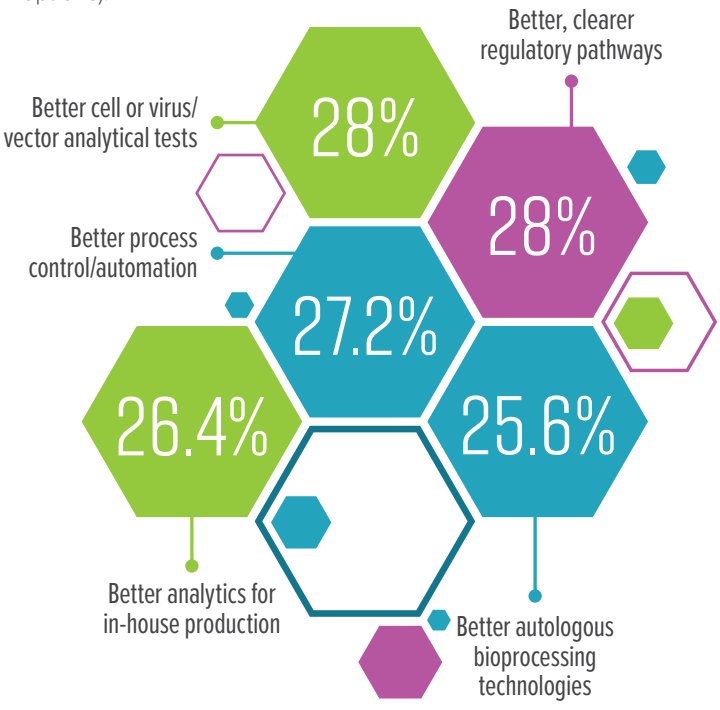
THE FUTURE OF BIOPHARMA

WHAT DOES THE INDUSTRY WANT AND NEED?

Eric S. Langer, President and Managing Partner, BioPlan Associates, Inc., shared these most-needed cell and gene therapy manufacturing improvement, systems, platforms, and infrastructure from his company's research [1] at the 2019 ISPE Biopharmaceutical Manufacturing Conference (as indicated by the percentages of survey respondents who chose these options):



FDA FORGES AHEAD TO SUPPORT CELL AND GENE THERAPY

The FDA is working to streamline the review and safety reporting requirements for gene therapy protocols [2].

NIH's Recombinant DNA Advisory Committee (RAC) will transition to become the Novel and Exceptional Technology and Research Advisory Committee (NExTRAC), focusing on evaluating new biotechnologies and emerging applications.

LEARN MORE ABOUT BIOPHARMA MANUFACTURING [3]

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