PHARMACEUTICAL ENGINEERING®

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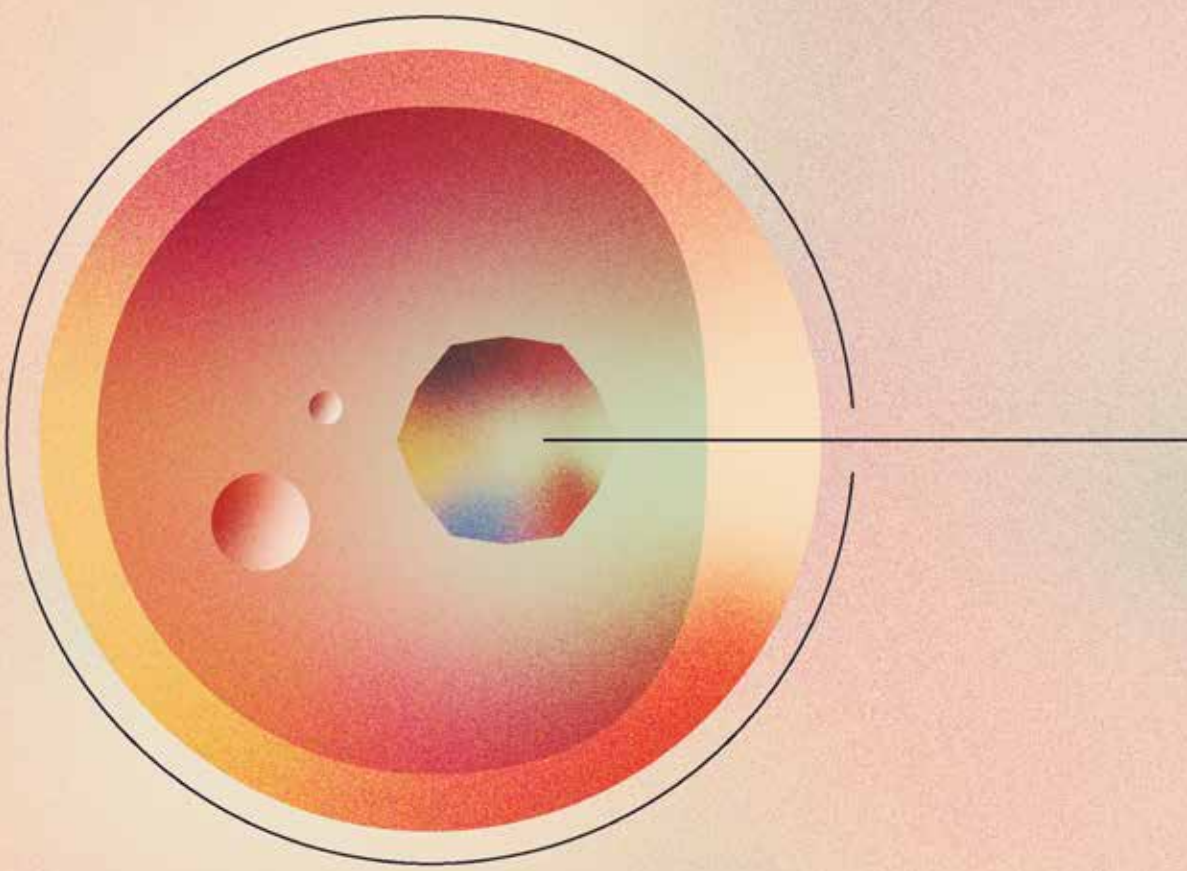
ATMPS AND C&GT

THE NEW FRONTIER



AI's Promise for ATMPs

Supporting Scalable Cell Therapy Using Allogeneic Workflows

Personalized Medicine: The Industry's Future

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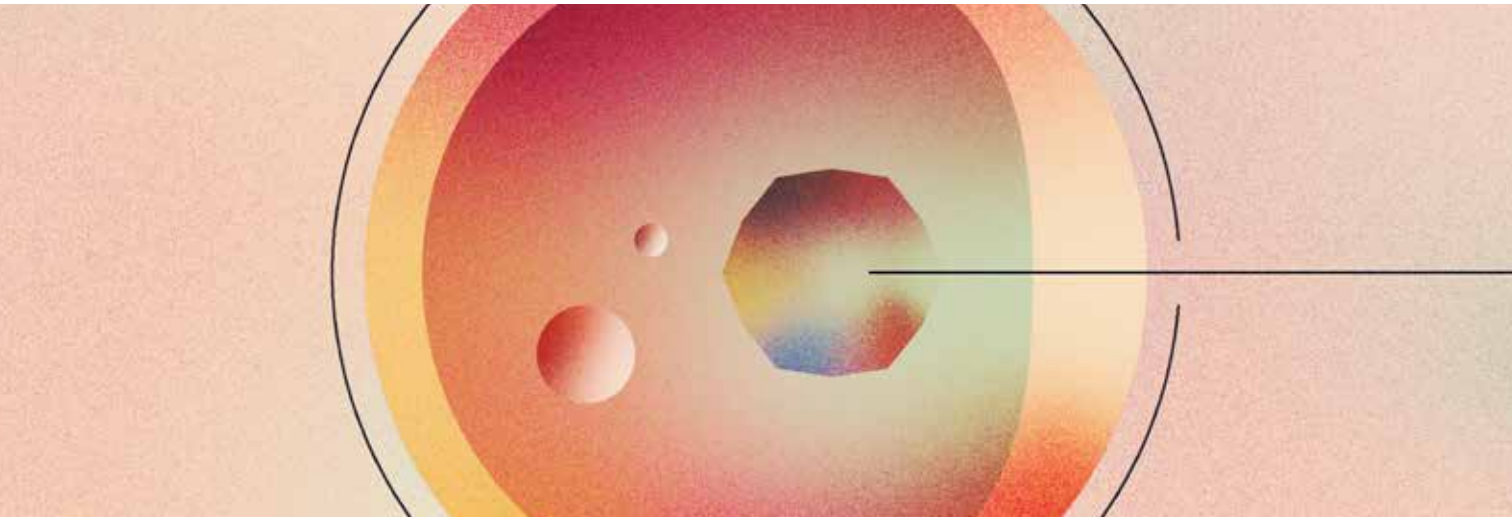

14 AI'S PROMISE FOR ATMPS

Industry 4.0 applications in biopharma involve the complete spectrum of data science throughout the entire product life cycle of many disparate entity types. Tools such as digitalization, modern data science, and the industrial internet of things are becoming requirements for modern implementations including advanced therapy medicinal products (ATMPs). This article addresses artificial intelligence and how it can help deliver on the promise of Industry 4.0 approaches to the entire product life cycle, from biology and medicine through product research and development, to validation, manufacturing, and post-launch surveillance.

26 SUPPORTING SCALABLE CELL THERAPY USING ALLOGENEIC WORKFLOWS

Historically, cell therapies are used to treat patients with cancer after relapse from other approved treatment modalities, or if no approved treatment is available. However, the introduction of allogeneic cell therapies has created exciting opportunities to broaden access to cell-based treatments. With advancements in manufacturing, developers are becoming increasingly interested in commercializing allogenic therapies, bringing them one step closer to becoming broadly available to more patients.

30 PERSONALIZED MEDICINE: THE INDUSTRY'S FUTURE

With so many options for personalizing our lives, is the personalization of medicine far behind? With all the data available, how can the industry bring personalized medicine to patients? This article explores what is currently available and where the pharmaceutical industry can move forward to better serve patient needs.

ON THE COVER The digital illustration represents gene therapy, cell editing, and virus transplantation.

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34 Changing Lives with Gene Therapies

The process of bringing new drugs and products to market requires creativity, thinking outside the box, and the courage to fail numerous times before making a single discovery. This rings especially true now, as the industry faces the COVID-19 pandemic and doubts about vaccines and therapies getting to market in record time to improve human health. This article presents a deep dive into gene therapies, the path to those therapies from vaccine development in the 1940s and 1950s, and how the road to developing these has forever changed the landscape of modern medicine.

40 Today's Pharma and Biotech Projects: A Phased Approach

This article revisits the concept of phased engineering, procurement, and construction (EPC) from a 1997 *Pharmaceutical Engineering* article, and updates it with risk-based considerations specifically regarding the commissioning, qualification, and validation (CQV) of general life-cycle principles for pharma and biotech projects. Enhancing the relationship between phases of a project, advanced planning, and more formal management of uncertainties could maximize the overall efficiency, productivity, and effectiveness of engineering projects. The use of a risk-based phased EPC-CQV approach will be key in meeting the increased global demand for capacity and successful emergency preparedness efforts.

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IMPLEMENTING LOW PH VIRAL INACTIVATION IN A CONTINUOUS PROCESS

Viral inactivation (VI) is a critical step in ensuring the safety of monoclonal antibody (mAb), Fc fusion, and recombinant protein therapeutics and it is typically an important component of an overall virus control strategy for downstream biotherapeutic production processes. Considerations for successful implementation of an inline VI process are discussed in this article.

62 SOFTWARE AS A SERVICE

THE JOURNEY TO BECOMING A LIFE SCIENCES SAAS PROVIDER

Use of software as a service (SaaS) applications within the life sciences industry is growing. This article reviews the issues and challenges faced by SaaS providers and identifies the qualities of successful providers for this highly regulated industry.

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

Advertising and Sales
Brad Ettinger, VP Marketing Communications & Business Development
bettinger@ispe.org

Carol Nettles, Advertising Sales Manager
+1 404-347-1755 cnettles@ispe.org

JT Hroncich, Advertising Sales Manager
+1 404-347-4170 jhroncich@ispe.org

Stock Photography and Illustration
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Letters to the Editor
Letters must include the writer's full name, address, and organization. Letters may be edited for length and clarity. Send correspondence to ssandler@ispe.org

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

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

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By Joanne R. Barrick, RPh


Joanne R. Barrick, RPh

ISPE Resilience in a Challenging Year

Thank you! It has been the honor of my life to serve as the ISPE International Board of Directors Chair in 2020–2021. I could never have imagined COVID-19 would still be such a significant issue at the end of my term.

I wanted to visit with as many of you as possible in person at Chapter and Affiliate events and conferences, but this was not possible. ISPE has been resilient, pivoting to virtual platforms faster than most other not for profits for conferences, webinars, and training. We have continued to deliver the pharma industry gold standard guidance documents and magazine. We are leading collaboration in interpretation and addressing several new pharma regulatory expectations, and are facilitating innovative technical solutions to manufacturing challenges. The lessons learned position us to be even more impactful in the future.

Thank you to the ISPE Board of Directors Executive Committee, the ISPE Board, Tom Hartman, ISPE's President and CEO, and all ISPE staff for your unwavering and dedicated efforts and support throughout the year. I look forward to serving on the Executive Committee for one more year as Immediate Past Chair.

A CHANGING WORLD

There have been so many significant events over the past 18 months: more than 4.7 million COVID-19 deaths, more than 6.1 billion vaccine doses administered, antibody treatments authorized, passenger travel into space, massively destructive forest fires in the United States, mud slides in Germany, and tsunamis in Japan. Achieving equality and embracing diversity and inclusion continue to be significant challenges in society.

In the pharma industry, we saw unprecedented collaboration and have achieved speed and agility never thought possible, but also exposed vulnerabilities in supply chain that must be resolved to assure a reliable supply of high quality medicines for patients we serve throughout the globe. Our industry continues to rise to the challenges, not only developing vaccines and treatments for COVID-19, but manufacturing and delivering unprecedented numbers of doses in a short time. Additionally, the pharma industry continued to manufacture many other drugs and treatments for numerous other illnesses while the pandemic raged with very few disruptions in supply. I have never been prouder to be part of the pharma industry. As we move forward, efforts to harmonize regulatory expectations will be paramount in assuring agility to meet the world's upcoming needs, with many yet to be identified.

LESSONS LEARNED

As ISPE moves forward, we will need to evaluate the parts of the lessons learned over the past two years that we will keep and continue and those we can discard. We have learned the value of 90-minute webinars: short enough for attendees to carve out the time, but long enough to deliver sufficient detail on important regulatory and technical

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topics. We have learned that virtual town halls can have numerous regulatory authorities represented and be very effective. Chapters and Affiliates have learned that virtual events enable regional sharing and participation.

The One ISPE initiative to refresh the Chapter/Affiliate operating model will progress, with the objective of enhancing ISPE's position as a global organization and will support growth in underserved and pharma-emerging areas of the globe. Biotechnology continues to be a more significant portion of the pharmaceutical industry and ISPE's portfolio of offerings is quickly evolving to reflect the change. New Communities of Practice and Special Interest Groups on ATMPs and Virology and future courses on ATMP manufacturing support the changing environment and the need to reskill some of our existing workforce. And finally, we have learned that both virtual and face-to-face conferences and networking have advantages. I will never again take the opportunity for in-person networking for granted!

I urge you to take full advantage of the benefits of being a member of the ISPE family. Most Board members choose to run for election and serve on the Board because we are grateful to the ISPE organization and the role it has played in our careers. This is a way to give back, but there are so many other ways. Please consider sharing ISPE with others. As included in our newly revised value proposition, ISPE gives us a platform and a chance to advance and shape the pharma industry—and who won't want to be part of that?!

No one could have imaged the devastation COVID-19 has caused in 2020–2021. It has transformed our world in ways we are still processing, but also illuminated the courage, resilience, and innovative spirit of ISPE and the broader pharmaceutical industry. There are still many unaddressed opportunities and patients around the globe are relying on us to deliver medicines to improve their lives.

ISPE creates a network where members can synergistically thrive, foster hope, and enhance pharma excellence for the patients we serve. We are emerging stronger than ever as individuals and as the ISPE organization. Thank you for being a member of the ISPE community. As your Chair, farewell and thank you again for this honor.

Joanne R. Barrick, RPh, is Advisor, Global Validation, Technical Services/Manufacturing Science at Eli Lilly and Company, and the 2020–2021 Chair of the ISPE International Board of Directors. She has been an ISPE member since 1998.

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Christa Myers

GRATITUDE AND JOY:
Celebrating Success

It is easy to forget to enjoy your success. We all get so focused on the drive to be better, do more, prove ourselves, prove something, and grow that sometimes we forget to stop, be grateful, and enjoy and celebrate all of our success.

As Women in Pharma® (WIP) started out, we focused on "leaning in" and "being enough," dealt with imposter syndrome, challenged biases of all kinds, and created ways to change the world. If you do not know any of those terms, look up some reading on these: they will change your perspective.

What we found out is that success and happiness are really centered around finding your own value in who you are and realizing that when you sit at any table, you bring value. Your value has nothing to do with titles, promotions, or what other people think about you. There is always something "more" to drive for, so enjoy the drive and keep driving.

HOW DO YOU GET TO THERE FROM HERE?

- Create a simple timeline. Define what you want to do, set a deadline, and write it down: about eight sentences for goals to be accomplished within a year is enough.
- List 15 things you have that you can bring to the effort to help you get to "there."
- List 10 people who can help you achieve your goals. Call each of them, and say, "I would like to get to this goal. What do you see that I already bring to the table that can get me there? What do I need to be aware of? What do I need to grow?" Write down their responses.

Be honest with yourself and start chasing opportunities to get some exposure to growth chances. Understand that growth sometimes happens with failure. Own that too. Keep growing.

You will get discouraged. When you do, call people on your list. They can help you achieve your goals. Sometimes they can help you to see you, or help you rewrite your story for others to understand better. Identify and address any self-talk that makes you feel and sound like a victim, then take responsibility for your own happiness and success and keep moving forward. Own that you bring a lot of value to this effort. Without self-value, no success will feel like success.

Without self-value, no success will feel like success.

CELEBRATE AND REVIEW

Start a gratitude list. Celebrate everything! Set small celebrations and rewards and acknowledge the great things that you are learning. Do something significant to celebrate: sing, dance, take yourself out for your favorite tea, and think about the great changes that you have made. Keep going.

Put a note on your calendar for 1 December. Review your goals and timelines for the year. Some deadlines were not met, sometimes your achievements did not happen in the way that you thought, some goals will need to be reset. Put a check beside every little thing you did, and look at how you did even more than you thought you would. Notice that you will be glad you did not achieve some things. That shows that your perspective has changed. That is huge growth.

On 2 December, set your goals for the new year. Ask yourself: what skills and lessons did I learn this year that will help me to become what/who I want in the coming year? What do I bring to the table even better/more/different than last year? How will I enjoy the ride more this year?

Get grateful. Joy is in gratitude, not in a title. But go after a title if you want it—just make sure you enjoy the success.

Christa Myers is Senior Associate, Pharmaceutical Market Director, at CRB, former Chair of WIP, and a current WIP steering committee member. She has been an ISPE member since 2007.

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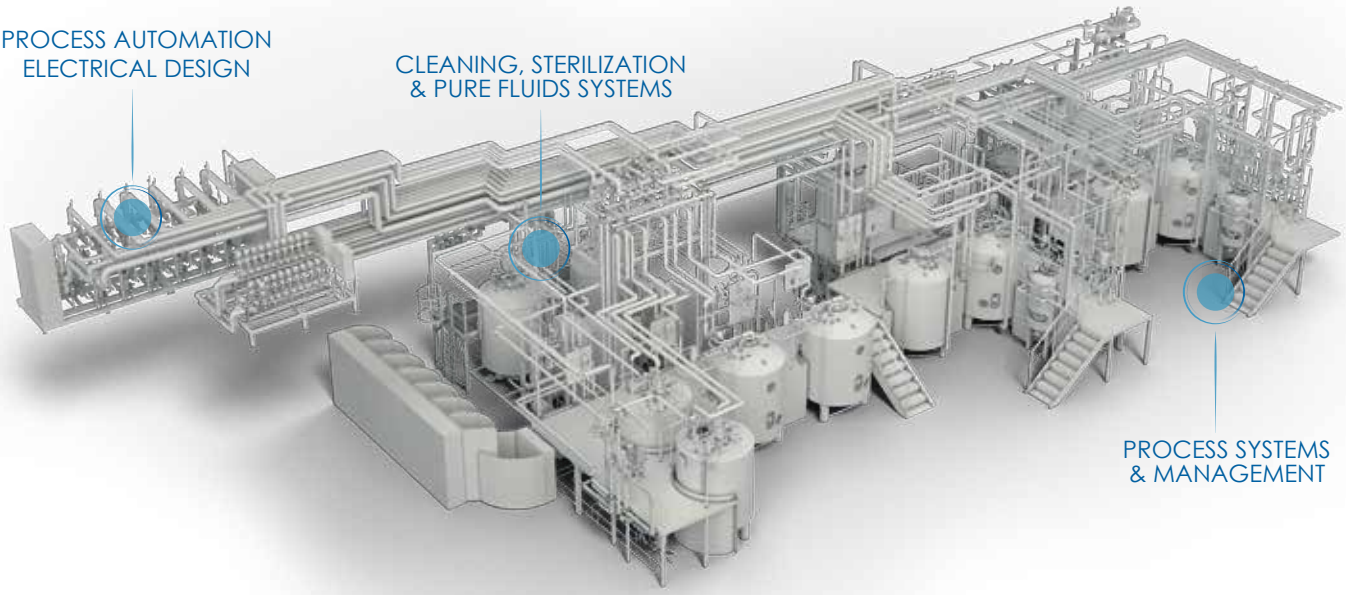

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 By John Clarke


John Clarke

WHAT A YEAR IT HAS BEEN!

The 2021 ISPE Annual Meeting & Expo brings my year as ISPE International Chair of Emerging Leaders (EL) and EL representative on the ISPE International Board of Directors to an end. I would like to say thank you to all the EL members and volunteers for the hard work throughout 2021, despite an ever-changing environment from both personal and professional points of view.

There has been so much achieved, and I would like to use my final article to focus on three of my own highlights from the year.

A NEW NAME FOR OUR COMMUNITY

In January, it was announced that the ISPE Young Professionals community would be renamed the ISPE Emerging Leaders community. This was a welcome improvement to better describe the diversity across our members. As we approach the one-year milestone since the change was made, we can reflect on the success of the changeover. This could not have been achieved without support from our Chapters and Affiliates. With their help, we have seamlessly switched out the name on all communications materials and adopted the title of Emerging Leaders both in name and philosophy.

OUR FIRST INTERNATIONAL HACKATHON

In February, the ISPE ELs held our first ever international event, a fully virtual Hackathon in association with Bayer. Over 50 participants representing 20 different ISPE Chapters and Affiliates took part in the event. For pre-selection for the grand final, each team was asked to put together an online video to showcase their ideas. The result was fantastic content from each team that highlighted the talent and commitment of the ELs involved to solve an industry problem. The event has provided a road map for organizing similar events in the future and I am excited to take part in the next one, which will coincide with the 2021 ISPE Annual Meeting & Expo.

WORKING WITH THE BOARD OF DIRECTORS

The most rewarding aspect of my tenure as the EL International Chair has been representing the Emerging Leaders on the ISPE International Board of Directors. Attending the board meetings and taking part in ISPE initiatives as the EL representative showed me the strategic and long-term vision for ISPE as an organization. It was always plain to see the value placed on ISPE members and volunteers and the criticality of the engaged network of Affiliates and Chapters.

I would like to sincerely thank the members of the ISPE Board for the year of guidance and development I have received from taking part in these discussions and decision-making during such a challenging year.

NEW LEADERSHIP IN 2022


Heather Bennett

It is with great pleasure that I introduce Heather Bennett as the ISPE International EL Chair for 2021–2022. Heather steps into the Chair role at the 2021 ISPE Annual Meeting in Boston, and Zen-Zen Yen becomes International EL Co-Chair for 2021–2022.

Heather acted as EL International Co-Chair for 2021 and offered great support to me and members of the EL community throughout the year. She has been an active member of ISPE, volunteering with the Bay Area Chapter and on the International EL Committee. Heather will be the EL representative on the Board, and will work with Zen-Zen to continue the success of our international EL community in 2022.

There has never been a better time to volunteer with your local ISPE Emerging Leader Affiliate or Chapter. Please get in touch by visiting https://ispe.org/membership/volunteer

John Clarke is a Process Lead with Pfizer in Dublin, Ireland, and the 2020–2021 ISPE International Emerging Leaders Chair. He has been an ISPE member since 2014.

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AI'S PROMISE FOR ATMPS

By William Whitford and Toni Manzano

Industry 4.0 applications in biopharma involve the complete spectrum of data science throughout the entire product life cycle of many disparate entity types. Tools such as digitalization, modern data science, and the industrial internet of things (IIoT) exist now, and examples from other industries such as Siri and Alexa, face identification, and self-driving cars can guide their implementation. While these new technologies have been empowering the pharma industry in, for example, the application of ICH Q10 and Q12, we are seeing a transition to these technologies being *required* for modern implementations including advanced therapy medicinal products (ATMPs). Industry 4.0 approaches promise benefits to the entire product life cycle, from biology and medicine through product research and development, to validation, manufacturing, and post-launch surveillance.

These digital technologies and applications are in the advanced stages of refinement and are even becoming available in commercialized products and consulting services. Regulators have actively endorsed and encouraged their incorporation. The largest current obstacle to achieving the goal of incorporating digital technologies and applications is convincing all industry stakeholders—operators, departments, and corporate-level executives—of the many benefits of modern data-driven technologies. Among the Industry 4.0 technologies, artificial intelligence (AI) is the most insightful application accelerated by the rest of the digitalization enablers, no doubt because AI has the ability to emulate human cognition.

ATMPs can require increased and/or unique requirements in process design. AI can be used to ensure the quality of the data, as well as the privacy of patients when their sensitive information is used to prepare the therapy. Use of such therapies results in an increased emphasis, even unique demands, on tools ensuring patient privacy and data security throughout data collection, generation, implementation, and storage.

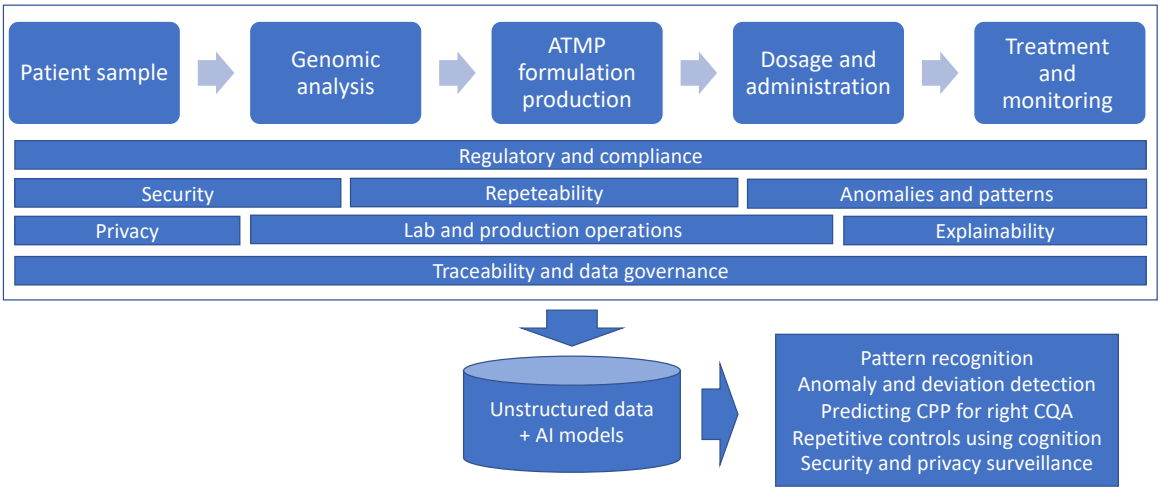
AI'S PROMISE FOR ATMPS

Of the many manufacturing digitization enablers, AI-driven applications are the most promising because of their ability to provide considerable insight into the current status and future direction of many systems supporting ATMP process design and manufacturing (Figure 1).

A note about the use of the term ATMPs in this article: Biological medicinal products supporting medicinal therapies based on genes, cell therapy, and engineered tissues are commonly referred to in the US as cellular and gene therapy (C&GT) products; in Europe, they are called ATMPs. We use the term ATMPs in this article to cover both terms.

The complexity associated with gene and cell biotechnology and the variation inherent to the processes of transforming the biomaterials into personalized drugs are ripe prospects for AI. Some ATMPs such as cell and gene therapy can have certain characteristics that present challenges for traditional process design and manufacturing. One characteristic is patient-distal cell processing, which creates challenges in track and trace and repeated decontamination of incoming process materials. Other challenges include establishing and maintaining patient-related data standards, security, privacy, curation, storage, and distribution; the extreme difficulty in providing second attempts at a therapy,

Figure 1: Typical ATMP workflow depicting opportunities provided by AI to improve difficult C-level management objectives in ATMP life-cycle complexity.



which imposes a burden to not only discover process deviations and product failure but also the added pressure to prevent them; new and more sophisticated sensing and analysis for the determination of patient-specific sample and product characteristics; autologous sample handling that often requires adjustment of process parameters to best handle unique cell/tissue sample characteristics; the orchestration of distributed control with any centralized processing of individual autologous cells and tissues that imposes added burdens; and the fact that as products and practices are so new, and operational critical process parameters (CPPs) are often not well understood, the production process can evolve even after technology transfer.

In autologous therapies, each patient must be linked to a single batch that has been manufactured and controlled by means of both singularities (specific target) and commonalities (universal specifications). The expected efficacy, quality, and safety of the issued drug under the ATMP framework is even harder to achieve, batch after batch, than in small or even large biological molecules. There is just one reason for this—the uniqueness of each patient causes continuous variability in all the key production factors [1]. For example, an individual patient's samples present a diversity in the current status of such measured parameters as the cell viability, cell division rate, and consequences to the cells' state from the patient's clinical drug exposure. A sample's variability in its initial state can greatly influence its characteristics and performance in product manufacturing, requiring increased process monitoring and advanced dynamic control. At the same time, personal information can often be deduced when AI is applied to generate process knowledge from the analyzed raw data. For example, economic status, location, habits, gender, or race can be deduced when reviewing the biopsychosocial context used to figure out the best conditions for the therapy's preparation. Therefore, such therapies

ATMPs can require increased and/or unique requirements in process design.

can have an increased emphasis, and even unique demands, on tools ensuring patient privacy and data security throughout data collection, generation, implementation, and storage.

The rise of computational power and cloud-based storage, and the increasing sophistication of AI algorithms, have enabled an evolution of both AI's capabilities and ethical implementation, taking into consideration the vulnerability associated with the data used to train automatic learning systems. AI combines advanced multivariable analysis, power computing, and algorithmic procedures to calculate insightful results in complex scenarios. As data is the fuel used to achieve successful outputs, it is part of the AI life cycle and must be considered as an asset by both management and experts who participate in the processes of ATMPs [2].

INDUSTRY 4.0 TOOLS IN PHARMA MANUFACTURING

The dream of Industry 4.0 is becoming realized in many sectors. The utility of AI in medicine includes disease identification and clinical diagnosis, therapeutics and personalized treatment, drug

Table 1: AI applications in pharma.

• Processing biomedical and clinical data	• Intelligent process automation
	• Tech transfer
• Enabling personalized/rare disease medicine	• Production/purification/finish
• Identifying clinical trial candidates	• Continued verification
• Predicting treatment results	• Protecting the supply chain
• Materials and drug supply chain	• Pharmacovigilance
• Demand forecasting	• Risk management plans
• Product development	• Phase 4 monitoring
• Regulatory affairs	• Drug adherence and dosage
• Predictive maintenance	

discovery and manufacturing, and more (Table 1). Operations computers have been incorporating higher structures of processing and becoming better connected to analytic output, instrumentation, and data lakes. While delayed, through the prescient efforts of thought leaders and such teams as the ISPE Pharma 4.0™ Special Interest Group, application of such smart factory or Industry 4.0 power in pharma is now becoming a reality.

One example of higher processing promoting Industry 4.0 goals is the application of recurrent neural networks (RNNs) in real time. RNNs are a type of neural networks that show a behavior similar to the functioning of the human brain, giving rise to predictions through sequential information that other algorithms cannot carry out.

This makes them powerful in the digital conversion of manufacturing operations by enabling such tasks as handwriting and speech recognition online [3]. New digital tools, such as RNN, are now available to support ATMP entity research, target validation, and cell engineering. These tools can also empower product characterization, release, or the detection of potential anomalies. Automation is particularly visible in the newer closed manufacturing modules, but advances are also being made in areas such as product development equipment, electronic records maintenance, QC, and operations. The significant advances in processes improving shipping, storage, and traceability hold much promise, especially for ATMPs. However, with some exceptions, these processes are only just being applied in the pharmaceutical industry in general [4].

THE IMPORTANCE OF DATA

The manual processes in historical data management created data entry issues, incomplete signoff, missing details, and troublesome access. Although AI's abilities have evolved, the data needed to feed the algorithms often remain locked in archaic media or siloed IT systems throughout the organization. Once accessible, the onerous process of standardizing and normalizing large datasets through manually directed analysis can prevent an organization from moving forward with AI initiatives [5]. This process, as well as the amount of diverse data now being generated (numbers, strings, pictures, files, geolocations, gene-sequences, etc.), determines a greater need for accessibility to archived data. Advancing regulatory releases (including in traceability and continued process verification [CPV]) demand the use of modern scientific methods for dataset governance, extraction, and repair. Some still do not realize that technological applications for required solutions to all of this currently exist. Therefore, data science has become a required discipline in the field of the life sciences to properly manage the raw material used in the new medicine era: personalized data [6].

A very significant need in the pharma industry is leadership in incorporating automated cloud-based software and establishing the standards required for rapidly accessible data structures. This would drive the implementation of powerful goals such as CPV, which requires real-time multivariable analysis to identify manufacturing patterns in real time to get adaptable batches at any time. ICH directives Q8–Q12, which promote innovation and continual improvement and strengthen QA, are now greatly enabled by such existing data science tools.

Data Types

Both product development and manufacturing are becoming increasingly dependent on massive volumes of disparate data. Many ATMPs require the protection of the patient health data involved in preparing such therapies, while also protecting the privacy of patients. Especially in the development phase, laboratory observations and even operating parameter measurements can exist in degrees of inconsistent labeling and structure. Even when working with more mature processes, because of the newness of many therapies and their dependence upon clinical information, important observations may come from disparate sources with inconsistent labeling or structure.

Unstructured data is one of the three main sources of valuable information in product development. The other two sources are structured and hybrid data. Structured data is the easiest to process, as it exists in defined tabular format. Unstructured data is the most difficult to process, because while it may represent accurate measurements or complex pretreatments, it is not organized in a regular, consistent manner. Examples of semi-structured or hybrid data are partially condensed laboratory results from disparate analytics or instrumentation or completed forms from hospitals. The rows, columns, semicolons, periods, and dashes may be clear to a reader, but they are difficult for a computer program to

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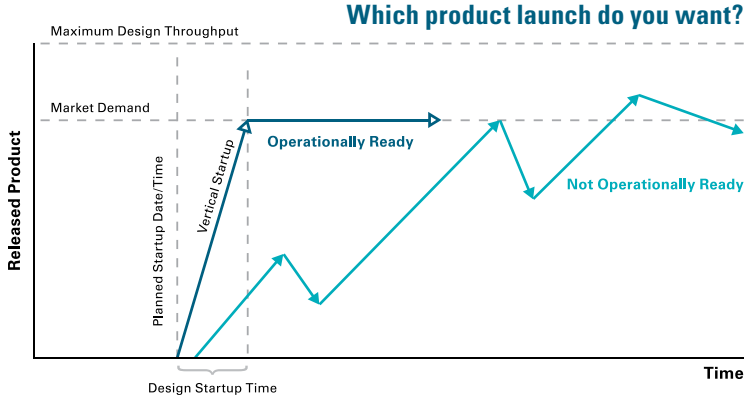

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organize. Advancements in AI-enabled intelligent data extraction can reduce the burden on developers by automatically preparing such data for interpretation and analysis.

Related issues include data labeling and annotation. In some projects, the extraction and formatting of semi-structured and inconsistently labeled data take up the majority of the project time. Artificial and augmented intelligence is greatly accelerating the solution to such data handling projects by providing significant advances in establishing both data interoperability and relevance through AI-empowered observability analyzers. The analysis and interpretation of the type and amount of data available today demand a collaboration among senior management, engineers, scientists, and computer systems professionals.

Artificial Intelligence

The timely analysis of the massive amount and types of data being generated in product research and process development is not only beyond human capability, it is also beyond the power of classic computerized statistical and mathematical functions. AI-based solutions in medicinal product design and manufacturing have become a disruptive technology in implementing Industry 4.0 innovations [7]. They are being supported by advances in computing power, mathematics, and IoT—providing improved data mining and modeling capabilities distributed in the cloud.

AI is becoming even more powerful through advances in its component technologies: neural networks (mimicking human decision-making abilities), genetic algorithms (mimicking the biological evolutionary process), and fuzzy logic (mimicking the human ability to draw conclusions with incomplete or imprecise information) [8]. Until AI-driven deep learning algorithm applications were developed, many computerized monitoring and inspection activities were too nuanced for true automation, but this is changing. Current applications not only replicate human activity, but a machine-learning equipped robot can iterate the process endlessly and accurately without cognitive or motor fatigue or distraction. Another activity supported by AI is the analysis of the monitored variables from past runs to determine their criticality and range of value to product quality, as well as to discover their interaction or performance relationships. This can be accomplished by categorizing past batches by quality, with the goal of predicting the batch quality from the discovered underlying key and critical process attributes (variables). A discovery process might begin with an unsupervised, statistically based clustering or pattern recognition algorithm to discern an underlying structure in the dataset. This approach can provide segregation of production batches under the hypothesis that the clusters represent degrees of product acceptability.

To complement this classification, one may apply a supervised anomaly detection algorithm, such as isolation forest (an algorithm to identify anomalies), to establish a concordance with the clustering analysis for all categorizations. Applying two independent and complementary classification algorithms can support the creation of a model capable of detecting good and suboptimal batches based on data from monitored in-process variables. Furthermore, this application may uncover subtle relationships between various process variables that would not be obvious to even subject matter experts. For example, a Bayesian network model can point to relationships between particular variables and suboptimal batches [9]. Multivariate interactions can be difficult to perceive by human mechanisms, but AI can help guide the subject matter experts to explore the finer details of these parameter values, the larger implications of the process variable they are measuring, and their relationships to process efficacy.

Machine Learning

Machine learning (ML) is a branch of AI in which models learn automatically from their earlier experience. As the program gains experience, the model learns from that exposure and adjusts to provide better performance. First, a model is trained on a portion of the initial available data set, and then the model is validated on the remaining data. This "trained" model is used to analyze new data.

A ML model is an in-silico representation of the patterns and relationships within a set of data. Training a ML model involves discovery of governing hierarchies, relationships, and structure within that data. The relationship of the data is then formalized into rules that guide the response to data describing new situations.

Three types of machine learning can be used to improve operations: unsupervised, supervised, and reinforcement. In unsupervised or descriptive learning, the program identifies patterns and categories in the data without feedback from this learning. Because higher or formal labeling of the data is not required, it is generally applied to find unknown clusters, associations, or patterns through similarities and differences between data points. In supervised learning, the machine learning algorithm produces an inferred (mapping) function from labeled sets of input/output pairs in provided training data. It is called supervised learning because it learns from the training dataset, like a teacher supervising (and correcting) the learning. The majority of ML applications use supervised learning. In reinforcement learning, the program's learning is reinforced from the gain or loss in the output results. This enables the program to learn in an interactive environment by trial and error, using feedback from previous actions. Reinforcement learning has been described as using "rewards and punishment" as signals for positive and negative behavior, where the goal is to build a model that will maximize the total cumulative success of the operation. It is now widely used in drug discovery and development, providing valuable results on the use of existing drugs for diseases other than those for which they were originally intended [10].

Augmented Reality

Augmented reality improves the delivery of sensory input experience by manipulating images, sounds, or context to either enhance defined aspects, or add entirely new elements. It has immediate use in both the design and operation of manufacturing processes, including guiding operators to the right procedures, thus

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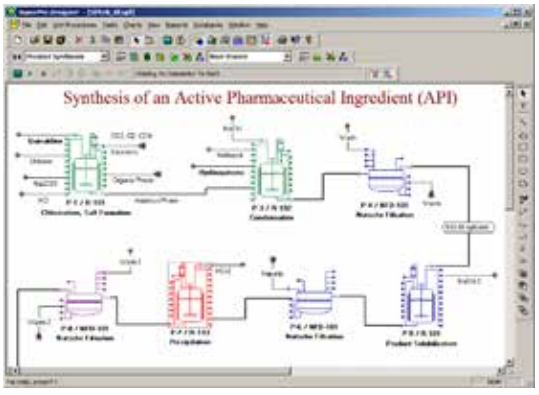

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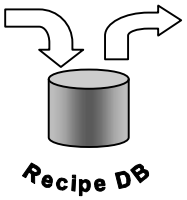

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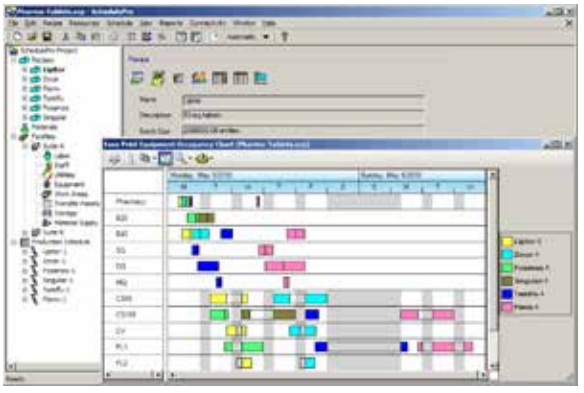

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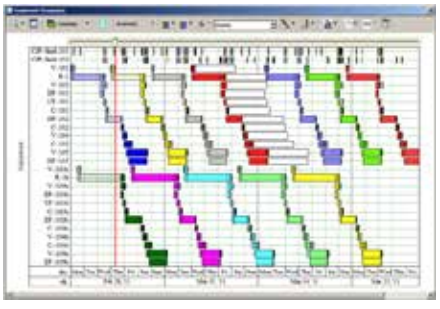

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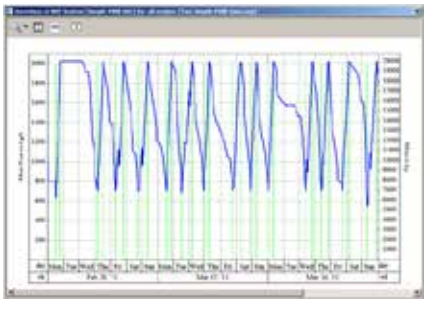

Managing inventories for input, intermediate, and output materials

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

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

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minimizing the risk of unnecessarily manipulating dangerous or critical assets. It also includes ergonomic and efficient process train design, data management, real-time monitoring, machine-to-human communication, and operator training [11]. One example is computer vision platforms that transform manufacturing suites into intelligent environments for greater operational control, real-time auditor insights, and innovative training experiences. These platforms use real-time data and embedded AI to transform rooms and equipment into intelligent digital twins, creating a semi-virtual environment where predesigned graphics, information, and people can seamlessly operate.

OTHER AI ENABLERS

Enhanced Industrial Sensors

The type, number, and economy of industrial sensors are advancing dramatically in their capabilities and practical applications—with many businesses, such as electronics and automobile manufacturing, taking advantage of them. It is anticipated that as the critical quality attributes (CQA) of existing ATMPs are better understood, the growing ability to inexpensively measure them in real time will greatly enable advanced control, prediction, and CPV.

Robotics and Autonomation

Some closed self-contained devices such as microbioreactor systems are supporting savings in facility space, capital, labor, media, and consumables. They are now providing integrated metabolite analysis; variable sparging, head gassing, feeding, and temperature control; and even clone selection software. Increased analytics sensor and AI applications is enabling the development of a new category of robotically administered processes and even automated, closed cell processing stations with dynamic controls that maintain tight control of multiple culture parameters and adjust to the disparities of autologous patient samples. Automation of many aspects of the process (including manipulation of samples and in-process work) is being advanced by AI support of cobots and mobile robots.

AI AND ATMPS

Pharmaceutical entity design and manufacturing are evolving in many ways, and AI is key in most of them. ATMPs are different from medicines based on chemical or even biological origin. AI is already proving valuable in supporting the manufacturing of classical pharmaceuticals and biopharmaceuticals. It is apparent that the power of AI in ATMP and precision medicine activities (the customization of healthcare to a subgroup or individual) will increase in the near future.

Many ATMP therapies have been proposed to treat heterogeneous disease, which is causing different biological entities, such as genes, proteins, mRNAs, miRNAs, and metabolites, to be examined on a global scale. The human body contains almost 20,000 proteins and protein-coding genes, 30,000 mRNAs, 2000 miRNAs, and over 100,000 metabolites. Not only is analysis of such large numbers of bioentities becoming possible, but a comprehensive understanding of their interplay is as well. We are seeing the possibility of using in-silico modeling to create profiles for identified subpopulations or even individuals. To get an idea of how much information must be managed in the life sciences, note that digitizing a single human genome requires around 3 GB of data to be stored and processed.

Analysis of any single type of omics data (such as genomics, proteomics, and transcriptomics) provides knowledge of some reactive processes. Because biological processes are so interrelated, understanding any single system in the context of the others is important. For example, regulation of protein expression is influenced by more than upregulated mRNA transcription, as this may or may not enhance its target protein expression. This is because of factors such as the protein's expression being influenced by associated metabolites and miRNA's ability to silence or degrade mRNAs. A more holistic approach, elucidating the interconnectivity and interdependence of many omics, requires a far more complete and comprehensive integration of multi-omic data. The necessity of managing complex relationships between such networks of multiple dimensions to understand the total reality appears in this context, as it does in, e.g., the earth's ecosystem.

Many online databases are being created to accommodate such multi-omics data. Integrated multi-omics analysis on large populations provides a path of information flow from one omics data type to another, thereby providing power for analysis supporting therapeutic development [2]. Such types of analysis, provided in a timely fashion, can also directly support the field of individualized or precision medicine.

Comprehensive integration of such multi-omic systems and non-omic data is challenging because of the size, heterogeneity, and complexity of the relationship between such datasets. AI is uniquely qualified to generate any number of models supporting a systems approach to such analysis because of its capabilities to interpret and generate knowledge about complex systems such as multi-omic frameworks.

ATMP production calls for integrated data acquisition throughout the manufacturing chain. Autologous cell therapies are one example, and some proposed gene therapies will be even more dependent on newer data science technologies. Therapeutic oncolytic viruses and RNA vaccines based on the profile of a specific patient's tumor are an example of patient information being integral to drug manufacturing. An ATMP manufacturer could use an AI-powered model to intervene directly in the product's nascent application in a patient's therapy. We can now see that data science not only supports drug manufacturing but also ensures its success in therapeutic application.

AI is supporting such manufacturing operations in many ways. As described above in the section on augmented reality, machine vision is already being effectively used to allow operators to engage in a synthetic experience training of operations technicians in new procedures. In supporting process automation and autonomation, machine vision relieves operators from the drudgery of dirty, dull, and dangerous activities currently done manually. An AI-empowered digital twin of any number of processes or

equipment can support activities such as determining the performance of an asset based upon past operation, predicting impending process completion or deviation, or performing a process virtually prior to actual operation in, for example, process development or material QC.

The future of autologous cell therapies appears to be closed, automated "factory-in-a-box" type cell processing. Such systems can reduce contamination, inconsistent sample handling, and human error. AI-empowered automated systems will provide increased reproducibility by ensuring more rapid and robust adjustment of CPPs. They can reduce development time because many distinct processes can be studied in the same research space with minimal concerns for cross-contamination. When increased capacity is required, scaling out can be easily accomplished by multiplying the number of units deployed. It takes significant monitoring, data curation, and dynamic control to coordinate the manipulation of the many unique cell phenotypes throughout the process steps.

Biological Systems Approaches

One goal of systems biology is to model complex biological interactions by comprehensively compiling information from interdisciplinary fields. It has been observed that the 20th century style of reductionism provides much understanding and labeling, of a systems' parts, but it is unable to complete our understanding of the system or interpret any components or subprocesses that are currently unstructured. Beyond multi-omic analysis, systems, or network, biology is a new approach to understanding the complex interactions of the molecules of life that uses an integrative approach to such complex systems expressing synergistic or emergent behavior.

AI-empowered network biology supports the mapping of the molecular relationships in normal and abnormal phenotypes. It promises to result in a more explicit and deterministic model, providing more predictive, preventive, and personalized medicine. It is impossible to functionally integrate the volume and diversity of multi-omics data by classical methods to produce this more holistic understanding [12]. The systems approach depends on advanced tools and methods to provide multi-platform-based omic data analysis and interpretation [13]. The tools employed have included network, Bayesian, correlation-based, and other multivariate methods, which are now being empowered by AI.

Control Systems

Not too long ago, bioreactor process control elements such as tank heaters were automatically PID (proportional–integral–derivative) controlled through output variables such as temperature, while

some control variables including glucose or glutamine levels were manually maintained. Progress has been made for years in the development of control strategies, optimization algorithms, and software frameworks for control systems. Current systems often employ supervisory control and data acquisition (SCADA) requiring a human machine interface (HMI).

Newer closed-loop bioreactor control for many variables is now being accomplished with adaptive model-based controllers. They provide a significant and flexible benefit in essentially two ways: (a) they provide for optimized constraints of bioreactor operation and for a constraint of the control signal itself to within optimal ranges; and (b) they modify their action to the result of their control activity and to other changes in the systems in real time. Their power is that they fully recalculate the optimal next step in each monitoring cycle of their operation. Much progress is being accomplished in communication standards for applications such as coordination of distributed control.

While the math for some of these systems has existed for some time, a number of developments in independent fields have actually enabled them. Hardware speed and algorithm diversity now support both linear systems and nonlinear systems in such iterative activities. More accurate and dynamic AI-driven base models are being developed to exploit the more statistically valuable data being supplied by additional monitoring capability, as well as the increasing cell culture systems knowledge. However, parameter estimation can still be based on either a model-free or model-based algorithm.

It is anticipated that AI applications will be powerful in controlling two sources of variability in ATMP: (a) due to variation in autologous sample condition, dynamic assessment control is required, and (b) due to the lack of parameters currently monitored in many of the small-scale processes, unrevealed variability exists in critical process conditions.

Sample Reception and Tracking

For autologous therapies, the reception, cataloging, and governance of hundreds of unique shipments of patient cells require dedicated operations. The clinical activities of blood sampling and cell preparation can be made more robust and safer through improved GxP-documented processing, cataloging, and transport conditions as well as by ensuring the patient's information remains secure. ATMP processes must ensure product safety and quality, as well as protect the integrity and confidentiality of patient information. The procedures established for organ transplants involve a central database and transport control, but these are too expensive for ATMP therapies. The procedures used in centralized cytogenetic therapy supporting the track and trace of amniocytes for cytogenetic analysis laboratories showcase many of the functions of a cell therapy facility. They must receive, track, and sterilely process thousands of human cell samples per year in a highly regulated enterprise. AI is being used in such systems to not only alert to existing excursions but also anticipate impending errors and prescribe actions to avoid them.

Culture Expansion

Autologous cell therapies use significantly different suites and equipment than that of master and working cell stocks, single-use bioreactor trains, and the individual but related styles of process monitoring and control used in allogeneic cell therapies. The individual origin of the patient-specific cells and the very small-scale cultures (<20 L) are the most significant differences, while the scale-up problem presents challenges of a similar nature. Finally, the now-common use of commercially distributed semi-automated culture instrumentation is unique to cell therapy. The individual performance of such cultures in defined processes, and their genotype-determined response to input variables, determine a need for the heightened dynamic control afforded by AI.

Analytics

The incoming material QC processes are generally similar to those of protein biologicals. However, in-process monitoring, final product QC, and release testing for a living cell product can be unique, ranging from a small molecule to protein biological, and involve such values as cell number, viability, cluster of differentiation (CD) markers, and chimeric antigen receptor (CAR) expression. Quantitation and analysis of viruses and nucleic acids are required for many platforms, and often employ new applications of standard equipment. Furthermore, the number and types of values demanded for process control are growing. AI-driven models can examine such results in real time, providing immediate advice or action on its curation and transmission as, for instance, in discovering new indications for existing medicines.

Cryopreservation and Shipping

The transfer of most cell therapy products requires cryopreservation. For autologous process trains, this involves the highly controlled dispensing and labeling of the samples in cryobags. For allogeneics, facilities for the semi-automated aliquoting of cell-based products on a large scale have been established. It can be difficult to automate the filling procedure for cryobags of different doses or other characteristics from a single batch. AI has the power to comprehensively monitor the cryopreservation process, compare progress to golden batches, detect impending excursions with enough time in advance in order to fix issues, and predict rates and endpoints to ensure success. For example, when trucks transporting vaccines requiring special cold conditions are monitored and analyzed by AI, systems can recommend the best routes to ensure the needed power supply during the transport.

ESTABLISHMENT OF AI

It is imperative for the management of the pharmaceutical industry to become fluent in AI's capabilities, general industrial potential, specific applications, and sources of applied products. While extremely powerful, simulating human intelligence and responses is difficult. It requires considerable amounts of data, computational capability, and time to train the algorithms. To begin, it is very helpful for an individual, group, or organization to

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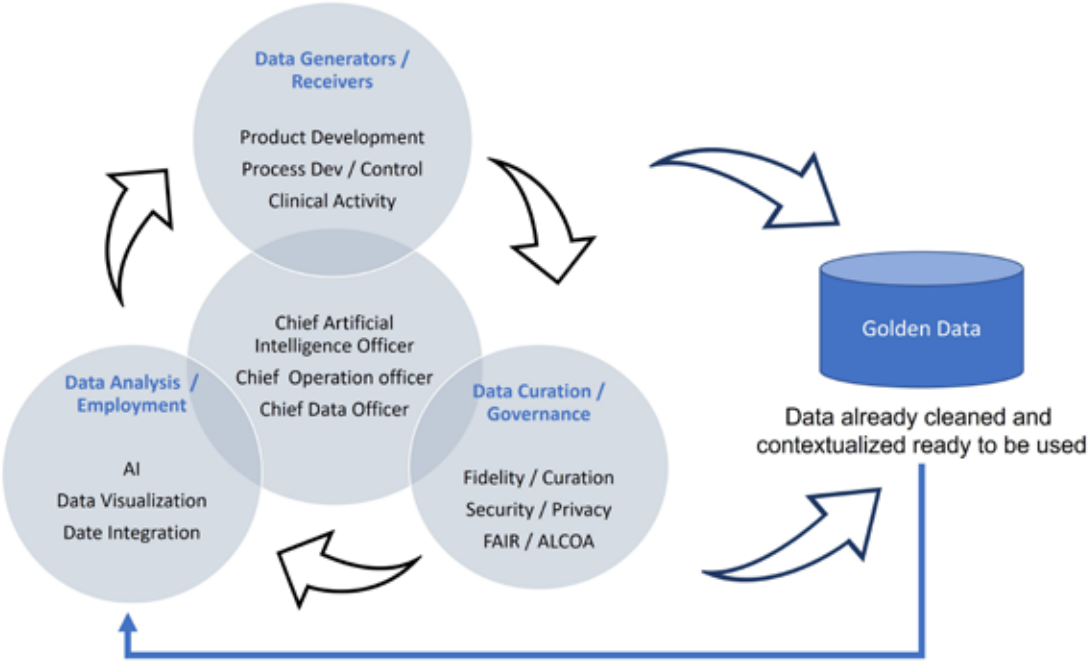
Figure 2: Data process steps in AI.



understand its current state in each area or category of potential growth. This also guides progress in the capability to apply it to the manufacturing process. Models have been developed to assist in the assessment of the current state of AI understanding and capability in many specific categories of application, as well as to guide the next steps of development.

For example, the AIO team at Xavier Health has developed an AI Maturity Level Characterization Model that enables the assessment and measurement of (a) the functional AI capability of an organization in defined operations or categories and (b) the current capability to improve in these areas over time. With a few exceptions, the organization is able to assess the practical ability of the human resources, departments, and culture to understand, implement, and operate applied AI tools or instrumentation. Rather than assessing the capability to create or maintain integral AI algorithms, the maturity model qualitatively measures the functional capabilities of an organization to work with AI-empowered tools, processes, and structures [14].

MANAGING EVOLUTION OF AI IN ATMPS

AI application requires multiple technological disciplines and different regulatory angles, including best practices in manufacturing, security, privacy, and ethics. For example, Maryann Conway, cofounder, Kaisura, said, "Conventional layered security defense alone will not solve the unique and distinct vulnerabilities and attack vectors associated with AI and ML data exploits. It takes the concurrent implementation of AI and ML-centric data governance, risk, and compliance protocols and the expertise and guidance of experienced AI security-focused experts [15]."

An AI application only can work when all of the required elements are perfectly harmonized to operate in synchrony under higher control. When AI is applied to ATMPs, the result affects specific patients, integrating multiple potential effects into ATMPs for which AI models have been specifically designed. AI can work in digital twins representing human cell cultures, organs, bodies, health systems, or groups of people with similar disease attributes. The singular goal of this entire process is to save lives and maintain a healthy society.

Managers and C-level executives in the pharmaceutical industry are responsible for understanding the challenge of deploying AI for ATMPs and the implications as outlined in Figure 2. The current digital framework makes it possible for data to lead biopharmaceuticals to a new industrial evolution by means of augmented capabilities based on mathematics. AI is able to identify root causes for problems constituted by multiple dimensions that are difficult to understand from a human perspective. AI is also providing recommendations and predictions or simply recognizing patterns from the intricate relationships of multivariable realities and continuous variability that traditionally has been ignored through static production recipes.

Diverse perspectives that will be governed by this new era of biopharma management include (a) the intrinsic value of every single byte of data used to train AI models, (b) systems to guarantee integrity in the data chain, (c) the required investment in

personnel and money, (d) understanding the shifted skills involved in implementing robust data policies, and (e) the mechanisms necessary to establish the full life cycle of Industry 4.0 elements involved in ATMP production.

Business methods evolution is understood as revolution when talking about Industry 4.0 technologies. This concept is magnified in pharmaceutical manufacturing when entertaining processes as complex as ATMPs. This evolution can also be contemplated in managing wars on diseases of the future, where therapeutic and prophylactic entities are enlisted to defeat a multitude of diseases and ensure a next step in societal evolution.

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About the authors

William Whitford is the Life Science Strategic Solutions Leader for the DPS Group Strategic Consulting Team, supporting innovative therapeutic development and manufacturing processes. He was an R&D leader, developing products supporting biomanufacturing. An invited lecturer at international conferences, Bill has published over 300 articles, book chapters, and patents in the bioproduction arena. He now enjoys serving on such boards and committees as the Editorial Advisory Board of BioProcess International. Bill's recent publications involve processes and facilities supporting sustainable biomanufacturing, Industry 4.0, bioprocess intensification, continuous biomanufacturing, ATMP and exosome production, 3D bioprinting, and biointelligent manufacturing. Bill has been an ISPE member since 2009.

Toni Manzano is the Cofounder and CSO of Aizon, a cloud company that provides big data and AI SaaS platforms for the biotech and pharma industry. He is Cochair of the Biomanufacturing IG and Cochair of the CPV of the Future initiative at PDA, Lead of the AI in Operations team for the AI Xavier University, and he teaches AI subjects at universities (UAB and OBS). He is a member of the Science Experts in the Spanish Parliament on big data and artificial intelligence topic. Toni has written numerous articles in the pharma field and holds a dozen international patents related to the encryption, transmission, storage, and processing of large volumes of data for regulated environments in the cloud. Toni is a physicist, and holds a master's degree in information and knowledge society and a postgraduate degree in quality systems for manufacturing and research pharmaceutical processes. Toni has been an ISPE member since 2015.

SUPPORTING SCALABLE CELL THERAPY

Using Allogeneic Workflows

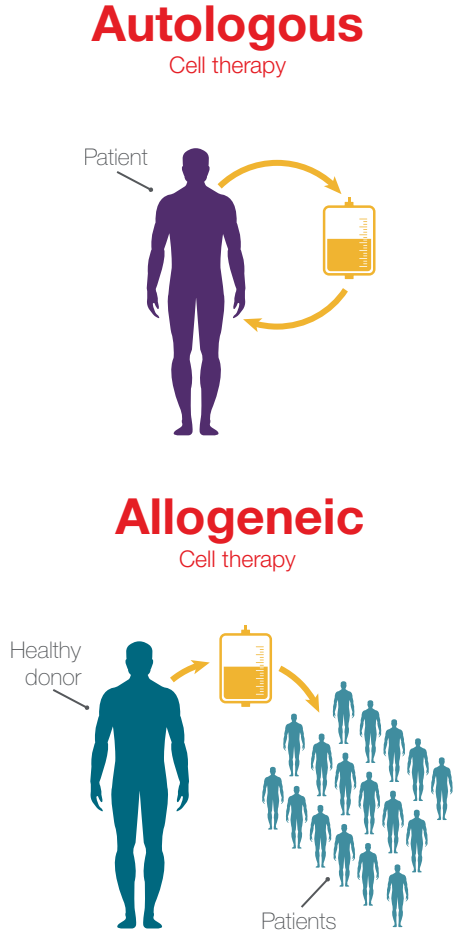
By Øystein Åmellem, PhD

Historically, cell therapies are used to treat patients with cancer after relapse from other approved treatment modalities, or if no approved treatment is available. However, the introduction of allogeneic cell therapies has created exciting opportunities to broaden access to cell-based treatments. With advancements in manufacturing, developers are becoming increasingly interested in commercializing allogenic therapies, bringing them one step closer to becoming broadly available to more patients.

Since first conceptualized in the nineteenth century, cell therapy has cemented its role in treating some of the most complex diseases and conditions. As one example, successful autologous and allogeneic bone marrow transplantation has become common practice in treating patients with leukemia, lymphoma, aplastic anemia, and immune deficiency disorders, with more than 18,000 patients receiving a bone marrow or umbilical cord blood transplant every year in the United States [1]. Beyond this application, stem cell and cell transplantation applications have garnered increased interest in recent decades, with incredible strides made in the twenty-first century.

Among those advancements, the introduction of allogeneic cell therapies is of specific interest. In the allogeneic approach, healthy donor cells are used to develop cell therapies, rather than relying on harvesting the patient's own cells to develop a personalized treatment. Personalized therapies—such as chimeric antigen receptor (CAR) T-cell treatment for lymphoma and leukemia—have shown

Figure 1: Compared to autologous therapies, allogeneic therapies offer increased scalability by using cells from a healthy donor to treat multiple patients.



incredible effectiveness, but traditional autologous workflows that rely on using a patient's own cells can limit availability of these treatments due to the high complexity and price.

The main difference between allogeneic and autologous therapies is the source of the cells. Allogeneic therapies are manufactured in large batches from unrelated healthy donor tissues (e.g., bone marrow or from lymphocytes such as natural killer (NK) cells and T cells), whereas autologous therapies are manufactured as a single lot from the patient being treated.

Unlike autologous workflows, which offer a one-to-one patient outcome, allogeneic workflows offer increased scalability because they use cells from healthy donors to create a cell bank system that can be used to treat multiple patients. The main driver for developing allogeneic therapies is to offer considerably more cost-effective and widespread therapies to more patients.

SCALABLE AND ACCESSIBLE

Allogeneic cell therapies rely on a single source of cells to treat many patients. This automatically makes them a more scalable alternative to autologous therapies. CAR T-cell therapies offer one opportunity where more efficient development and manufacturing can make a profound impact, providing potentially more effective treatment options for some of the most vulnerable cancer patients.

The growth in CAR T-cell research is exploding. Although only a handful of cell and gene therapies are on the market, the US FDA predicts that by 2025, it will grant up to 20 cell and gene therapy approvals per year [2].

Current autologous models for developing CAR T-cell therapies are time consuming: it can take three weeks on average from when the cells were first collected to treatment of the patient with a CAR T-cell therapy. This is an expensive and lengthy process with little room for error, with patients who are desperate for treatment. Researchers and organizations continue to work diligently to optimize the manufacturing process to develop safe and effective CAR T-cell therapies as efficiently as possible, in the hope that one day they can be manufactured at a lower cost and made available to any patient who could benefit from them.

Scientists are hopeful that allogeneic workflows can make CAR T-cell therapy more accessible by manufacturing therapies using healthy donor cells or induced pluripotent stem cells (iPSC)-based cell platforms [3]. These can be used to treat multiple patients as an "off-the-shelf" treatment. Beyond the scale this empowers, these healthy T-cells are in better condition than the patient's own cells to be reprogrammed, proliferate, and injected into the patient to fight the cancer.

Materials and Manufacturing Innovations

Allogeneic therapies can be more cost effective because they can be mass produced to treat multiple patients, but the workflow is still time consuming. Just as with autologous models, it takes three weeks or more from cell collection to development and administration of allogeneic cell therapy. But, as technology companies, in collaboration with drug developers, continue to design fit-for-purpose workflows and solutions designed specifically for the development of allogeneic cell therapies, this approach will continue to gain steam and show comparable or even favorable improvements over autologous models.

As one example, Thermo Fisher Scientific has developed a new xeno- and serum-free cell culture media specifically suited for allogeneic T-cell manufacturing using healthy donor materials. The media's formulation is designed to increase the drug product yield by extending the duration of the manufacturing time (Thermo Fisher Scientific unpublished data), while maintaining the desired T-cell phenotypes that are demonstrated to correlate with favorable clinical responses [4].

The importance of cell culture media has been reported by researchers in the field. According to a recent article in the *Journal of Clinical Haematology*, "Subtle changes in media formulation such as changing protein source from human serum to serum-free, concentrated, platelet extract has a dramatic impact on the effectiveness of T-cell therapies" [5].

Similarly, innovations in manufacturing are enabling a fundamental shift in the scale of cell therapy production, ultimately helping a greater number of patients benefit from these therapies. Careful selection of healthy donor T-cell materials for manufacturing allogeneic therapies may contribute to a more robust

manufacturing of the drug by minimizing the challenges related to the considerable biological variability seen in autologous T-cell materials, which often have a history of previous chemotherapies and stem cell transplantation. Setting up a reliable, consistent, and scalable manufacturing system is key to producing cell therapies on a wider scale.

Closed-system solutions also promise to improve the efficiency and safety of cell processing operations [6]. Cell therapy is a complex and labor-intensive process that can require open manipulations that can introduce process variability and/or contaminants. Processing involves multiple steps and procedures including cell isolation and activation, gene editing, cell expansion, and wash and concentration. For a successful, commercially feasible cell therapy process, it is important to be able to conduct these activities as simply, safely, and efficiently as possible. Closed systems provide the highest containment and product safety protection for these fragile substances.

Using equipment and products that scale from research to manufacturing can cut process development times and delays by eliminating the need to learn and optimize new systems while also permitting multiple batches to be processed in a shared clean room. Removing human involvement and error from this process further supports consistency of both autologous and allogeneic therapies by creating a reproducible and automated manufacturing workflow for these therapies.

RISKS AND CHALLENGES AHEAD

Thanks to recent advancements, cell therapies are receiving increased attention: the Alliance for Regenerative Medicine's Annual Report 2020 lists more than 1,200 active, or actively recruiting, clinical trials for cell therapies being developed for diverse diseases [7]. But only a handful of cell therapies have been approved and are on the market. Although this field is continuing to expand, thanks to the innovations highlighted previously, challenges remain that must be addressed.

When working with allogeneic therapies, there is an increased risk in some applications (e.g., T-cells) of immunological response from the patient that could be life-threatening, such as severe graft vs. host disease. Because these situations use donor cells instead of the patient's own cells, new technologies are emerging to address and prevent these life-threatening events. Clustered regularly interspaced short palindromic repeats (CRISPR) and transcription activator-like effector nucleases (TALEN) gene-editing technologies are used to address the safety concerns related to using donor T-cells. Additionally, a purification step is often taken to remove the remaining donor T-cells to ensure a safe drug is delivered to patients [8]. Purification steps are routinely used in cell therapy manufacturing, using magnetic beads conjugated with specific antibodies that isolate specific immune cells for further drug manufacturing or to remove unwanted cells from the drug product. CRISPR-based technologies are also under testing in clinical trials to advance the treatment of inherited genetic diseases (e.g., beta thalassemia) and CAR T-cell therapy.

On the other hand, NK cells, which are a type of lymphocyte (a white blood cell) and a component of innate immune system that play a major role in the host-rejection of both tumors and virally infected cells, are emerging as a "natural" allogeneic alternative to the use of donor T-cells. There are fewer safety concerns to manage with NK cells. Recently, chimeric antigen receptor (CAR)-NK cells have shown promising clinical responses in the treatment of CD19-positive blood cancers [9]. Due to the increased risk and safety profile in certain allogeneic platforms, it is expected that regulators are looking for extensive safety documentation before we will see such therapies approved [10].

REGULATORY HURDLES

Another key challenge associated with cell therapy of any kind—not just allogeneic therapies—is related to regulatory guidance. Cell and gene therapy in the US is under the FDA's Center for Biologics Evaluation and Research (CBER). Regulations for cell and gene therapies were established relatively recently and are still evolving. There are efforts underway to harmonize the global regulations of cell therapies.

Because cell therapy can be influenced by differences in donor and tissue sources, product characteristics may not be well defined in early clinical stages of development, making them harder to regulate. Identification of relevant biomarkers remains a challenge that could allow for the selection of donor materials with an expected cell therapy drug response and biomarkers to monitor the quality attributes during the manufacturing of the drug. Among other challenges are the issues with analytical testing, such as assay specificity, sensitivity, accuracy, and reproducibility, which can be important for demonstrating batch-to-batch consistency and product comparability. Early and frequent collaboration with regulatory agencies during both the approval and development phases is paramount.

In allogeneic cell therapies, specifically, there are robust requirements to maintain traceability from donor to recipient once the therapy has been delivered. There are additional guidelines that need to be followed to minimize the risk of transmission of diseases (e.g., through viruses) from the donor to the recipient [11]. For example, determinants of donor eligibility should ensure that the unrelated allogeneic cells or tissues are obtained from donors who have been appropriately screened and tested for identified communicable diseases that may arise from viruses and bacteria.

These regulations are continuing to move forward in both the development and delivery of these therapies. Ultimately, as technology evolves to make these processes more safe, scalable, and reproduceable, we can expect to see openness from regulators to embrace these systems.

CONCLUSION

There is huge promise around allogeneic therapies, and scientists and regulators are well on their way to addressing some of the major challenges and making these therapies a more widely available option for patients. Innovations to optimize and standardize

the workflow will go a long way toward supporting scalable cell therapy development and manufacturing. Just as cell therapies have allowed us to activate cells for a medical effect, allogeneic workflows can deliver these results for a larger percentage of patients. In the future, we can expect to see expanded applications for cell therapies.

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About the author

Øystein Åmellem, PhD, has held leadership positions in research and development, product management, and business for over 21 years at Thermo Fisher Scientific. Øystein is responsible for development and commercialization of products and services, including the cell therapy market. His training is in the field of molecular cell biology and he received his PhD from the University of Oslo. Øystein's academic career focused on the study of physiological and molecular mechanisms of tumor cell growth and involved investigating the method of actions for a novel group of anticancer compounds developed by Norsk Hydro.

PERSONALIZED MEDICINE:
The Industry's Future

By Caoimhe Vallely-Gilroy

With so many options for personalizing our lives, is the personalization of medicine far behind? With all the data available, how can the industry bring personalized medicine to patients? This article explores what is currently available and where the pharmaceutical industry can move forward to better serve patient needs.

In modern society, we are used to personalization making everything around us reflect our personality and tastes. From streaming channels and online shopping recommendations, to restaurants with a wealth of food options, to music suggestions that are customized to our liking, we are now accustomed to having our worlds shaped for us. Why, then, should our medicine be any different? Every human is unique, and biology does not offer a one-size-fits-all approach. Why should our diseases, and our treatments, not be unique to us?

Personalizing medicine is not new: targeted therapy has existed in oncology for over 20 years, with genomic testing allowing the best drugs and drug combinations to be selected for the specific cancer type. In a more common example, most patients know, from experience and empiricism, which painkiller works best for them despite not knowing the complicated underlying biomedical processes. By making this choice, patients are personalizing their treatment plan for minor aches and pains.

Advances in molecular diagnostic technologies, unstoppable advances in storage capacity and computing power, and sophisticated machine learning algorithms allow us to push the boundaries in treatment pathways [1]. From image analysis of skin lesions to the very DNA of tumor cells, this all will allow doctors in the future to choose the optimal drug for their patients.

HOW TO BEST SERVE PATIENTS

Knowing that this is where the healthcare industry is headed—and listening to what patients want—what changes need to be made in the pharmaceutical industry to best serve patients in the future? How does the industry address the question of what patients really need? At this stage, one may say the level of "personalization" mentioned is still meeting the needs of a mass population.

From the choice of existing drugs—A, B, or C—the doctor predicts which one might work best for their patient, and at which dosage interval and concentration. However, with modern molecular design tools, it is only a question of time before pharmaceutical companies will take a common drug backbone and modify it so that it is specific to an individual's need.

The future of true personalized medicine is the design and manufacture of one drug for one patient [2]; whether this is possible or sustainable for the pharmaceutical industry depends on the clever utilization of one of the most untapped resources: data.

By harnessing the power of data, the possibilities are truly endless, from a drug discovery perspective right through to clinical management of a patient's condition.

As Mike Gualtieri from analyst firm Forrester Research put it at a 2015 conference: "I disagree with the notion that data is the new oil. It's as infinite as the power of the sun. And just like the power of the sun, we're barely using it at the moment" [3].

For centuries, doctors have focused on patients' symptoms, but what we call disease is probably only a classification of underlying molecular events that may differ from patient to patient. And treatments of these diseases were themselves variations of what was considered a remedy. Remember, the FDA is only 115 years old. Before that, there was virtually no oversight of what doctors could administer [4].

We now have regulations and documentation that manufacturers are producing products in a controlled environment under robust, stable conditions. We have data detailing where each drug is sold most often, and even what brand of drug is most widely prescribed in particular geographies.

The wealth of data that may help patients can come from a variety of sources, be it commercial data from insurance companies or information collected as part of the pharmaceutical manufacturing process to blueprint disease mechanisms known in the biomedical literature.

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Figure 1: The data continuum touches every aspect of the patient experience.

Map onto that what pharmaceutical research and development (R&D) knows about the mechanism of action of their successful compounds and new data coming directly from the patient that we have only just started to analyze, and the next generation of therapeutics available to patients will be more efficient and more efficacious.

THE CURRENT STATE OF PERSONALIZATION

All of this data can contribute to improved drug development, enhanced manufacturing processes and quality, and targeting of healthcare providers and patients for clinical trials well into Phase IV [5]. But from a scientific point of view, it is important to consider the following questions:

- Across the end-to-end process of drug discovery to patient treatment, what variables are unknown?
- Are we missing an opportunity to collect and apply additional data?
- How much data actually needs to be available and collected in order to create a truly personalized patient experience?
- Where does data need to be collected from at each point in the process?

In the clinical development stage of drug development, we have previously treated all patients in a trial the same; however, new data modalities allow us to slice and dice these cohorts into virtual subgroups by asking specific questions and collecting additional data that is personal to the patient's individual behavior:

- Do people whose fitness regime is better than average respond differently to the drug?
- Do they exhibit fewer adverse effects?
- Do lifestyle choices impact the outcome of a drug under investigation?

If we would have been able to revisit failed clinical trials, this strategy could have allowed some of them to meet the strict FDA criteria for approval. Across R&D, specific efforts are underway that illustrate how we are integrating new platforms and methods to unlock the power of data. One example is multiomics data (big data sets consisting of several "ome" data, such as genome, proteome). By providing platforms that allow scientists to better use clinical and translational data, there is increased generation of innovative ideas for new biomarkers and drug targets by integrating multiomics data from multiple sources [6].

QUALITY AND QUANTITY OF LIFE

Consumers—and patients—are not only focused on quantity of life, but also quality of life. If we manage and incorporate differentiators to drugs across the entire holistic patient journey—be they wearables, smart caps, devices, or apps—we could extrapolate further critical data. This would flip the paradigm completely.

Instead of treating people once they become sick, we would move into the area of preventive medicine. In the same way we have pre-knowledge and a warning system when something is about to go wrong or needs additional attention with our cars, our

> Instead of treating people once they become sick, we would move into the area of preventive medicine.

healthcare could have the same—if not better—mechanisms. The most powerful form of personalized medicine is enough data and expertise to stop a disease or condition before it even manifests.

WEALTH OF DATA

People are already tracking and collecting data about themselves [7] via a variety of devices. The most widespread consumer data collection sources are wearables that monitor electrocardiographic and heart health, sleep, and fitness, as well as smart homes, smartphones, and devices that use GPS.

On top of that, elite athletes are constantly measuring stress, exercise regimen, respiratory rates, strain, and recovery time. If these parameters are measured in elite athletes to ensure peak performance [8], why would the rest of the world also not use them? With the advancement of mobile technologies and the popularization of smart devices, we are developing digital health management tools to help patients better manage diseases and daily life.

THE UNIQUENESS OF OUR DNA

Electronic tools may enable the pharmaceutical industry to monitor patients' lifestyle and quality of life. Ultimately, the most unique and fundamental individuality is in the DNA of people. This is the foundational key for personalized medicine.

To unlock this data, we are at the stage where generating genomic profiles of a patient is relatively affordable and efficient. DNA sequencers now come in all form factors and throughput levels. The Oxford Nanopore [9] is a device the size of an iPhone that can help sequence DNA with little preparation in field laboratories and on the go. The newest machines from Illumina [10] sequence several human genomes in a day, at a cost of less than USD $1,000 per sample. So, reading DNA is easy. Storing all that information is a bit harder. And interpretating what it means is really difficult. Until we have a good understanding how a genome encodes the mystery of life, and that includes everything from gene regulation to protein folding, our utility of DNA information is limited.

Pharmaceutical companies focus on well-understood biomarker genes to monitor patient diversity, mostly on a per-gene level, sometimes for two or three genes at a time. However, there are more than 20,000 genes encoded in the human genome. It is going to be a long time until we can fully leverage patients' genome information, if ever. How could this data be used? For example, DNA is transcribed into RNA, and that RNA is then translated into proteins. Think of DNA mutations that impact the rate or efficiency at which proteins are produced, ultimately yielding more or less of a vital protein.

This "personal medicine" would become truly personal: for example, by editing individual nucleotides in the context of the patient's genome. At this stage, this is all blue sky and probably not affordable to anyone. But then, think that the first human genome sequence is just 20 years old, and it cost several billion USD at the time.

CONCLUSION

Is the future of personalized medicine a mix of nature and nurture? If so, does the pharmaceutical industry move toward becoming a preventive industry rather than curative, and when? We have a unique opportunity to integrate the data at our fingertips and to create new methodologies of healthcare and patient management. These aforementioned aspects will impact the pharmaceutical industry and, ultimately, the patient experience, accelerating and transforming the way of getting much-needed medicines to the patients who need them.

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About the author

Caoimhe Vallely-Gilroy is Head of Digital Health and Therapeutics at Merck. She is a passionate advocate of patients' rights and wishes. Caoimhe focuses on the connected patient experience and works to promote and empower patient autonomy with their own health and health data. Caoimhe has a background in clinical development, from leading and managing clinical trials, protocol analysis, strategy development, and implementation to ethical oversight and regulatory affairs. Prior to Merck, she held positions at Roche Pharmaceuticals, Novartis Pharma AG, and Actelion Pharmaceuticals Ltd. Caoimhe has a bachelors degree in genetics, MScs in biomedical science and translational medicine, and is currently pursuing a PhD at the Institute of Clinical Trials and Methodology, University College, London.

CHANGING LIVES with Gene Therapies

By Wendy Haines

The process of bringing new drugs and products to market requires creativity, thinking outside the box, and the courage to fail numerous times before making a single discovery. This rings especially true now, as the industry faces the COVID-19 pandemic and doubts about vaccines and therapies getting to market in record time to improve human health. This article presents a deep dive into gene therapies, the path to those therapies from vaccine development in the 1940s and 1950s, and how the road to developing these has forever changed the landscape of modern medicine.

A look back at vaccine development illustrates the road that the industry has traveled. In the 1940s and 1950s, the poliovirus ravaged the world. In the 1940s, the paradigm for vaccine development was to isolate a live but weakened microorganism. The attenuated virus would then be administered to subjects to produce a low-grade, innocuous infection to confer long-standing immunity. Dr. Jonas Salk's approach was unique, and he and colleagues developed noninfectious killed poliovirus (using formaldehyde) that maintained its antigenic properties [1]. Drs. Albert Sabin and Hillary Koprowski also worked on the poliovirus in the 1950s, and they developed an live attenuated poliovirus vaccine, which was a trivalent oral vaccine that contained all three strains of the poliovirus.

THE PATH TO GENE THERAPIES

We then fast forward to a time when researchers looked to viruses to potentially deliver corrected genes for genetic disorders (see Figure 1). Initially, many people thought this was an outlandish idea that would not come to fruition. However, in the late 1970s, Dr. Jude Samulski discovered how to clone the adeno-associated virus (AAV) during his doctoral studies, which helped pave the way for the use of gene therapies in many incurable diseases [2]. In 1988, the goals of the Human Genome Project were first declared by the U.S. National Academy of Sciences. The project grew to become a collaborative, international program to map and understand all human genes [3]. I was fortunate to be part of a research team working at the National Institutes of Health on the Human Genome Project to identify genes involved in brain development [4]. Francis Collins, then-director of the National Human Genome Research Institute, stated after the publication of the majority of the genome in February 2001, "It's a history book—a narrative of the journey of our species through time. It's a shop manual, with an incredibly detailed blueprint for building every human cell. And it's a transformative textbook of medicine, with insights that will give health care providers immense new powers to treat, prevent, and cure disease."

Adenoviruses (AdVs) are nonenveloped, icosahedral DNA viruses with virion sizes ranging from 70 to 90 nm that belong to the diverse Adenoviridae family [5, 6]. AdVs were first isolated from human adenoid tissues in 1953. AdVs usually cause nonsymptomatic respiratory tract infections in both humans and animals, but they can be life-threatening to immunocompromised individuals [7, 8]. Moreover, the ability of AdVs to infect many cell types facilitated their exploitation as vectors for gene delivery to generate new tools for innovative treatments of important diseases, such as cancer and cardiovascular disorders [9–12].

AAV

AAV is a small, 25-nm nonenveloped virus with a linear single-stranded DNA genome that belongs to the Parvoviridae family [13, 14]. To date, 13 distinct serotypes (AAV1–AAV13) exist, more than 100 variants have been isolated from human/

Figure 1: A timeline for the development of gene therapies.

1953 – Structure of DNA characterized as double helix, Watson, Crick, Wilkins, and Franklin	1973 – Discovery of genetic engineering technique allowing genetic material from 1 organism to be artificially introduced, replicated, and expressed in another, Cohen and Boyer	1990 – First viral vector technology gene therapy clinical trial for severe combined immunodeficiency (SCID), Blaese and Anderson	1996 – Creation of first generation of lentiviral vectors (LVVs) based on HIV, Trono and Naldini
2003 – First gene therapy product regulatory approval – gene therapy to treat squamous cell carcinoma by The National Medical Products Administration	2009 – Clinical trail using adeno-associated virus (AAV) vector for a genetic eye disorder, 8 years later this trial led to first gene therapy approved by FDA	2012 – Development of gene editing technique called CRISPR/Cas9 to modify specific DNA sequences, Doudna, Charpentier, and others	2012 – First AAV-based gene addition therapy approved by European Medicines Agency (EMA) for lipoprotein lipase deficiency (LPLD)
2016 – EMA approves first ex vivo gene therapy to treat adenosine deaminase severe combined immunodeficiency (ADA-SCID)	2017 – FDA approved first in vivo gene addition therapy for a genetic eye disease that causes progressive vision loss, FDA approved a CAR T-cell therapy for patients with relapsed/refractory large B-cell lymphoma (EMA approved in 2019)	2018 – First CRISPR/Cas9 clinical trail evaluating CRISPR/Cas9 for gene disruption in beta hemoglobinopathies	2020 – Finalization of 6 gene therapy guidelines from FDA with draft guidance for research and clinical development of gene therapies

nonhuman primates, and no diseases have been associated with AAV infections [14–17]. AAV serotypes have different transduction efficiencies for different tissues, which are dictated by their capsid sequence [16, 18]. The transduction efficiencies of AAV serotypes have been harnessed to target a particular tissue or cell type to deliver gene therapies. The first AAV vector-based clinical trial was performed over 20 years ago; it used a cystic fibrosis transmembrane regulator (CTFR) transgene via a recombinant AAV vector (rAAV) in adult cystic fibrosis patients with mild lung disease [19]. In 2012, the European Commission approved an rAAV1 vector encoding lipoprotein lipase as a therapy treatment for patients with this enzyme deficiency [20].

AAV is a preferred vector for gene therapy because of its lack of disease associated with wild-type virus, the ability to transduce nondividing cells, and long-term robust transgene expression. AAV vectors are the preferred delivery system for in vivo application because they deliver systemically via the vascular system, are nonpathogenic, and can infect a broad range of dividing and nondividing cells, and the various serotypes display differential tissue tropism [14, 21, 22]. AAV vectors have essentially replaced the adenovirus for gene delivery with the initiation of a large number of clinical trials, with more than 100 trials either recruiting or active/not recruiting in the US [23]. In contrast to the adenovirus vectors used in gene therapy studies, AAVs elicit a milder course of innate immune reactions, which is a key factor of a favorable safety profile and low toxicity [24].

GENOME EDITING AND CRISPR

Genome editing, a method used to precisely alter the DNA sequence of a cell, is broadly used as a research tool and is now being used to develop gene therapies. As progress in gene editing techniques continued, the CRISPR-Cas9 system (or CRISPR, which stands for clustered regular interspaced short palindromic repeats) emerged.

In 2011, Drs. Emmanuelle Charpentier and Jennifer A. Doudna were interested in a bacterial immune system that used an enzyme called Cas9 to "cut up" the genes of invading viruses. Charpentier published findings on how a pair of bacterial RNA molecules controlled this process [25]. The scientists then developed a way to turn the viral defense system into a programmable gene-editing tool, and they synthesized a new molecule, the single guide RNA, which merges the key features of the two bacterial RNAs and directs Cas9 to cut a specific site in the DNA [26].

In 2020 Charpentier and Doudna won the 2020 Nobel Prize in Chemistry "for the development of a method for genome editing" [27]. According to Fyodur Urnov, a gene-editing scientist at the University of California, Berkley, "The number of discoveries in biomedicine that have had the impact that Jennifer's and Emmanuelle's had can be counted on the fingers of one hand: recombinant DNA, PCR (polymerase chain reaction), DNA sequencing, and now CRISPR. We have never had a technology as powerful and versatile as genome editing with CRISPR."

The CRISPR-Cas9 system is a powerful tool for genome editing because it is simple to use, demonstrates site-specific activity, and has limited off-target effects [28]. The CRISPR-Cas9 system consists of the Cas9 nuclease that, when complexed with a short guide RNA, can be directed to create a double-stranded break in a wide variety of DNA sequences in both eukaryotic and prokaryotic genomes [26, 27]. CRISPR-Cas9 systems are being applied to create new cell therapies, either through ex vivo editing of cells followed

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by transplantation of engineered cells into a patient or through in vivo editing of a patient's cells by delivering the CRISPR-Cas9 system using viral vectors (AAV) or nanoparticles [29–34].

The CRISPR-Cas9 system has been adapted from multiple bacterial species—including Streptococcus pyogenes, Streptococcus thermophilus, and Neisseria meningitidis—to efficiently generate targeted gene modifications in human cells and consists of a Cas9 nuclease that is co-expressed with a single guide RNA molecule [26, 28, 35–37]. Cas9 forms a complex with the 3' end of the single guide RNA, and the protein-RNA pair recognizes its genomic target by complementary base pairing between the 5' end of the single guide RNA sequence and a predefined 20-base pair DNA sequence, known as the protospacer (38). By simply exchanging the 20-base pair recognition sequence of the expressed single guide RNA, the Cas9 nuclease can be directed to new genomic targets [39].

CASE EXAMPLE

With an understanding of how viral vectors and CRISPR have changed the landscape of modern medicine, let's review an example of using both of these technologies to provide a cure to a fatal genetic disease, Duchenne muscular dystrophy (DMD).

DMD is a rare, X-linked, fatal, degenerative neuromuscular disease that is estimated to affect 1 in 5,000 newborn boys worldwide [40-42]. DMD is caused by mutations in a single gene, the DMD gene, that result in the lack of a functional dystrophin protein [43]. Dystrophin links the F-actin in the cytoskeleton with beta-dystroglycan and the extracellular matrix through its N- and C-terminal domains, respectively [44]. Mutations causing the premature truncation of dystrophin translation result in nonfunctional and unstable dystrophin proteins that are typically undetectable with standard diagnostic techniques [45]. Dystrophin is a critical component of the dystrophin-associated protein complex in muscle cells. It is not only essential for the maintenance of muscle fiber stiffness but also for protection against mechanical stress during muscle contraction [46–49].

Given the essential role of dystrophin in protecting skeletal and cardiac muscle cells from mechanical stress, patients with DMD experience loss of critical functions resulting from progressive muscle tissue degeneration with motor symptoms [50, 51]. In young males diagnosed with DMD, motor delays are followed by a functional decline, resulting in the loss of ambulation in their early teen years, wheelchair dependency, and an inability to perform daily activities, such as feeding [23]. Additionally, loss of diaphragm function can result in increasing respiratory impairment, cardiac dysfunction, and ventilator-assisted breathing in their teens and twenties, with disease progression leading to cardiomyopathy, respiratory failure, and premature death [52]. There is no cure for DMD, and although palliative treatments are available (essentially, physiotherapy, assisted ventilation, and glucocorticoids), most patients have no satisfactory symptomatic or disease-modifying treatments [42].

Over 7,000 different mutations have been reported in DMD patients [53]. The commonality of these mutations is a nonfunctional dystrophin; however, many DMD patients can unexpectedly produce trace amounts of Becker muscular dystrophy (BMD)-type dystrophin [54]. The deletion of exon 45 is one of the most common deletions found in DMD patients, whereas deletion of exons 44 and 45 is generally associated with a less progressive allelic form of muscular dystrophy, known as BMD [43]. Therefore, if exon 44 could be bypassed in the pre-messenger RNA (mRNA) transcripts of these DMD patients, this could restore the reading frame and enable the production of a partially functional BMD-like dystrophin [44]. Deletions of exons 44 and 45 are associated with very mild Becker phenotypes and have even been found in asymptomatic individuals [55]. Patients with a deletion bordering exon 44 skip exon 44 spontaneously, although at very low levels. This results in slightly increased levels of dystrophin when compared with DMD patients carrying other deletions and most likely underlie the less severe disease progression observed in these patients compared with DMD patients with other deletions [43, 56, 57]. Gene therapy for DMD should address the underlying genetic cause of the disease by specifically restoring functional dystrophin to key tissue targets in skeletal muscle, including the diaphragm and the heart, by introducing a functional gene to compensate for the mutated or absent dystrophin gene.

Novel Gene Therapy Approaches

Two companies using AAV viral vectors for the treatment of DMD are Astellas Gene Therapies (formerly Audentes Therapeutics) and Regenxbio. Astellas Gene Therapies uses the AAV vector approach, encoding a modified U7 small nuclear RNA (snRNA) to carry an antisense sequence to induce cells to skip over faulty sections of the genetic code in the dystrophin gene to restore productive levels of functional dystrophin protein [58]. Astella Gene Therapies is collaborating with Nationwide Children's Hospital to conduct a first-in-human clinical trial with this gene therapy in DMD patients who have a duplication of exon 2 in the DMD gene [58]. Currently, both preclinical and ongoing clinical studies support

future AAV-U7 snRNA-based exon-skipping therapies to treat DMD. Furthermore, AT702, an AAV-antisense therapy that induces exon 2 skipping to treat DMD patients with duplications in exon 2 and mutations in exons 1–5 of the dystrophin gene, is being developed [58]. Two additional products are being developed by Astellas Gene Therapies, AT751 and AT753, which are exon-skipping therapies indicated in the treatment of DMD patients with genotypes amenable to exon 51 and exon 53 skipping [58]. The same vector backbone for AT702 is used for both AT751 and AT753, which allows for accelerated development for use in the clinic. Across these three products or programs, 25% of DMD patients can be treated, with future candidate therapies targeting up to 80% of DMD patients [58].

The Regenxbio approach is different from that of Astellas Gene Therapies, but it also uses an AAV vector to deliver therapy to muscle cells. RGX-202 uses a proprietary novel AAV (NAV) vector of the serotype 8 capsid (AAV8) that encodes microdystrophin to be delivered to muscle cells [59]. The NAV Technology Platform is composed of exclusive rights to AAV7, AAV8, AAV9, and AAVrh10 and more than 100 novel AAV vectors, with over 100 patents and patent applications worldwide covering NAV vectors [60]. There are numerous benefits to using the NAV vectors compared to early generation AAV vectors, including broad application across multiple disease states, the lower likelihood of triggering an immune response, improved gene expression with long-lasting treatment in a smaller dose, and a less-complicated manufacturing process [60]. RGX-202 is composed of a unique C-terminal domain for improved function, a muscle-specific promoter (Spc5-12) to direct expression of microdystrophin in skeletal and heart muscles, and additional features to reduce immunogenicity and improve gene expression [59]. RGX-202 is a single administration therapy, and the preclinical phase of development is in progress, with plans for first-in-human clinical trials in mid-2021.

Several methods can be used to deliver DNA or RNA to cells in our body and can be modified to deliver CRISPR components. The methods can be divided into two distinct categories: viral and nonviral. One nonviral method utilizes lipid nanoparticles (LPNs) and mRNA. Advantages of LPNs are expansion beyond delivery to the liver, increased potency, and improved tolerability. In the LPN platform, an encapsulated mRNA encoding Cas9 and a guide RNA, and, if necessary, a donor DNA template, are used to deliver these components to the liver. CRISPR Therapeutics has partnered with the Massachusetts Institute of Technology to develop drug therapies using LPN technology and CRISPR to target the liver [60, 61]. The advantages of using mRNA with CRISPR for drug products are tissue specificity, expression duration control, and increased potency. Additionally, CRISPR Therapeutics partnered with CureVac for mRNA/CRISPR programs to target liver alignments [61].

Viral vectors can target numerous organs to deliver DNA encoding Cas9 with guide RNAs into specific tissues in the body [61]. Examples of organ systems being targeted for viral vector/CRISPR technology products include muscle, lung, and the central nervous system. AAV vectors are the primary vector being paired with CRISPR technology. Advantages of AAV as a viral vector for in vivo delivery include reduction of immunogenicity, self-inactivation, and improved tissue specificity.

As mentioned previously, with the numerous mutations that can lead to DMD, Vertex Pharmaceutical/CRISPR Therapeutics have several different gene-editing programs that target the many disease-causing mutations. Vertex Pharmaceuticals is partnering with CRISPR Therapeutics to combine an AAV vector with CRISPR technology to treat DMD [61, 62]. This therapy uses an AAV vector to deliver DNA encoding Cas9 to guide RNA into specific tissues in the body, such as muscle tissue, to produce a gene therapy for DMD [61, 62]. To treat DMD, Vertex Pharmaceuticals/CRISPR Therapeutics uses CRISPR gene-editing technology and AAV9 virus to restore dystrophin protein expression by reframing the mutated DMD gene [62].

CONCLUSION

The genetic cause of DMD is known, but a treatment for the disorder did not exist until gene editing became a possibility, as is the case with numerous genetic disorders. The ability to attack genetic disorders at their root cause will forever change our world and provide hope where there was none. We live in an exciting time—a time where we can get therapies to people who had no way of reversing their genetic disorders and who now have the opportunity to undergo treatments to help control the different presentations of their diseases. I believe we will witness the successful curing of a variety of human diseases, both genetic and acquired.

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About the author

Wendy Haines is the Associate Director of Technical and Scientific Services at PharmEng Technology and has over 20 years of toxicology experience. She has BS degrees in pharmaceutical sciences and biology from Campbell University, a PhD in Toxicology from the University of North Carolina, Chapel Hill, and is a board-certified toxicologist (DABT). She impacted human health laws at the Environmental Protection Agency (EPA) in 1997, worked on the Genome Project between EPA and NIH, and later conducted her PhD at the EPA performing directed research for the Office of Pesticides. Wendy was a study director and oversaw pre-clinical trials at a contract laboratory, and she was a consulting research toxicologist for the National Toxicology Program. Wendy has performed toxicological safety evaluations on more than 250 different drug products for clients all over the world. She is a Past President of ISPE CaSA, Past Chair of the International YP Committee, and currently serves on the Pharmaceutical Engineering Committee (PEC). She has been an ISPE member since 1996.

TODAY'S PHARMA AND BIOTECH PROJECTS:

A Phased Approach

By Robert Dream, PE, CPIP, José C. Menezes, PhD, and Antonio R. Moreira

This article revisits the concept of phased engineering, procurement, and construction (EPC) and updates it with risk-based considerations specifically regarding the commissioning, qualification, and validation (CQV) of general life-cycle principles for pharma and biotech projects. Enhancing the relationship between phases of a project, advanced planning, and more formal management of uncertainties could maximize the overall efficiency, productivity, and effectiveness of engineering projects. The use of a risk-based phased EPC-CQV approach will be key in meeting the increased global demand for capacity and successful emergency preparedness efforts. This article revisits an article on this topic published in *Pharmaceutical Engineering*® in 1997 [1].

The general outline of a pharma or biotech engineering project includes phases and tasks that typically span 2–3 years (Figure 1). The recent pandemic emergency response and the level of readiness demonstrated by reusing/converting existing capacity have shown that compression of these project timelines can be achieved in practice.

In today's business environment, where every project is a one-shot approach with aggressive objectives (higher quality, shorter schedule, diminishing resources), there is a tendency to compress a project to the point where many of the normal development activities (e.g., process definition, facility design, procurement, construction) take place at once. We used the phased approach (Figure 1) to compress the schedule. That can be supported by risk-based management to select and prioritize critical project aspects. Concurrent activities to compressed project activities may offer some short-term relief, but this approach can cause coordination problems within the design and interference problems during construction. This will lead to cost overruns and schedule delays due to rework of the design or the need to make changes in the field.

This article is not intended to be an in-depth presentation of all aspects of project design, construction, commissioning, qualification, and process performance qualification and validation

Figure 1: Phased approach using risk-based EPC-CQV.

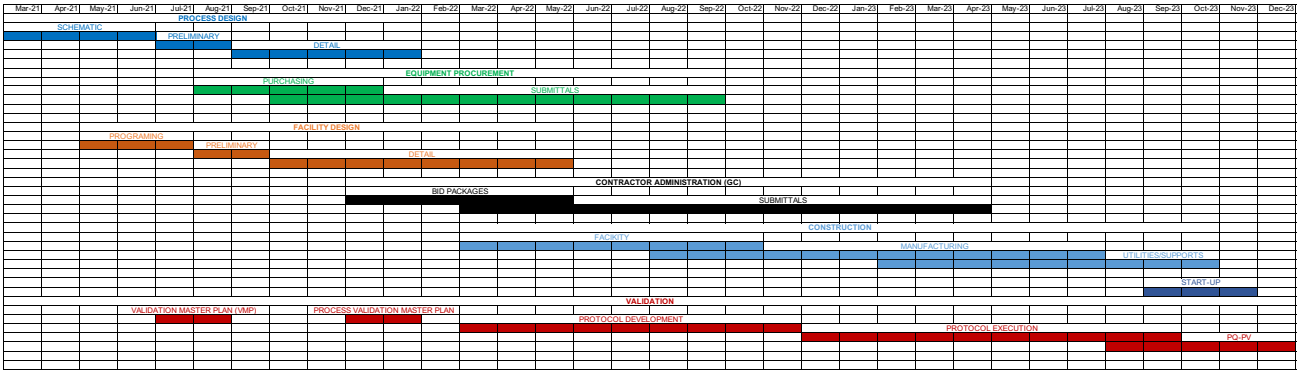
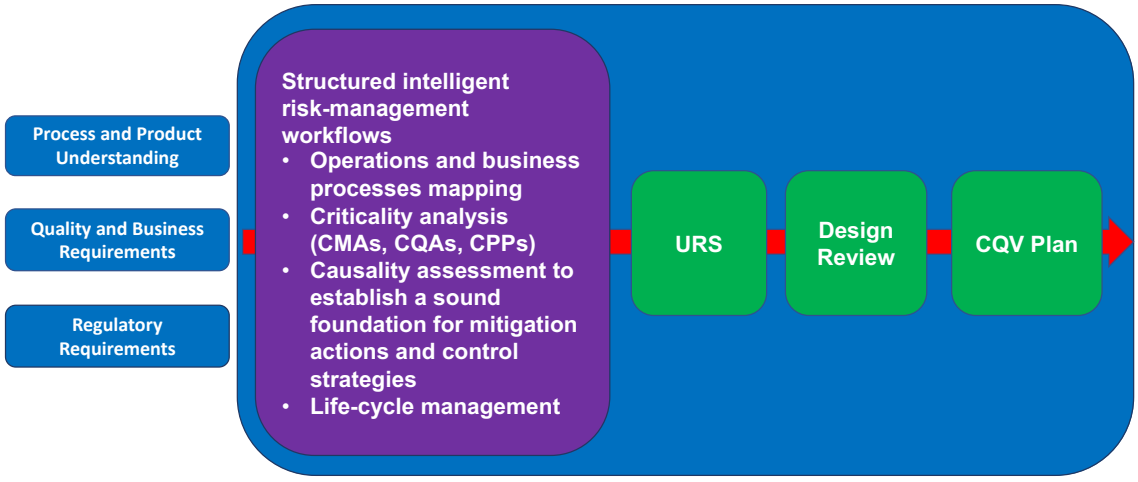


Figure 2: Setting a risk-based CQV plan.



(PPQ/PV). Instead, the article discusses phased EPC-CQV, the relationship between the phases of a project, and how advance planning could maximize productivity.

CHALLENGES IN TODAY'S PROJECTS

The current global pandemic has placed considerable pressure on biopharmaceutical manufacturer suppliers to meet increased demands, and various pharma manufacturers are working toward specific goals. Individuals involved in specific pharmaceutical manufacturing segments want the most flexible process and facility design possible while still incorporating the best technology and anticipating future industry trends. Quality assurance is involved at earlier stages, imposing requirements for regulatory compliance and validation, which have changed significantly with the introduction of risk-based CQV and the ongoing use of life-cycle validation (continuous process verification [CPV]) instead of annual quality reviews. Financial planning requires a higher return on investment, and capital funds appropriation.

Under these conditions, there is a tendency to use the "shotgun" method to finish the project by attempting to run as many concurrent project tasks as possible. Without a higher level of coordination that uses risk management and risk-based decision-making to manage conflicting scenarios and the impact of uncertainties, the shotgun approach is only partially effective. This is because work is completed without the required input, resulting in engineering and construction rework that adds to project costs. Engineering rework resulting from untimely input or poor project coordination can add 10% or more to the cost of a project depending on the circumstances. Changes to a project during construction can add 15%–25% to a project cost. Negative schedule impacts can include late changes that can end up extending the project schedule.

The optimal situation is to understand the relationship between different aspects of a project, to overlap the phases as much as is practical, and to ensure that the proper inputs occur so that rework is not required. The planning and design of a project generally follow the development of the process or manufacturing area, along with procurement of major equipment and the design of the corresponding facility. Once the design is well underway, construction management and construction will commence. At the completion of the construction phase, commissioning and the field phase of qualification will take place. The exact relationship between the activities may vary from project to project along with their relative durations and the degree of overlap.

VALIDATION AND LIFE-CYCLE MANAGEMENT

Validation as defined by the GMP regulations in the largest International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) regions has changed significantly since 2011, which is when the US FDA introduced the use of explicit risk-based life-cycle management considerations and ongoing, continued, or continuous process validation as a new way to assess product quality consistency, process robustness, and facility compliance [2].

The FDA defines process validation as the collection and evaluation of data originating from three stages [2]:

- Stage 1: Process Design/Characterization: The commercial manufacturing process design is defined based on knowledge gained through development and scale-up activities.
- Stage 2: System Qualification/Continued Process Performance Qualification: The process design is evaluated to determine if the process is capable of reproducible commercial manuacturing.
- Stage 3: Continued Process Verification: Ongoing assurance is gained during routine production where the process remains in a state of control.

Table 1: Definitions of different stages of qualification [3].

Qualification	Definition
User requirements specification (URS)	The set of owner, user, and engineering requirements necessary and sufficient to create a feasible design meeting the intended purpose of the system.
Design qualification (DQ)	The documented verification that the proposed design of the facilities, systems, and equipment is suitable for the intended purpose.
Installation qualification (IQ)	The documented verification that the facilities, systems, and equipment, as installed or modified, comply with the approved design and the manufacturer's recommendations.
Operational qualification (OQ)	The documented verification that the facilities, systems, and equipment, as installed or modified, perform as intended throughout the anticipated operating ranges.
Performance qualification (PQ)	The documented verification that the systems and equipment can perform effectively and reproducibly based on the approved process method and product specification.

This approach is also endorsed by the European Medicines Agency (EMA). Annex 15 of the EU's GMP regulations issued in 2015 states that for products developed under a quality by design (QbD) framework, a risk-based process control strategy should be scientifically established during development and tested in the PPQ qualification stage to provide a high degree of product quality assurance and, most importantly, safety and efficacy [3]. This strategy should be applied to evaluate the required attributes for incoming materials, critical quality attributes, and critical process parameters to confirm product realization and regularly evaluated based on the best knowledge and data available.

Both the FDA and EMA guidelines emphasize the importance of applying risk-based procedures to justify and manage all critical quality aspects over the life cycle of a project, from CQV to control strategy definition to postapproval changes that may occur on the process, plus drug product formulation, facilities, methods, suppliers, and supply chains. CQV activities are heavily influenced by the way a process is designed and the depth of knowledge available (Figure 2). The qualification stage of an existing process design should use risk management not only to be comprehensive and to help close any knowledge gaps, but also to help prioritize activities, define a suitable level of effort in qualification, and document activities capturing the context and rationale used (Table 1). Thus, risk management has been considered a new GMP requirement since 2015.

Efficient and successful process validation depends on the use of a structured workflow that includes operations or business processes mapping, criticality analysis, risk evaluation, risk-benefit balancing, threshold definition (between acceptable/residual risks and unacceptable risks that require mitigation), adequate controls, a life-cycle management plan for recurrence of risk reviews, and a mechanism to incorporate continuous improvement opportunities (current project and across the portfolio).

DIGITAL RISK MANAGEMENT

The adoption of digital risk management solutions to speed up the introduction of risk-based CQV and modern risk-based life-cycle management has been gaining momentum. The use of digital solutions holds great promise as it establishes a robust knowledge management framework on which to build consistency and traceability over a project and across multiple projects [4].

There is continued support from the FDA regarding the general use of automation and digital solutions in pharma processes. The FDA is expected to release a new guidance document, Computer Software Assurance for Manufacturing, Operations and Quality System Software, in 2021 [5]. Computer software assurance (CSA) aims to bring agility to the adoption of new digital platforms supporting manufacturing operations and will extend the existing computer systems validation (CSV) requirements by enforcing verification over life cycle in a CPV sense.

Conditions exist today that promote an enhanced approach to process design and qualification activities that will result in acceleration and agility in postapproval change management over the project life cycle, as described in ICH Q12 [6]. These processes take advantage of state-of-the-art digital tools to automate risk-based CQV and CPV programs. The use of structured risk and knowledge management approaches will promote faster delivery of safe and high-quality products to the patients that need them.

VALIDATION MASTER PLAN

Development of a pharmaceutical project is not complete without consideration of the process, equipment, and facility validation. Today, planning of the validation program begins as soon as the process and facility concepts are firm. Conceptual flow diagrams and equipment/facility layouts are reviewed to ensure that the proposed design can be validated prior to operation. Validation planning also establishes acceptance criteria for the various equipment and process systems, a key part of the specification and procurement of these systems.

This early development approach avoids later changes during design or construction and anticipates the time (schedule) and resource (personnel, training, cost) demands that will be placed on the team during final execution of the commissioning and qualification (C&Q) and validation in the field. The validation master plan is prepared to outline the overall plan for the project C&Q and validation in terms of what systems will be commissioned,

Table 2: Validation master plan outline example.

I. Overview – Why a master plan?
- a. Define the terms
- b. Define the criteria

II. Validation activities
- a. Calibration
- b. Commissioning
- c. Installation qualification (IQ)
- d. Operational qualification (OQ)
- e. Start-up
- f. Process performance qualification (PPQ)
- g. Process validation (PV)
- h. Change control

III. Facility
- a. Building
- b. Building utilities
- c. HVAC systems
- d. Process utilities
- e. Process systems
- f. Room layout
- g. Personnel flow
- h. Material flow
- i. Waste flow
- j. Finished goods flow

IV. Process description drug substance
- a. Upstream
- b. Downstream
- c. Miscellaneous

V. Process description drug product
- a. Preparation and formulation
- b. Stopper washing and sterilization
- c. Vial washing
- d. Siliconization
- e. Depyrogenation
- f. Filling
- g. Stoppering
- h. Lyophilization
- i. Sealing/capping
- j. Isolators
- k. Miscellaneous

VI. Automation concepts and objectives
- a. Utility system
- b. Process utilities
- c. Product manufacturing
- d. Sterilization
- e. Lyophilization
- f. Data archiving
- g. Alarms and alarm response

VII. Validation resources
- a. Internal
- b. External
- c. Organization

VIII. Documentation schedule outline
- a. Overall protocol definition
- b. Protocol writing (IQ/OQ)
- c. Protocol execution (IQ/OQ)
- d. Calibration
- e. Automation protocol writing
- f. Automation protocol execution
- g. PPQ protocol writing
- h. PPQ protocol execution
- i. Process validation protocol writing
- j. Process validation protocol execution

IX. Validation execution schedule
- a. Equipment specifications
- b. Vendor audits and liaison
- c. Preshipment acceptance testing
- d. Construction review and audits
- e. Installation review and audits
- f. Installation qualification
- g. Calibration
- h. Operational qualification
- i. Performance qualification
- j. Media fills

X. Other activities
- a. Regulatory interface
- b. Management updates
- c. Support services and other requirements
  - i. Calibration
  - ii. Microbiological environment testing and monitoring
  - iii. Chemical testing
  - iv. Validation equipment
  - v. Materials and component requirement

qualified, and validated and to what extent. It also identifies a tentative schedule, personnel requirements, and training resources (Table 2). The master plan is also a good vehicle to use to begin discussions with the regulatory agencies regarding their participation in the review and approval of the process and facility.

COMMISSIONING AND START-UP

Once construction is completed, the commissioning and start-up phase of the project can begin. This phase includes the following components:

- Testing by equipment/system suppliers
- Inspection of facility and equipment systems
- Operator training
- Functional testing
- Assembly of documentation
- As-built drawings

Many of the tasks involved in the commissioning and start-up of a project are also needed as part of the validation program. Overall planning will prevent double handling of information or the possibility that information provided by a contractor could get lost in the transition.

The schedule for commissioning and start-up should be integrated with the schedule for validation. At the end of this phase, the facility and manufacturing processes are turned over to the owner by the contractor.

PREPARING AND EXECUTING VALIDATION

Portions of the process, manufacturing equipment, and facility will be specified, designed, and constructed to comply with the FDA and/or Pharmaceutical Inspection Co-operation Scheme (PIC/S) current Good Manufacturing Practices (cGMPs) as appropriate. As part of cGMP compliance, qualification and validation studies will need to be performed. The purpose of qualification/validation is to develop documented evidence that only what is from a risk-based point of view is critical: process equipment, utilities, and support services processes. All these can then be performed within a CQV approach and be reliably, repeatedly, and reproducibly verified by CPV program.

The qualification of process and facility systems should be scheduled based on their completion. Qualification will overlap with commissioning and start-up of the systems. Some systems may be validated simultaneously, whereas the testing of others may be dependent on the previous completion of testing of support/utility systems that supply them. For example, media fill tests cannot begin until a sterilizer is qualified, and the sterilizer cannot be qualified until the clean steam generator supplying it is qualified.

The validation program involves the challenging (testing) of all services and equipment using appropriate methodologies and comparing the results with acceptance criteria described in previously approved qualification/validation protocols. Representatives from QA/QC, production, material science and technology (MS&T), and engineering are involved in the review and approval of all qualification/validation protocols prior to their execution. These same representatives will also review all final documentation and reports on completion of the test work.

A complete qualification package will include an installation qualification (IQ) and an operational qualification (OQ) and may include performance qualification (PQ) protocols. An IQ and OQ will be performed for all services and equipment, whereas a PQ will be performed only for those systems or processes that may affect the characteristics, quality, efficacy, and safety of the final drug product(s).

Installation Qualification

During the IQ, a complete review of the installed system (service or equipment) will be performed. The protocol will provide a systematic method to check the system's static attributes prior to normal operation. A detailed discussion of the system will be written and should include a description of what the system is intended to do and all its major components. The system will be reviewed following the completion of installation to verify that the system is the same as what was specified. System engineering drawings, manuals, data sheets, and specifications (URS) will be used to document proper component installation and placement. The location of the system drawings, manuals, data sheets, and specifications will be documented. The system will be examined for proper connections and installation of the supporting services (e.g., water, steam, and electric) and components (e.g., filters, coils, fans, piping, gauges, valves, and controls).

Any exceptional conditions noticed during the IQ will be identified for review on a deviations list. Exceptional conditions will be investigated and the appropriate course of action (explanation, correction, requalification studies) determined. All test data will be documented. The data collected during the IQ will be packaged and summarized either individually or as part of an IQ/OQ/PQ package for presentation, review, and approval.

Operational Qualification

On satisfactory completion of the IQ, the OQ will be performed. The OQ will describe the operational tests to be undertaken, important measurements to record, and control tolerances of parameters critical for the proper operation of the system. Test objectives, methodologies, and acceptance criteria will be defined. Calibration of the critical instrumentation in the system will be documented during the OQ. Execution of the OQ will involve testing and measuring. Controls will be manipulated to test the ability of the system to provide proper temperature, humidity, flow, etc. Indicators, recorders, and interlocks will be monitored. "Worst case" or "peak load" challenges may be defined and incorporated into the testing strategy to challenge the system's capacity. Any exceptional conditions found during the OQ will be identified for review on a deviations list and the same steps followed as those for investigating and determining about exceptional conditions, etc.

Performance Qualification

After completion of the IQ and OQ, the PQ will be performed for those systems requiring it. The PQ will be used to test systems whose operation would affect the product(s). The PQ will integrate procedures, personnel training, materials, equipment, and processes. Test objectives, methodologies, and acceptance criteria will be defined prior to execution. A sufficient number of replicate studies will be performed to determine the ability of the system or process to achieve reproducible results. Testing may include analysis for chemical, physical, and microbiological constituents and will challenge the ability of the system or process to perform the intended function. The protocols may incorporate "worst case" or "peak load" challenges into the intended operating range of the system or process. Exceptional conditions and the other steps described above will be followed.

Process Validation

After the utilities and equipment have been qualified, the validation protocols and programs for the products prepared in the facility are performed. These studies will include facility cleaning and sanitization, process equipment changeover cleaning, filter integrity, process simulation media fills, and the actual process validation studies. By their nature, these studies integrate the facility, equipment, processes, and trained operators and are conducted by the users of the facility.

CONCLUSION

Using the phased approach for projects discussed in this article will help to produce the highest quality project while meeting stated objectives. We have observed reductions of 30% or more compared with the usual project time frames by using the streamlined phased and risk-based prioritized approach described here. The key to successful project execution is to identify and understand the relationship between different aspects of the project (Figure 1). The integration and streamlining of activities in project execution represent a solid plan for a successful outcome and exceptional drug product(s) delivery to the patient.

Project selection takes on different faces in different corporations. While the primary goal of any project is to ensure product availability to patients at sustainable and profitable levels, some projects will focus on industrial processes and others will focus on commercial processes. From the authors' point of view, projects must be linked to the highest levels of strategy in the organization and must be in direct support of specific business objectives.

In this difficult time, project execution is more important than ever. Projects can range from building or appropriating manufacturing sites and hospitals in just a few days to allocating limited quantities of lifesaving equipment. The biopharma industry has played a critical role in responding to the crisis. The use of

phased- and risk-based approaches is able to provide the global supply of state-of-the-art new therapeutics.

The original article from 1997 is available here: ispe.org/pharmaceutical-engineering/november-december-2021/1997-article-phased-approach

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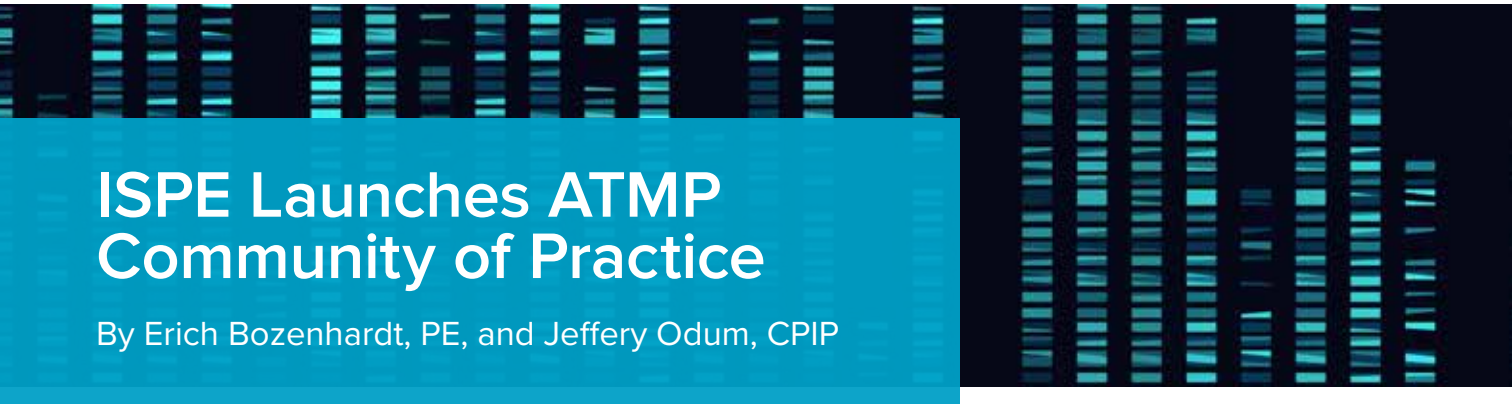
About the authors

Robert Dream, PE, CPIP, is an industry leader with broad experience in the biopharmaceutical industry from early process development to commercial manufacturing. Product experience includes vaccines, recombinant proteins, mAbs, and ATMPs/C&GTs. Robert has been working in the biopharmaceutical industry for 30 years and has been involved in manufacturing, regulatory compliance, process development and validation, and financial planning of drug substance and drug products. Robert has helped organizations to expand their operations and businesses worldwide, including planning, audits, CMC, and BLA preparations and submittals. He has managed contracts and improved CAPEX and OPEX on many projects, and provided oversight, procurement, and program management for clients globally. His work has been published in numerous industry textbooks and technical journals. Robert has participated in seminars and technical conferences for ISPE, INTERPHEX, AICHE, ASME, IBC, PDA, CPhI, and CHI and lectured at universities and training organizations. Robert has been a member of ISPE since 1990.

José C. Menezes, PhD, is Director since 2007 of a program in pharmaceutical engineering at the Technical University of Lisbon, covering QbD, PAT, QRM, and LCM. He is Founder and Chairman of award-winning 4Tune Engineering Ltd., a leading and pioneering company for almost two decades in MS&T and QRM applied to biopharmaceutical engineering. José has published four books, more than 100 peer-reviewed papers, given about 250 international conference presentations, and supervised about 80 MSc and PhD theses, on the above subjects. He is the recipient of several national and international awards, including a presidential award on innovation and excellence in industrial partnerships. José has been an ISPE member since 2006.

Antonio R. Moreira is Vice Provost for Academic Affairs and Professor of Chemical, Biochemical, and Environmental Engineering at the University of Maryland Baltimore County (UMBC), where he has also been Chair of the Department of Chemical and Biochemical Engineering, Associate Dean of Engineering, and Associate Provost for Academic Affairs. Prior to joining UMBC, Tony spent nearly 10 years in the private sector with senior management positions at International Flavors and Fragrances, Inc., and Schering-Plough Corp. (Merck & Co.). He has significant experience with R&D, scale-up, and commercialization of biotechnology products such us alpha interferon, GM-CSF, and monoclonal antibodies. He is a frequent speaker at international biotechnology conferences and symposia, has authored or coauthored over 200 publications and presentations, and has overseen over $20 million in research contracts and grants. He holds a BS in chemical engineering from the University of Porto, Portugal, and MS and PhD degrees in chemical and biochemical engineering from the University of Pennsylvania. He has been an ISPE member since 1992 and is currently Chair of the Board of Directors of the ISPE Foundation.



ISPE Launches ATMP Community of Practice

By Erich Bozenhardt, PE, and Jeffery Odum, CPIP

"The only constant in life is change." This quote is as true today as it was 2,500 years ago when Heraclitus laid out his philosophy. In the last five years, the word "cure" has been used to describe new therapies targeting many different cancer and hereditary diseases. The potential of these therapies to improve human health is profound. These breakthrough therapies utilize advancements in bioengineering that are a step beyond the traditional biopharmaceutical products. A lot of knowledge and experience has been gained from biopharmaceuticals, which can be applied to these new therapies. To advance the scope of diseases treated and evolve the manufacturability of the therapies, a focused effort is needed.

Advanced therapy medicinal products (ATMPs) and cell and gene therapies (C&GTs) are based on genes, cells, or tissues delivered to patients to provide a therapeutic benefit, based on a specific target of interest. For ATMPs, the therapy is a cell, engineered tissues, or the manipulation of the patient's genome. This is in contrast with current manufacturing processes for compounds that are synthetically derived (i.e., small molecule) or proteins or peptides expressed by cellular systems (i.e., large molecule biopharmaceuticals). The development, regulatory path, facility design, qualification, and manufacture of ATMPs present significant challenges to manufacturers, engineers, and suppliers. The GMP regulations are evolving as novel processes are presented and manufacturing paradigms are being tested. This fuels a need for sharing experiences and good practices for ATMPs to help our members find solutions that enable patient health.

NEW COMMUNITY OF PRACTICE

ISPE has elected to form an ATMP Community of Practice (CoP) to expand the industry's and ISPE's body of knowledge. The new CoP will leverage the manufacturing, analytical, and regulatory knowledge of recognized subject matter experts (SMEs) to raise issues and identify solutions that result in:

- Manufacturing (from vial to vial) processes and techniques that reduce cost of goods with consistent product quality. This includes the development of a robust control framework to ensure product quality, including CMC/GMP and unique equipment challenges.
- Robust analytical and stability methodologies, and strategies for raw materials, in-process, and accelerated product release.
- Identifying and determining solutions for complex regulatory issues that, when resolved, will result in accelerated speed to market.

NEW FOCUS ON ATMPS

One of the first focus tasks of the CoP will be the finalization and launch of the new ATMP–Autologous Cell Therapies Guide, focusing on manufacturing facilities development and design. The guide is expected to be published by the end of 2021. The purpose of this guide is to address facility engineering issues and how to provide cost-effective facilities to ensure that products of the highest quality are consistently manufactured. Where nonengineering issues are involved (e.g., microbiological topics and operational issues unrelated to the facility), information will be included to show engineers the importance of such topics and the impact they have on facility design.

The new guide acknowledges that the term ATMP is quite broad, including allogeneic and autologous cell therapies, gene therapies, personalized vaccines, and tissue engineering, and that these are emerging therapies utilizing rapidly evolving technology and equipment. In recognition of this, the guide focuses primarily on autologous cell therapies intended for parenteral use while providing content that may be applicable to other types of ATMPs. For example, segregation principles for individual patient autologous cell therapies, addressed in this guide, may also be useful for a personalized vaccine facility.

The guide's launch will also provide opportunities for engagement in conferences for both ISPE and other industry organizations with the guide's content.

Publication of the guide will be the first content contribution from the ATMP CoP. The next guide about ATMPs will be on the

manufacture of allogenic-based cell therapy products. Work will begin on the second guide in the first quarter of 2022.

Another focus area for the CoP will be on the development of training material for the launch of new ISPE professional training. The initial goal will be a course that focuses on the new guide, targeting autologous cell therapy manufacturing. Future materials will address allogenic manufacturing and potential advances in specific areas such as supply chain management and regulatory compliance.

Since experiences with ATMPs are rapidly growing and evolving, the CoP will develop webinars, iSpeak blog posts, and conference presentations to build the base of knowledge within the community. The CoP will be closely collaborating with other ISPE CoPs where there is a mutual interest. For example, practices around multiproduct facilities handling active viruses are applicable to both the ATMP CoP for viral vectors and the Biotechnology CoP for vaccines. The collaboration will also include assisting with developing ATMP tracks at ISPE conferences in 2022.

HOW TO GET INVOLVED

The ATMP CoP is looking for members to join, share, and expand the body of knowledge within ISPE and the industry. Registration for the CoP is available online by logging into ispe.org, selecting "My account," choosing the "MY INTERESTS AND COMMUNITIES" tab, then checking "ATMP" under the "Communities of Practice" at the bottom of the page.

For questions about the CoP, contact Erich Bozenhardt, ATMP CoP Chair, at ebozenhardt@unither.com

About the authors

Erich Bozenhardt, PE, is Chair of the ISPE ATMP CoP.
Jeffery Odum, CPIP, is Chair of the ISPE Biotechnology CoP.

2021 ISPE BIOTECHNOLOGY CONFERENCE AND WORKSHOP

Cell and Gene Therapies Star in Conference Keynotes

The 2021 ISPE Biotechnology Conference and Workshop began on 22 September with a series of keynote presentations on a range of topics related to cell and gene therapies and advanced therapy medicinal products (ATMPs). Presenters included regulators and individuals whose organizations worked on developing vaccines for COVID-19. The virtual conference spanned three days.

Here are highlights from opening day keynote presentations:

Rapid Growth of INDs

Wilson W. Bryan, MD, Director, Office of Tissues and Advanced Therapies (OTAT), CBER/FDA, gave the first keynote, "Development of Cell and Gene Therapies During COVID-19 Pandemic." He gave an overview of expanded recent development of cell and gene therapies and the investigational new drug (IND) applications to the US FDA that have increased in the last few years.

Bryan said that this is an exciting time for the development of cell and gene therapies: in 2016, 223 new INDs were received by the FDA; by 2020, that number rose to 666. He said that research INDs for gene therapy have increased, although those have somewhat plateaued between 2019 and 2020 (161 in 2019 and 160 in 2020; many of the previous increases occurred after 2006, when there were just 67 INDs).

Wilson said that the science of gene therapy is moving forward rapidly, building on the human genome project, development of new vectors like adeno-associated virus and lentivirus, genome editing such as clustered regularly interspaced short palindromic repeats (CRISPR), and even use of nanoparticles. The use of chimeric antigen receptors T-cell therapy (CAR-T) has resulted in five CAR-T gene therapies approved to date by the FDA; a total of seven gene therapies have been approved.

Research INDs for cellular therapies have been on the rise, with a lot of activity in just the last few years: 91 in 2019 and 151 in 2020. He suggested that some cell therapies may have anti-inflammatory activity that may be relevant to addressing COVID-19, which could account for the rise in the applications during the pandemic. Six cellular therapies have been approved to date by the FDA; he pointed out that one, Stratagraft, was approved this year despite the pandemic.

Wilson emphasized that the FDA supports cell and gene therapies through its Breakthrough Designation (BTD) and Regenerative Medicine Advanced Therapies (RMAT). BTD, which began in 2012, has granted 37 applications in OTAT (about 31% of submissions). RMAT has granted 62, or about 35%, of submitted applications since its launch in 2017. FDA Guidances also support cell and gene therapy development, he said.

The pandemic has presented challenges such as study subjects' hesitancy to travel to investigational sites and added expenses for trials when patients are not enrolled quickly or drop out because they cannot make study visits. There have also been gains such as the adaptation to telemedicine and wearable devices, which have become popular and essential to adapting clinical trials during the pandemic. Recruitment and enrollment for clinical trials is often done remotely now, including obtaining informed consent; more remote monitoring; and adjustments of endpoints by sponsors, on which the FDA is working closely with sponsors. The FDA has been less open to modifying clinical trial analysis in areas such as sample size/study duration and suggested the use of interim analysis, he said, due to the concern that stopping early or not having sufficient sample size could affect the amount of data available for interpretation, which in turn could affect achieving the study's objective of advancing development. He did note that the FDA has been open to new approaches to imputing missing data, which is more of an issue due to the pandemic.

Regulatory Aspects for ATMPs

Francesco Cicirello, Director, Quality Assurance, Envelo Biosciences; Richard Denk, Senior Consultant, Aseptic Processing and Containment, SKAN AG; and Matthew J. H. Davis, Senior GMP Inspector, Therapeutic Goods Administration (TPG; Australia) discussed "Regulatory Aspects for ATMPs based on PIC/S Annex 2 2A and EU GMP Annex 1" in a question and answer format.

In response to a question about contamination control strategy, Cicirello noted that in considering the contamination control strategy in Annex 2 2A, ATMPs are not just one product but many different types of products such as CAR-T, vector, or mRNA vaccines. For all, contamination control needs methods to prevent contamination, which is mostly engineering and processing related.

For contamination control under Annex 1, Davis observed that in ATMPs, contamination control poses a significant risk, greater than

for nonsterile products, and noted that control strategy has been addressed in both PIC/S and European GMPs. He said it is important to consider all routes to contamination in a process and how to manage and prevent it, as well as ensure that the overall control strategy is fully understood and communicated. While the term "contamination control strategy" may be a new one, he noted that manufacturers may have all of the controls in place—they simply need to bring these together and that contamination control is an output of risk management. Cicirello agreed that raising awareness and bringing elements together in a holistic way are key.

In response to a query about how to align discussions about use of barrier systems under Annex 2 2A and Annex 1, Cicirello reiterated that there is overlap. He suggested recognizing differences in the various types of ATMP products.

Vaccines and Monoclonal Antibodies

Rino Rappel, Chief Scientist and Head, External R&D, GSK Vaccines, gave an overview of virus development before and during COVID-19 in "Vaccines and Monoclonal Antibodies to Regain Our Freedom." He observed that the pandemic shortened traditional timelines for discovery and development to just 10 months for the COVID-19 vaccines. While technologies were already available to support this development, a large investment by the public sector helped to move the vaccines forward.

Electronic Batch Records in Cell Therapy

Jessica Beyer, Director, Cell Therapy Manufacturing, Bristol Myers Squibb (BMS), presented on "Implementation of Electronic Batch Records in Cell Therapy." BMS uses autologous process for cell therapy; this process requires scale-out. Electronic batch records (EBRs) can help with the speed needed for these processes, she explained.

EBR is an electronic system that provides proof of successful execution of a production process. EBR interacts with other systems such as equipment tracking and use, inventory management and use, sample management systems, standard operating procedures, and quality systems.

A manufacturing execution system (MES) is an information system that drives the execution of manufacturing operations and generation of an EBR. EBR and MES are two of the key computerized systems used for GMP cell therapy operations; others are global patient services (used for apheresis site approval, patient enrollment, and other steps in the process) and laboratory information management system (LIMS) (used for sample inventory management, sample chain of identity [COI] and chain of custody, and other steps).

EBR is important throughout the process for inventory controls, order creation, COI-based lot numbers assignment, manufacturing order trigger in MES, and other elements. MES helps with scheduling (including ensuring material is available, among other benefits); manufacturing (helps eliminate errors or missed documentation, among other benefits); data integrity (enforces good documentation practices and all elements of ALCOA principles); and disposition (batch record review is done as review by exception, which significantly reduces batch review time).

> The pandemic has brought gains such as the adaptation to telemedicine and wearable devices, which have become popular and essential to adapting clinical trials during the pandemic.

Beyer noted that electronic records are almost required for cell therapy due to the quick turnarounds necessary to produce those therapies. In summary, MES offers benefits in cell therapy over paper records: MES guides the operator in a very manual process; makes appropriate procedures readily available; maintains chain of identity; limits rework or delays; drives compliance in execution; supports analytical data in a proactive way; reduces variability; increases probability of success; and supports review by exceptions, which enables a faster release process without compromising compliance.

CMC and Accelerated Development

Carolyn Laurencot, Associate Director for Regulatory Science and Review, Division of Cellular and Gene Therapies, Office of Tissues and Advanced Therapies, FDA Center for Biologics Evaluation and Research, FDA, presented on "Cellular and Gene Therapy Products: a CMC Regulatory Perspective," outlining some CMC issues with accelerated development.

These include: promising clinical results and accelerated clinical studies can give less time for product development; assay development can lag behind clinical studies; requirements for licensure are unchanged; stability studies challenges include initiating stability studies earlier, while needing potency assay for stability, and there can be potential issues if manufacturing or testing issues change; and planning early for biologics license application (BLA) and commercialization.

She listed CMC information that should be in an IND, including information that describes the composition, manufacture, and control of the investigational product; information should be sufficient to assure identity, quality, purity, and potency of the product; the amount of information submitted will depend on the phase and scope of the initial clinical investigation; and as development proceeds, supplemental CMC information will be needed as appropriate to address expanded phase and scope of clinical investigations.

In summary, the number of CGT products being evaluated clinically has reached an all-time high; CGT products are complex biologics requiring significant forethought regarding product development, especially those in accelerated development; concurrent CMC development during clinical development of the product is crucial and FDA advice should be sought; significant investment of effort into understanding product attributes and analytical testing at all phases of clinical studies is crucial; product and process characterization and assay development should be started early and continued through the product life cycle; process and analytical testing changes are expected during the life cycle of a CGT product, so plan ahead, and try to resolve potential preclinical and CMC issues early in product development.

BioNTech and mRNA Vaccine Development

Oliver Hennig, Senior Vice President Operations, BioNTech SE, gave an overview about the development process for the Pfizer-BioNTech COVID-19 vaccine and other mRNAs in "BioNTech's Road to One Billion Doses of mRNA Vaccines." BioNTech's collaborations include work with Pfizer, University of Pennsylvania, Gates Foundation, and others on various initiatives including seasonal flu, infectious disease indications, HIV and tuberculosis, and rare diseases.

Hennig talked about why mRNA is good for vaccines: It does not require the addition of adjuvants or use of a viral vector for administration; it offers highly scalable production; it is high purity and animal free; and it is nonintegrating into DNA and noninfectious, unlike attenuated live virus and DNA-based virus.

In addition, mRNA offers a highly individualized approach to oncology targets, and he described the process for using mRNA for those applications, where blood/tumor cells from the patient are used; for the vaccine, the genetic code of the virus is used.

Oxford and Adenovirus-Vectored COVID-19 Vaccine

Sandy Douglas, Academic Clinician at the Jenner Institute, University of Oxford, who led their team in working on COVID-19 vaccine development, gave an overview of the development and the partnership with AstraZeneca in "Manufacturing an Adenovirus-Vectored COVID-19 Vaccine: From Bench to Millions of Doses in Months." He traced the development in the early months at Oxford of large-scale process and multi-site international manufacturing strategy early in 2020 before joining forces in May 2020 with AstraZeneca.

Douglas gave some background on adenovirus vector basics, noting that prior to COVID-19, the Oxford platform had been used for other vaccines development and demonstrated consistent safety and immunogenicity in phase I and II clinical trials. Adenovirus vector's benefits include "plug and play" versatility because there is no need for tailor-made processes for each vaccine.

Prior to the pandemic, Douglas's group was not in a position to do large-scale manufacturing, but in February 2020 the group thought that it was possible that their academic group could help with developing a vaccine for COVID-19. There was a platform and clinical trial capacity, but they could only make about 1,500 doses, where there was a need for more than 1.5 billion doses.

The group needed to increase productivity and both scale up and out. Productivity was increased to a new fed-batch upstream, scale-up went from 30mL to more than 1000L in months, and scale-out included collaborating with multiple partners. They also needed to very quickly supply for phase III.

In late February 2020, the group switched to a continuous phase I/II/III strategy, going from first human recipient in late April 2020 to more than 1,000 recipients in May 2020. They switched to a "just in time" supply of multiple trial batches, and developed a proposal for rapid scale-up of fed-batch process to 200L.

Collaboration came initially from a Dutch CMO/supplier consortium in the UK and the Netherlands, and some funding came through the UK government for the 200L engineering run. Scale up moved quickly: in March 2020 to 50L, and April 2020 to 200L. Partners in India and China were added, initiating a goal of 1000L scale. Coordination and communication were key at this stage, he noted. By April, the group obtained more funding from the UK government and was able to scale up to 200L by May, which was when AstraZeneca joined the initiative.

The process development summary from his presentation: antigen-repressing cell bank/promoter combination; single-use materials and common unit operations throughout; innovations of two-cycle low MOI USP and direct loading of clarified lysate on AEX in DSP; product quality in line with precedent and regulatory expectations. When ready for 1000–4000L production, they used parallel tracking tech transfer for speed and distributed manufacturing with central coordination.

Disclaimer: This is brief and informal synopsis of presentations by regulators during a conference presented by ISPE in September 2021. The content of this article has not been vetted by any regulatory agency and does not represent official guidance or policy of any agency.

—Susan Sandler, Senior Director, Editorial

Finalists and Winners Announced for Two Article of the Year Awards

Pharmaceutical Engineering® has announced the finalists and winners of the Roger F. Sherwood Article of the Year for 2019 and 2020. The 2019 award finalists and winner were not announced last year due to the pandemic. Winners of both awards are being recognized at the 2021 ISPE Annual Meeting & Expo in Boston.

2019 AWARD

The 2019 award was given to content published during that calendar year. Finalists were selected from 35 feature and technical articles published during calendar year 2019 by a subcommittee of the Pharmaceutical Engineering Committee (PEC).

The 2019 Roger F. Sherwood Article of the Year is "Regulating Online Pharmacies and Medicinal Product E-Commerce" (Nov-Dec 2019) by Sia Chong Hock, Mervyn Ming Xuan Lee, and Lai Wah Chan. The article explores the growth of e-commerce for prescription and over-the-counter (OTC) medicinal products. Online pharmacies offer many advantages to consumers, including lower costs, convenience, privacy, and a wider range of choices. For businesses, using online platforms removes the need for a physical store, helps manage stock-keeping units, and can increase price competitiveness. But online pharmacies come with risks that are a concern for global regulatory authorities. The article explores issues including laws against counterfeit drugs, accreditation systems, and other actions that help protect consumers when they shop for medicines online.

"The issue of supplies that are safe and effective is critical in our society," said Ferdinando Aspesi, Senior Partner, Bridge Associates International, and Chair of the PEC. "In several countries, products purchased on the internet are not properly regulated or monitored as are those purchased through regular pharmacies. The risk is that consumers may purchase counterfeit products or those from dubious origins, or even products unapproved in that country.

"The message of the winning article is that the industry should continue to work with the regulators across the world to ensure that each country has proper regulations in place and a list of authorized internet sites is available," Aspesi said. "It will provide assurance to patients that the quality and safety of the products offered is satisfactory. This article covers a review of where these proactive systems are in place and addresses issues of patient care, regulations, and internet technology applicable in a holistic way."

2019 AWARD FINALISTS

- "Automated Parts Washer Factory Acceptance Test" (Mar-Apr 2019) by Olivier Van Houtte, Paul T. Lopolito, Dijana Hadziselimovic, and Neo Aik Ann
- "Inline Dilution: An Agile Capability for Downstream Manufacturing" (May-Jun 2019) by Lindsey Daniel, PE, and Avril Vermunt
- "Holistic Control Strategies for Continuous Manufacturing" (May-Jun 2019) by Christine M. V. Moore, PhD, Thomas P. Garcia, PhD, Douglas B. Hausner, and Inna Ben-Anat
- "Accelerated Pharmaceutical Product Development, Registration, Commercialization, and Life Cycle CMC Lessons, Part 1" (Jul-Aug 2019) by Christopher J. Potter, PhD, Huimin Yuan, PhD, Nina S. Cauchon, PhD, Liuquan Lucy Chang, Derek Blaettler, Daniel W. Kim, PharmD, Peter G. Millili, PhD, Gregory J. Mazzola, Terrance Ocheltree, PhD, RPh, Stephen M. Tyler, Geraldine Patricia Taber, PhD, and Timothy J. N. Watson, PhD
- "A New Qualification Approach for Mobile Purified Water Systems" (Jul-Aug 2019) by Fritz Röder
- "Why ISPE GAMP® Supports the FDA CDRH Case for Quality Program" (Nov-Dec 2019) by Siôn Wyn, Christopher J. Reid, Chris Clark, Michael L. Rutherford, Heather D. Watson, Lorrie L. Vuolo-Schuessler, and Arthur D. Perez, PhD
- **Winner:** "Regulating Online Pharmacies and Medicinal Product E-Commerce" (Nov-Dec 2019) by Sia Chong Hock, Mervyn Ming Xuan Lee, and Lai Wah Chan

Winners of the 2019 and 2020 Roger F. Sherwood Article of the Year awards are being recognized at the 2021 ISPE Annual Meeting & Expo.

Keep Your Knowledge Up-to-Date with the Newest Guidance Documents from ISPE

Produced by pharma manufacturing industry professionals and reviewed by regulators and practitioners in the field, ISPE Guidance Documents are considered the gold standard for technical documents. Expand your collection today with ISPE's newest Guides to ensure your practices align with industry and regulatory standards.

The ISPE APQ Guide: Management Responsibilities & Management Review sets a clear expectation regarding the role of strong leadership in terms of demonstrating and communicating "strong and visible support for the pharmaceutical quality system." The second publication in the Advancing Pharmaceutical Quality (APQ) Series, this Guide provides a practical tool for organizations to strengthen their leadership systems and advance cultural excellence.

The ISPE GAMP® Good Practice Guide: Enabling Innovation – Critical Thinking, Agile, IT Service Management discusses how critical thinking based on product and process knowledge and quality risk management can enable the removal of barriers to the introduction of new and innovative technologies. Practical considerations are presented, such as ways to increase the maturity level of an organization's critical thinking ability, the appropriate use of traceability tools to eliminate duplicating documentation as audit evidence, and approaches to IT/IS service provider assessment and governance.

The ISPE Good Practice Guide: Knowledge Management in the Pharmaceutical Industry focuses on how Knowledge Management (KM) can enable a more effective Pharmaceutical Quality System and provide quality, operational, and employee engagement advantages. The first such guidance in the pharmaceutical industry, the Guide promotes uniting KM with Quality Risk Management to enable better risk-based decisions.

LOOKING FOR SOMETHING ELSE?

Explore ISPE's collection of Guidance Documents at **ISPE.org/publications/guidance-documents**.

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2020 AWARD

The 2020 award is awarded this year to recognize content published in 2020. Finalists were selected from 35 feature and technical articles published during calendar year 2020 by a subcommittee of the PEC.

The 2020 Roger F. Sherwood Article of the Year is "Implementation of a Formal Energy-Efficient Design Process" (March-April) by Aoife Hamill, BE MSc, John Hanley, PhD, MPhil, CEng, and Vincent Lane. The article describes a formal energy-efficient design (EED) process that has been in use across all industries in Ireland since 2014 and addresses the benefits of integrating this type of study into the design process. Improving efficiency in a highly regulated environment can be a challenge, but companies in even the most regulated industries in Ireland (e.g., pharmaceutical, biopharmaceutical, and semiconductor manufacturers) are adopting the methodology. The article was derived from the authors' experiences across many projects and in the development of the Irish standard I.S. 399, which establishes energy-efficient design as a management system (complementing ISO 9001 and ISO 50001). It provides companies with a robust strategy for delivering energy, environmental, quality, and competitiveness objectives.

"The article deserves the award because it describes a proactive methodology for the implementation of a formal energy-efficient design process that addresses both energy consumption and long-term sustainability," said Aspesi. "Our society is facing a major challenge in climate change and we need to minimize the use of energy and the release of emissions to produce energy.

"The article covers an example of proper management (including manufacturing process design) of the energy required to produce our products. It addresses the paramount need to minimize the CO_2 release in the atmosphere and to contribute to industry and world sustainability. The article shows the applicability of this approach in three different manufacturing processes where the manufacturing of an active pharmaceutical ingredient is usually the most energy-intensive manufacturing process in the pharmaceutical industry." Aspesi added, "It is commendable that the Irish authorities and the Irish pharmaceutical industry have taken this approach not only to reduce costs but also to address the common good of society."

2020 AWARD FINALISTS

- "Evaluation of Visual Inspection in Parenteral Products" (Jan-Feb 2020) by Sambhujyoti Das
- "Chlorine Dioxide Gas Decontamination vs. Liquid Disinfection" (Mar-Apr 2020) by Jennifer A. Longstaff
- **Winner:** "Implementation of a Formal Energy-Efficient Design Process" (Mar-Apr 2020) by Aoife Hamill, BE MSc, John Hanley, PhD, MPhil, CEng, and Vincent Lane
- "Good Engineering Practice in Risk-Based Commissioning & Qualification" (May-Jun 2020) by William Bennett, PMP
- "ICH Q12: A Transformational Product Life-Cycle Management Guideline" (May-Jun 2020) by Eli Zavialov, PhD, Albert V. Thomas, Saroj Ramdas, Terrance Ocheltree, PhD, RPh, and Connie Langer
- "Quality & Regulatory Solutions for PAT in Continuous Manufacturing" (Sep-Oct 2020) by Gabriella Dahlgren, PhD, Kevin A. Macias, Antonio R. Moreira, PhD, Duncan R. Thompson, Christoph Herwig, PhD, Robert Dream, PE, CPIP
- "Operational Risk Management in Global Supply Scenarios" (Nov-Dec 2020) by Klaus Finneiser

ABOUT THE AWARD

ISPE's Roger F. Sherwood Article of the Year award was established in 1993 to increase article submissions and improve the quality of those received. In the early years, judges rated each issue's technical articles against a set of six criteria, then selected an annual winner.

Almost three decades later, while recognizing the merit of the original intent, the award has been refreshed 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.

Although various judges have taken part in assessing articles over the years, one constant remains: recognition of quality and excellence in content through identifying finalists and a single winning article for each publication year.

FOR MORE INFORMATION

Congratulations to all finalists and winners! For more information about the Article of the Year, visit the PE Online site at ispe.org/pharmaceutical-engineering/about/article-year-award

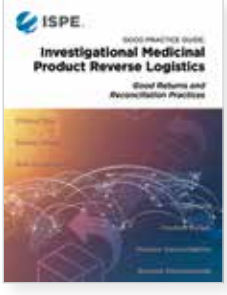
Pharmaceutical Engineering® Wins Award for COVID-19 Special Report

Pharmaceutical Engineering has been recognized for the second year in a row with an award for its content. The magazine received a 2021 APEX Award of Excellence for the four-article "Special Report: COVID-19 Impact," published in the July-August 2020 issue. The recognition was in the category of COVID-19 Media–Government/Association content.

The Special Report was developed early in the pandemic, during April and early May of 2020. It provided a look at how leaders in ISPE saw the situation from both industry and personal viewpoints, as well as touching on several important areas including managing drug shortages, pandemic preparation, and a primer on vaccine development. The Special Report included these articles:

- "*Pharmaceutical Engineering* COVID-19 Impact Survey: How the Industry Is Responding to the Pandemic" by Susan Sandler
- "Engage with Health Authorities to Mitigate and Prevent Drug Shortages" by Deborah Tolomeo, Karen Hirshfield, and Diane L. Hustead
- "Pandemic Preparedness and Business Continuity" by Wendy Haines
- "How Vaccines are Developed" by Frieda Wiley

The APEX awards are an annual competition for publishers, editors, writers, and designers who create print, web, electronic, and social media. Managed by Communications Concepts, Inc., the awards recognize excellence in publishing by professional communicators. The APEX Awards are based on excellence in graphic design, editorial content, and the ability to achieve overall communications excellence. Learn more at www.apexawards.com/



New Good Practice Guide on Reverse Logistics Solutions for Clinical Trials

The number of clinical trials conducted across the globe rises each year as researchers and pharmaceutical companies strive to develop new or improved medicinal products that will ultimately improve lives. The pharmaceutical industry has developed standards and best practices in almost every aspect of a trial. However, there is one area that lacks foundational best practices: medicinal product accountability, reconciliation, and return for destruction—also known as reverse logistics.

"The new ISPE *Good Practice Guide: Investigational Medicinal Product Reverse Logistics—Good Returns and Reconciliation Practices* is the first collection of best practices in reverse logistics for the investigational product supply chain," said Guide Team Member Cat Hall, Vice President, endpoint Clinical. "It includes steps to plan for and implement a successful reverse logistics process within any investigational supply chain and outlines areas of consideration when defining reverse logistics processes within an organization."

Most current reverse logistics processes lack effective planning, thorough application of risk management, and well-defined roles and responsibilities. This results in inefficient and costly processes that often cause delays in study closure as failure to account for study materials can affect the acceptability of trial data. Establishing better standards is also complicated by gaps in and lack of harmonization between good clinical practice (GCP), good manufacturing practice (GMP), local environmental laws and regulations, and import/export and customs regulations.

Written by top experts in the field, the guide includes an outline of the aspects to consider to effectively manage investigational product returns and discusses the key requirements of a good reverse logistics process and common pitfalls to avoid. Topics covered include regulations, product characteristics, trial conduct considerations, logistics, and the use of technology. Additionally, a timeline of activities is presented as an example checklist of best practices.

For more information about the guide, visit ispe.org/publications/guidance-documents

—Marcy Sanford, Publications Coordinator

MEET THE ISPE STAFF

LYNDA GOLDBACH

In each issue of *Pharmaceutical Engineering®*, we introduce a member of the ISPE staff who provides ISPE members with key information and services. Meet Lynda Goldbach, Manager of Publications, Publications Department.

Tell us about your role at ISPE: what do you do each day?

I work primarily on our Guidance Documents, assisting our volunteer teams through the development process, and manage the publication of all the guides. I also do the final production for both print and electronic versions. I used to work on PE magazine, in the marketing department producing our brochures, newsletters, and other promotional pieces, and managed our member database when we had a lot fewer members.

What do you love about your job?

I love working with our members and learning about all the different areas of the pharmaceutical industry. One of my favorite things is taking the rough-looking guide drafts and turning them into a real "book."

What do you like to do when you are not at work?

I like to spend time with my husband and daughters, either at home crafting or at Disney World (our "second home"). I also enjoy teaching tricks and agility moves to our two Australian shepherds.

Celebrating 35 Years at ISPE

On October 29, 1986, a nervous teenager started her first day at ISPE. She was hired to perform data entry on a temporary, part-time basis. At the time, there were six people on staff, including the new hire and Executive Director Bob Best, and less than 2,000 members. The small staff size meant it would be "all hands on deck" for every facet of operations. It also meant that this new part-timer had the opportunity to learn anything she wanted to about ISPE—and so she did. She worked on *Pharmaceutical Engineering,* produced countless materials for the marketing department, and managed the member database. Eventually, she found her home in Guidance Documents in 1998.

Thirty-five years, four CEOs, 46 ISPE employees, and 16,000 members later, this nervous teenager has evolved into one of the most important contributors to ISPE as an organization, and to the industry as a whole. A skilled graphic designer and production/layout professional, her mark is on all Guidance Documents produced by ISPE, with the exception of one (if you're curious, the first *Baseline Guide on Bulk Pharmaceutical Chemicals*). She's collaborated with hundreds of volunteers to develop our prestigious ISPE Guidance Documents, the gold standard in the industry. To date, she has worked on a total of 240 unique products in the Guidance Documents space, including bound, PDF, CD, and myriad translated editions!

Please join me in thanking Lynda for her dedication and contributions to the organization and industry and congratulating her on a very happy 35th ISPE Work Anniversary!

—Rochelle May, Senior Director, Publications

PE Magazine Wants Your P+E!

Tell us about your Chapter and Affiliate events and conferences, trainings and Women in Pharma® meetings, Emerging Leaders activities, and Communities of Practice and Special Interest Group work, and we'll share it with all of ISPE in *Pharmaceutical Engineering's* People+Events (P+E) section. Be the reporter and we'll be the editor, helping you share your information in the magazine.

Please submit articles and short items for ISPE Briefs to ssandler@ispe.org—ISPE Briefs can be up to 400 words, articles can be up to 1,000 words. Photos are welcome: at least 300 dpi or >1 MB.

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IMPLEMENTING LOW PH VIRAL INACTIVATION

in a Continuous Process

By Kakolie G. Banerjee, PhD, Eric Karl Zimmerer, Joelle Genevieve Johnson, Ushma Mehta, Elizabeth M. Goodrich, and Corinne E. Miller, PhD

Viral inactivation (VI) is a critical step in ensuring the safety of monoclonal antibody (mAb), Fc fusion, and recombinant protein therapeutics and it is typically an important component of an overall virus control strategy for downstream biotherapeutic production processes. Considerations for successful implementation of an inline VI process are discussed in this article.

Market drivers have motivated biomanufacturers to set cost reduction and faster production targets while maintaining viral safety and product quality. Transitioning from batch manufacturing to a continuous VI or inline VI (iVI) mode (Figure 1) enables manufacturers to better achieve these targets while providing other advantages, such as a reduced footprint and more streamlined production. Additionally, the smaller equipment facilitates transition to single-use flow paths, which eliminates cleaning and sanitization.

Low pH VI is performed after protein A chromatography to deliver robust inactivation of enveloped viruses. Studies have shown that pH, time, and temperature are critical operating parameters. VI efficacy may also be impacted by protein concentration, isoelectric point (pI), ionic strength, presence of aggregates, buffer systems, and process impurities. The ASTM standard E2888-1 defines conditions that ensure ≥ 5 log reduction value (LRV) of model enveloped rodent retrovirus when a post–protein A eluate is incubated at pH ≤ 3.6 for > 30 minutes [1].

Maintaining the feed at target VI conditions for the required duration while under continuous flow is achieved by passing through an incubation chamber. Because the kinetics of VI are rapid, typically achieving > 5 LRV at pH < 3.6 in under 30 minutes [2–4], manufacturers could benefit from shorter exposure times, which would enable the production of pH-sensitive biomolecules

Figure 1: Batch manufacturing process vs. a low pH iVI process.

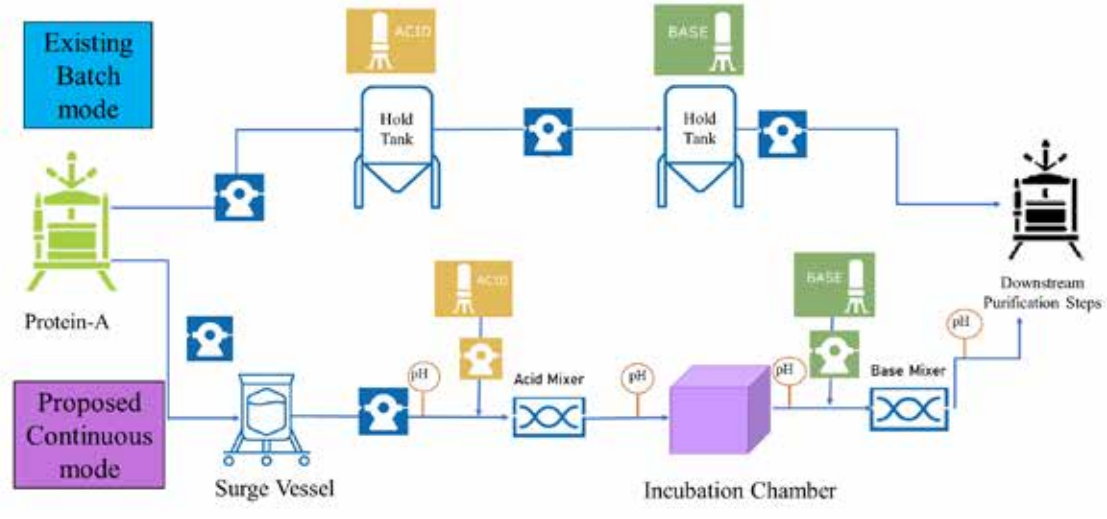
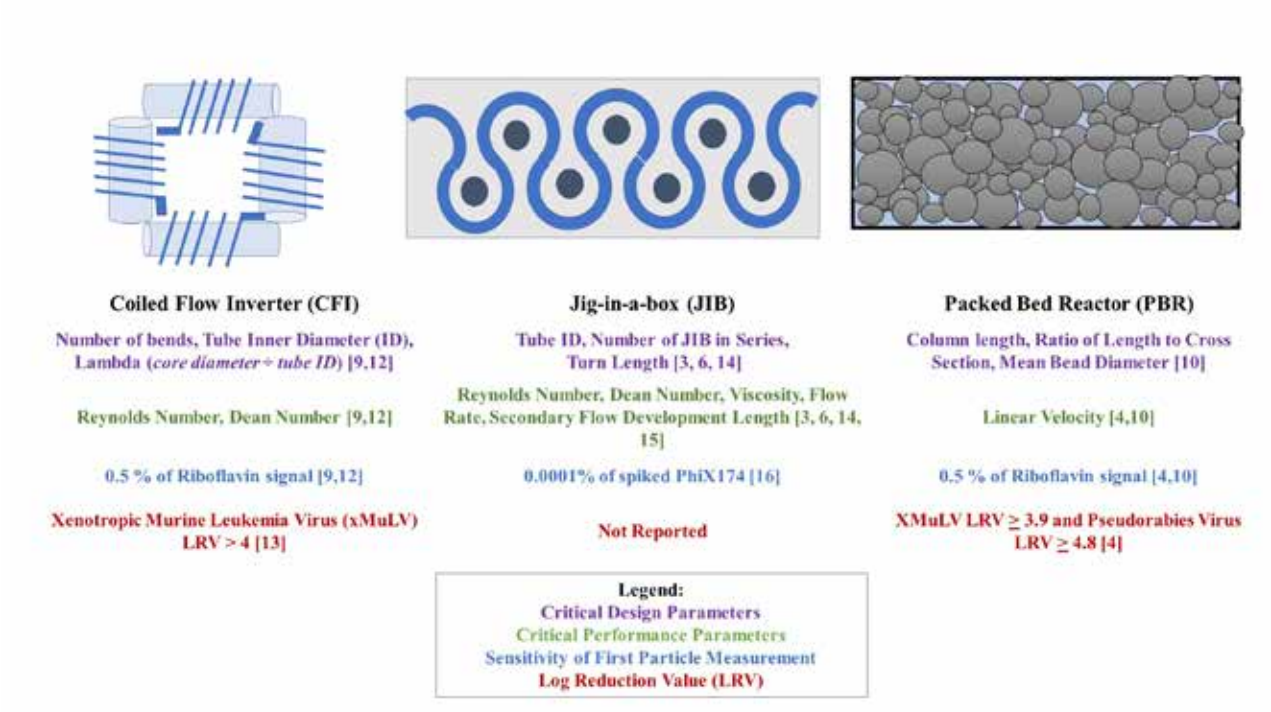


Figure 2: Incubation chamber designs.



without compromising product quality [5]. In this article, available incubation chamber designs are presented with a discussion on how industry can adopt these technologies to transition from existing batch processes to iVI.

INCUBATION CHAMBER DESIGN

Critical parameters of VI include incubation time and inactivation pH. Ensuring adequate incubation time in a continuous process is a key concern due to fluid dynamics that result in nonuniform residence times. Several technologies for iVI are being developed to narrow the residence time distribution (RTD) and guarantee a desired minimum incubation time.

Current incubation chamber technologies for iVI belong to two categories: cyclical flow reactors (CFR) and packed bed reactors (PBR). Coiled tubing used in a CFR design decreases the RTD by inducing secondary flow motions [6, 7]. Two CFRs have been developed for iVI: the coiled flow-inverter (CFI), developed by Bayer [8], and the serpentine tubular flow device (jig-in-a-box, or JIB), developed by Boehringer-Ingelheim [9]. The CFI comprises a series of helical coils arranged at right angles, while JIB is designed with a flow path of alternating 270-degree turns [6].

Alternatively, the PBR uses a packed bed of nonporous, inert beads to minimize the RTD. The RTD is dependent on different critical design and operating parameters specific to each incubation chamber technology [4, 10, 11]. Therefore, a mechanistic understanding of the parameters that affect RTD is necessary to guarantee robust performance. Chamber performance is characterized by injecting pulses of tracer molecules into a flow path and measuring the dispersion of the pulse exiting the chamber. This information is used to generate metrics for the chambers, as shown in Figure 2.Upon chamber commercialization, the data provided on RTD and VI will enable manufacturers to select a suitable chamber for their process needs.

LC i SYSTEM IMPLEMENTATION

Manufacturers need to consider process-associated challenges and possible mitigation strategies for successful implementation of an iVI system.

Post–Protein A Process

Eluate from the protein A affinity capture may deliver a variable feed profile to the iVI process, which can be challenging to control because acid titration is dependent on both inlet feed concentration and pH. Titration methodologies must be established that enable the system to react precisely to the incoming feed conditions. A feedback loop could utilize inline pH and protein concentration measurement to adjust the acid injection rate dynamically as concentration changes in order to bring the feed to the target pH. Alternatively, installing a surge vessel post–protein A (Figure 1) would allow the pooling of the eluate to provide a more

Manufacturers need to consider process-associated challenges and possible mitigation strategies for successful implementation of an iVI system.

homogeneous protein concentration to be delivered for titration. Additionally, a surge vessel would mitigate the risk of negative impact caused by possible process interruption.

pH Sensor Accuracy and Stability

Accurate pH measurement is required to ensure the feed reaches the target pH for VI. During operation, pH sensors can drift or lag, which may result in an incomplete VI. An incomplete VI is associated with pH inaccuracy [16]. Strategies to minimize risk include well-characterized, robust sensors with defined operational limits and extensive pH stability performance data collected over extended periods of operation. Additionally, a system design that enables sampling for offline pH measurement would provide the capability to perform a single-point readjustment of the online pH reading. Periodic sensor recalibration will be an important operational requirement.

Incubation Chamber Size

The iVI system must provide a residence time that ensures exposure of the feed to the target pH for the required incubation time. Because lower incubation times risk incomplete VI, the chamber size should be adjusted to factor in the shortest residence time and desired safety margin [2]. In addition to these design considerations, biomanufacturers will need to assess their process for minimum and maximum low pH exposure time, feed characteristics, and flow rate to define a chamber size that delivers the appropriate RT with a safety factor.

VI VALIDATION IMPLEMENTATION

Although chamber design studies have established theoretical considerations for designing an iVI system, implementation in a manufacturing environment requires process-specific validation. With iVI, two possible strategies for validating efficacy of the VI process include:

1. Perform validation studies in the inline operating mode using a small-scale chamber with a fluid flow profile equivalent to the process-scale chamber and that encompasses the range of design and operating parameters of process scale. Data from spiking studies generated on the scale-down model can be used to demonstrate the required VI. System-induced virus loss from mechanisms such as shear or adsorption loss should be quantitated so that the claimed LRV can be solely attributed to low pH.
2. If the iVI process uses an incubation chamber with a flow profile that has been well characterized, viral inactivation can be validated using established static hold methods combined with a knowledge of the experimentally-determined minimum residence time (MRT) of the selected process-scale incubation chamber. This validation will require the supplier to characterize the MRT for the range of conditions under which the chamber can be operated. In addition, this validation may require an initial body of work by the supplier to prove an equivalent LRV in iVI compared to static VI at the same exposure times [4, 7, 9].

CONCLUSION

The biopharmaceutical industry is innovating to meet increasing production demands while assuring patient safety. Transitioning from batch manufacturing processes to continuous operating modes embodies this objective, enabling flexible and streamlined manufacturing. As a critical piece of the overall virus control strategy for biotherapeutic production, low pH virus inactivation can be successfully integrated into a continuous processing train by ensuring that the critical parameters of pH and incubation time are robustly controlled.

Major challenges of implementing continuous processing operations include robust sensing and maintenance of operational requirements, managing heterogenous feed inputs, and process validation. Recent advances in incubation chamber design, along with an increased understanding of key considerations for robust design and control of iVI systems, are big steps toward facilitating the adoption of fully continuous biomanufacturing to improve patient access to life-saving therapies.

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About the authors

Kakolie G. Banerjee, PhD, is a Scientist III in virology and microbiological sciences at MilliporeSigma. She is a virologist in the process solutions business, supporting bioprocessing efforts. Her work includes viral inactivation and clearance studies using model mammalian viruses and bacteriophage. Prior to that, Kakolie worked as a Staff Scientist at Sample6 (now Corvium, Inc.) and helped develop an AOAC-certified high-throughput phage-based method to detect foodborne pathogens. She received her BS in life science from the University of Dehli, India, a MS in food safety from North Dakota State University, and a PhD in food science from Pennsylvania State University.

Eric Karl Zimmerer is an Engineer I in the biocontinuum group at MilliporeSigma. He is an early career scientist and received a BS in chemical engineering from the Pennsylvania State University. Since joining the biocontinuum group, he has assisted in the development of lab-scale systems for continuous bioprocessing and application of digital technologies to continuous bioprocessing.

Joelle Genevieve Johnson is a Scientist I in the virology and microbiology group at MilliporeSigma. She graduated from Arizona State University with a BS in biochemistry. Previously, she worked in an evolutionary bioinformatics lab, focusing on genetics- and genomics-based approaches to analyze mutation patterns in ciliates and marmosets. She also took part in an internship at the Max Planck Institute of Colloids and Interfaces in Potsdam, Germany, working in a structural glycobiology laboratory.

Ushma Mehta is a Regulatory Consultant for continuous intensified process and cell therapy at MilliporeSigma. She has over 15 years of experience in the life sciences and bioprocessing. Ushma has published peer-reviewed papers on virus removal strategies in both batch process and continuous intensified processing. She has a broad range of experience as a virology scientist in designing and executing virus clearance and inactivation studies across different unit operations of monoclonal antibody and recombinant protein purification templates. She holds a BS and a MS in microbiology, analytical, and medicinal chemistry (Mumbai, India) and completed a graduate certificate course in biopharmaceutical international regulatory affairs at Northeastern University. Ushma joined ISPE in 2020.

Elizabeth M. Goodrich is an accomplished bioprocess engineer with over 30 years of experience in protein purification development and scale-up as well as system design and process automation. She currently leads the process technology applications and innovation team at MilliporeSigma, working to develop continuous biomanufacturing solutions that incorporate novel process, analytical, and digital solutions. Elizabeth holds a BS in chemical engineering from the Massachusetts Institute of Technology.

Corinne E. Miller, PhD, is R&D Director of Virology & Microbiological Sciences at MilliporeSigma. She has more than 25 years of experience in life sciences and bioprocessing. She leads a team conducting bacterial and viral clearance characterization for sterilizing and virus filtration, virus inactivation technologies, microbial integrity testing for single-use and sterile connection and sampling technologies, bioburden assessment, and efficacy for biotherapeutic processing. Corinne began her career as a cellular and molecular biologist, and has led product development teams on assay and detection technologies for DNA sequencing, nucleic acid and protein detection, ELISA, cell-based gene expression, and influenza drug resistance. She has worked on instrument platforms for high-throughput imaging and array-based surface plasmon resonance. She has a BS in microbiology from the Pennsylvania State University and a PhD in cellular and molecular biology from the Massachusetts Institute of Technology.

THE JOURNEY TO BECOMING
a Life Sciences SaaS Provider

By Charlie Wakeham, Stephen R. Ferrell, CISA, CRISC, CDPSE, and Loretto Vuolo-Schuessler

Use of software as a service (SaaS) applications within the life sciences industry is growing. This article reviews the issues and challenges faced by SaaS providers and identifies the qualities of successful providers for this highly regulated industry.

SaaS providers serving the life sciences industry range between two extremes:

- Technology companies that are expert in creating and managing SaaS offerings but lack experience with life sciences regulations (point 1 in Figure 1).
- Mature software vendors with a proven history of supplying applications fit for use with life sciences regulations but with little or no experience with managing a SaaS offering (point 2 in Figure 1).

Companies at each of these extremes will need to adapt and embrace change to ultimately become successful SaaS providers to the life sciences industry (point 3 in Figure 1).

Note that it is not recommended for a regulated company to engage with a provider lacking both SaaS experience and life sciences experience (labeled as exclamation point inside a triangle in Figure 1).

A SaaS deployment model as featured in this article can increase risk for the regulated company, as this model leaves them the least control over the application, its environment, and its configuration.

Many SaaS providers may rely on vendors supplying third-party infrastructure as a service (IaaS) to them. Understanding the associated risks and concerns of such arrangements is important for both the SaaS provider and the regulated company.

"SAAS SMART, REGULATION NAIVE" PROVIDERS

SaaS providers that are new to the regulated market, regardless of the maturity and the potential cross-industry applications of their product, may perceive the needs of their regulated customers as invasive in nature; however, failure to address those needs creates a significant barrier for SaaS providers hoping to expand their business into the life sciences. The work SaaS providers do and the artifacts they create in developing, implementing, and maintaining their applications must support their customers'

Figure 1: Conceptual illustration of the journey to success as a SaaS provider in the life sciences industry.

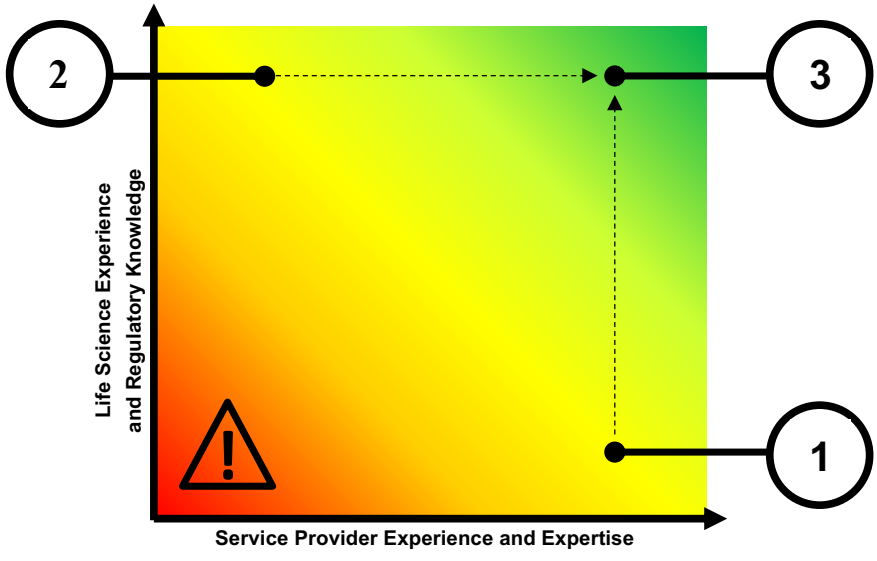
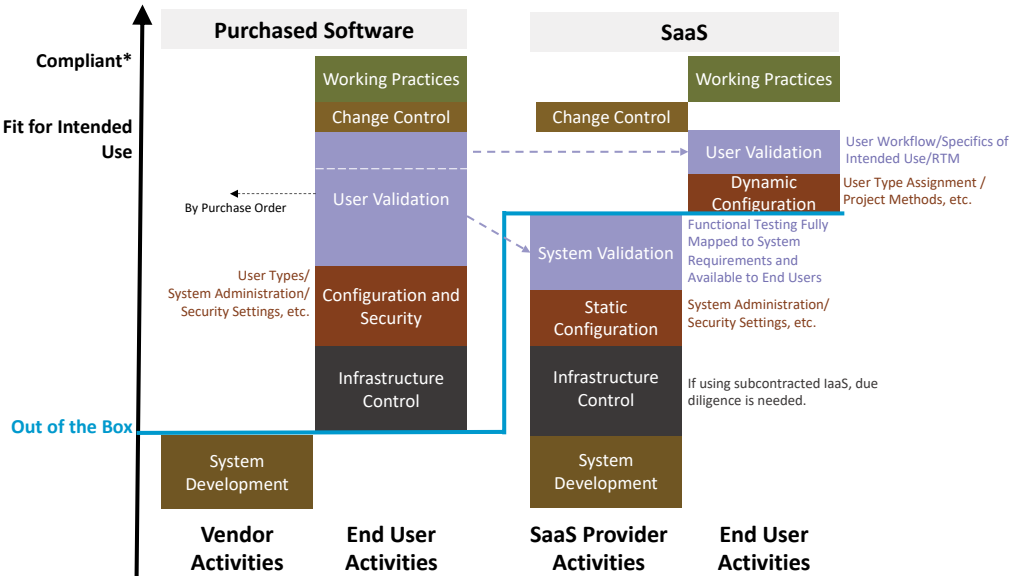


Figure 2: Comparison of activities for purchased software vs. multitenant SaaS in a regulated environment.



*Compliant is not just meeting regulatory requirements; it includes actively safeguarding patient safety, product quality, and data integrity.

regulated use of the SaaS system and help them ensure that the system is fit for purpose.

Providers may discover that many of the good business practices already incorporated within their business model may meet the life sciences industry requirements, but it is essential that they become familiar with life sciences terminology so they can explain how their business practices meet the specific regulatory requirements of their customers. Even if the SaaS provider does not use dedicated GxP terms and approaches, they must be able to demonstrate their understanding of the business process their application is intended to support, as well as the use of a defined software development process and controls and operational controls such as security and privacy.

Multiple ISPE GAMP® guidance and regulatory resources are available to help SaaS providers understand life sciences regulations.

ISPE's *GAMP® 5* Guide [1] and the supporting Good Practice Guide series provide guidance regarding the basic elements necessary to design, develop, test, and implement a computerized system that is fit for purpose. SaaS providers can use this guidance to understand the expectations and perform a gap analysis between their business practices and regulatory and industry best practices.

In recent years, as smartphones and tablets have become omnipresent, opportunities to create mobile applications that may support regulated activities have increased. The delivery of smartphone applications is almost exclusively the domain of SaaS providers. Guidance on regulatory expectations in this area is available in the ISPE *GAMP® Good Practice Guide: A Risk-Based Approach to Mobile Applications* [2].

Suppliers of software as a medical device (SaMD) need to meet specific regulatory expectations [3, 4]. They therefore will have additional demands for their SaaS and cloud providers.

Vendors seeking to provide a SaaS offering in the life sciences industry should pay special attention to ensure that they have the ability to translate and explain their controls and good practices to a customer's auditor or even (in exceptional circumstances) a regulatory authority. This is discussed further in the section on validation responsibilities.

"REGULATION SMART, SAAS NAÏVE" PROVIDERS

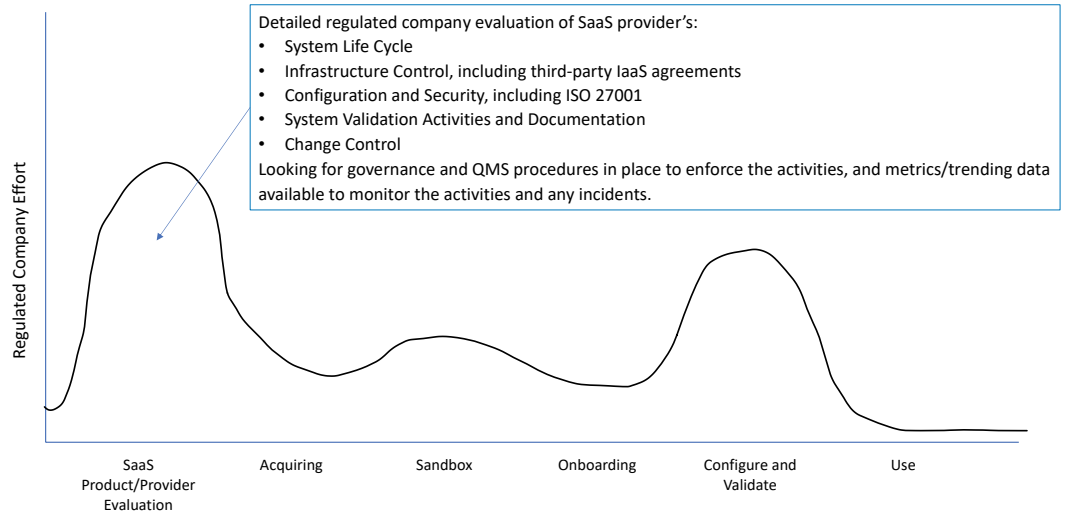
Driven by regulated customer demand for cloud benefits, many mature life sciences software vendors are transitioning existing products to a SaaS offering, launching new products on a SaaS model, or both.

Often, these vendors are expert in the regulations and requirements for the life sciences industry but may not realize the fundamental paradigm shift in their development and support procedures required to become a SaaS provider.

Paradigm Shift

Figure 2 shows the activities of a conventional software vendor and the extent of the additional responsibilities and activities of a SaaS provider. The vendor organization needs to appreciate how much the regulated company's state of compliance relies on their SaaS provider, and to plan their journey from software vendor to SaaS provider accordingly. As shown in Figure 2, this transition shifts the responsibility and control for many activities from the end user to the vendor. The regulated company will need to rely on many of the activities and

Figure 3: Conceptual graph of a regulated company's level of effort from a compliance perspective.



the corresponding documentation performed by the vendor to support their activities.

Final responsibility for validation for intended use and compliant operation remains with the regulated company, who are heavily dependent on the scope and quality of activities for system development, infrastructure, configuration, security, validation, maintenance, support, and change control completed by the SaaS provider. The user validation in a purchased software offering is effectively split in two for SaaS:

- System validation—used here to denote the provider's validation of their SaaS product to demonstrate that system functionality meets their published system requirements.
- User validation—the life sciences company's validation that the configuration is fit for its intended use leveraging the SaaS provider's system validation activities.

This topic is discussed further in the section on validation responsibilities later in this article.

System Life Cycle

Software, whether delivered as a purchased product or via a SaaS model, must be developed and managed according to a formal process, with specifications governing the software content, and documented testing verifying that the software meets specifications. The specifics of software development and delivery approaches for SaaS applications are discussed later.

QMS Transparency

Traditionally, mature life sciences software vendors have adopted a robust quality management system (QMS), but they may have limited the information they make available to customers during audits (for example, by restricting access to the internal release testing).

Assessing the SaaS provider's QMS is a critical and fundamental part of the regulated company's software selection process. Figure 3 illustrates the relative extent of customer activity from a compliance perspective, from initial assessment to operational use of a SaaS application. Given that the regulated company will depend on the SaaS provider's infrastructure controls, internal testing, system validation, software release cadence, and so on, it is vital that the regulated company can efficiently and easily assess the provider's QMS as needed.

Given that the regulated company will become utterly dependent on the SaaS provider's infrastructure controls, internal testing, system validation, software release cadence, etc., it is vital that the regulated company can efficiently and easily assess the provider's QMS as needed.

Validation Portal

A validation portal, with access granted only to prospective and current customers, offers a controlled, centralized repository for QMS information, as well as validation information and system documentation, within the bounds of protecting the SaaS provider's intellectual property. This portal ensures that the regulated company has timely, as-needed access to the latest versions of all of these items, including in support of a regulatory inspection. The validation portal also gives the SaaS provider a place to direct people to change information, risk evaluations, and test scripts.

KEYS TO SAAS PROVIDER SUCCESS

Impact of Provider Choices

When marketing a SaaS product to the regulated life sciences market, the provider must understand the unique delivery and functionality constraints that are critical to successful product commercialization in this market. Successful market penetration,

ongoing adoption, and regulatory compliance necessitate that the SaaS provider document, properly architect, and provide a reasonable level of transparency as to the service model they are seeking to deliver. The following sections discuss critical issues that SaaS providers must address to encourage life science companies to accept and use their services.

Infrastructure Controls

Traditionally, the server and network infrastructure supporting life sciences applications was subject to a documented configuration and qualification process. For most regulated companies, the infrastructure qualification process is an accepted part of IT's job function and has been considered a low-risk activity. However, when organizations migrate infrastructure to the cloud and adopt remotely dispersed, third-party-managed infrastructure, they must perform due diligence to ensure the infrastructure is appropriately managed and monitored by the third-party provider.

There are only a small number of providers who have specialized in offering a traditional life sciences infrastructure qualification approach. Most IaaS providers use automated, real-time management and monitoring systems to ensure the ongoing availability and performance of their service provisions.

As discussed later in greater detail, IaaS and SaaS providers that seek to commercially support the regulated life sciences market should attain and maintain ISO/IEC 27001 [5] certification and/or ensure that SOC 2 Type 2 [6] attestation reports are available. The concepts of risk management, mitigation, change and configuration management, and incident handling can provide regulated life sciences companies with a measure of assurance that the IaaS provider has established ongoing controls that are regularly audited by licensed third-party IT governance professionals. To aid regulated companies' understanding and acceptance of this approach, several of the larger cloud platform providers have created supplemental materials to trace their internal controls, reports, and third-party certifications to life sciences regulatory expectations.

Tenancy and Data Segregation

As a SaaS provider, there are important distinctions when considering an offering into the life sciences market. If the intention of the application delivery is to provide customers with a fully customized and unique experience, there may be an additional opportunity for the regulated company to control and ensure compliance; however, such applications are unlikely to be supportive of multitenant delivery. Single tenancy is not practically scalable over the long term and would require the addition of resources to manage potentially siloed versions of the customized application.

The additional resources necessary to support single tenancy can place a strain on the service provider, and only a small number of providers offer this. It is more likely that the provider delivers the SaaS application in a multitenant environment. Although the end user has the ability to configure a SaaS application to their intended use, they will, in most cases, lack the ability to heavily customize it.

Multi-tenancy can present a challenge for a regulated company to justify the potential for comingled data on a platform shared by other parties. However, the architecture of modern multitenant database applications is designed to securely segregate each organization's data, such that these fears are largely unwarranted.

The SaaS service provider should comfortably be able to articulate how data segregation works within the application, and provide transparency around any risk assessment or testing that has occurred to ensure that data segregation and integrity are always maintained.

Certifications and Audit Reports

The pursuit of third-party governance certifications is becoming an acute requirement for a service delivery provider. Many companies will opt to certify against ISO/IEC 27001 or to procure a SOC 2 Type 2 audit report. SOC 2 Type 1 is also popular, but it represents a point-in-time analysis and is therefore less useful to both the service provider as evidence of controlling conformance, and to the regulated company seeking a provider able to prove ongoing good practice. Beyond an 18-month window, the effectiveness of a certification as assurance of ongoing good governance practice may be diminished.

ISO/IEC 27001 certification and SOC Type 2 reports are similar in that they both provide assurance that the SaaS provider has a substantive IT governance process and that this process is in a perpetual state of measurement, monitoring, continual improvement, and risk management. Regulated companies can leverage ISO/IEC 27001 certifications and SOC 2 Type 2 reports [7] when seeking to ensure that an IT governance framework both exists and is being managed. Indeed, for a regulated company auditor, many of the concepts, semantics, and outputs of ISO/IEC 27001 would be similar to the QMS they might have in their own IT department.

Attaining the certification and/or audit report can provide immediate assurance to a regulated company that the service provider has a mature understanding of good governance practices and is often leveraged to offset many of the traditional expectations related to installation qualification. Note that a regulated company will also expect that third-party certifications are in place for the SaaS provider's foundational infrastructure.

Software Development

To comply with the expectations of global regulatory bodies, regulated life sciences companies have, for the best part of the last 25 years, developed and refined approaches for the verification and validation of third-party software applications.

It is vitally important then that SaaS providers that wish to sell their products in the regulated market understand how their system life cycle functions and are prepared to provide a level of auditability that might otherwise be alien to vendors that do not service this vertical market. Providers that are veterans of the

regulated software space are generally well informed and understand *GAMP® 5* approaches, and are familiar with the acceptable evidence that a regulated company will expect to see. When the software version will be immediately and contemporaneously adopted by all multitenancy users after release, responding using an Agile approach is particularly essential to address any defects or patches quickly. As use cases and user stories are developed, the regulations themselves (21 CFR Part 11, EudraLex Volume 4 Annex 11, etc.) should be held in equal footing as other requirements inputs.

Planning

Most vendors and providers have adopted an Agile approach to software development, which necessitates the creation of sprint planning, and typically a test-first design. Although these are perfectly reasonable approaches and are indeed favored when it comes to the rapid development of high-quality software, the documentation expectations of most regulated companies tend more toward formal, discrete documentation based on past experiences. In turn, the regulated company may need to revise their expectations from using the V-model as a waterfall (linear-sequential) development life cycle, resulting in approved documentation as the output from each stage. Regulated companies will be better served viewing the V-model as a relationship diagram between activities and verifications and the Agile artifacts that record them.

From the outset, the SaaS provider should apply critical thinking to their consideration of what artifacts are required to demonstrate traceability throughout the software development and system life cycle, and how those artifacts can be shared for leveraging by a regulated company. Many software development and/or management tools will inherently include "preservation of information" (artifacts such as specifications, test cases and records, and so on), which may obviate the creation of discrete and formal documentation. A SaaS provider developing and maintaining a high-quality software offering to be sold in the regulated space should ensure that their development and maintenance artifacts demonstrate the traceability of the verification activities against their specifications in whatever tool or format is used.

The planning of a commercial release should consider not only the delivery of functionality but also the delivery outputs needed to satisfy regulated customers. The SaaS vendor must therefore ensure that the tools they use that contain records/data supporting the validated state (e.g., test records) are secure and the records are adequately protected and suitable for leveraging by the regulated company.

Requirements

A working knowledge of the regulations that the SaaS provider's intended customers must adhere to should be considered as part of the requirements-gathering process when defining the minimum viable product and through all subsequent deliveries. Product managers for software serving the life sciences market should carefully consider regulatory constraints from process and functional perspectives as an additional input source for user stories, use cases, and requirements on the whole. The SaaS provider must also consider which aspects of the final product pose the highest risk to data integrity, patient safety, and product quality.

For example, simply following verbatim the US requirements of 21 CFR part 11 with regard to audit trails and electronic signatures, without understanding the system use and workflows, can result in poorly designed and therefore ineffective or inefficient features and controls.

At the requirements-gathering stage, it is also important for the SaaS provider to consider the infrastructure requirements for the application in scope, the security boundaries, and the tool set to be employed to ensure that data are secure, maintain integrity, and are encrypted as appropriate. Commonly, SaaS-delivered applications have SSL certificates with 256-bit encryption and are monitored by a combination of applications engaged in intrusion detection and prevention, file integrity management, mirroring, and some level of data loss prevention.

Configuration

The definition and management of configuration are best characterized in two ways: static and dynamic. Static configuration is the foundational definition of system settings and interfaces that are necessary to deliver the software in a repeatable and controlled manner. The management of static configuration and any subsequent risk assessment or testing offset configuration should be an integral part of the SaaS provider's change management approach.

A configuration that is not well managed or is in a persistent state of change can potentially have a downstream effect on the functionality and performance of the application. Though this is true for any SaaS delivery regardless of the target market, the challenges of configuration are more acute in the life sciences market due to the additional layer of regulatory compliance. Changes in the static configuration by the SaaS provider should be assessed for potential impact on the application and verified where needed to confirm the application is not adversely impacted by the changes.

Dynamic configuration involves those items within the application that are configured and managed by the regulated company. Though it would be impractical to test every combination of every potential configuration, the SaaS provider should provide some level of assurance that a typical user configuration consistently meets its intended purpose. Additionally, the SaaS provider can offer customers their insights on suggested configurations and how to test these specific configurations. The provider should ensure that release cycles are planned in advance and well communicated to their customers to allow adequate time for remedial software assurance activities, including user validation.

Risk assessment

SaaS providers often perceive risk through an exclusively commercial lens. Features that could be impactful to the timelines and commercial strategy of the SaaS provider are often prioritized.

However, it should be noted that features that are particularly complex to the software architect and engineer may not carry a particularly high risk from a regulatory perspective. It is important to consider an additional facet of risk, namely those aspects of the service delivery or functions of the software that could, given the intended use case of the application, have a potential impact to the integrity of the data owned by the regulated company.

Testing

The software testing process should be holistic, but in the regulated context, the level to which a function is tested is largely driven by its perceived and documented risk to data integrity, product quality, and patient safety. The SaaS provider must be able to provide some level of transparency as to what was tested, the rigor of the testing, and the ongoing change and configuration management plan. These are vital concepts for the SaaS provider to adopt to enable the regulated company to both leverage the testing and gain assurance that the work being done by the service provider can be synergized with compliant workflows at the operational level.

Service providers often do not share information about software testing with third parties because they are concerned about the potential risk to their intellectual property. It would be naive to dismiss that risk out of hand. However, it would be equally naive for the SaaS provider to attempt to sell their product in the regulated space without understanding that customers have a reasonable expectation of a level of transparency about what has been tested, and the process that underlies the testing. This is why the planning aspect from a documentation perspective is an important commercial reality for the service provider.

The level of transparency and portability of the SaaS provider's testing may correlate with the implementation time, adoption speed, and perceived level of effort for the regulated companies' own validation requirements.

Software Delivery

The delivery of a SaaS application presents a shared challenge for both the provider and the regulated company. The regulatory and functional aspects of the software should be given as high a priority as any other customer feature because regulated companies will not be able to effectively use the delivered software without these key functional components.

The DevOps concept has fused traditional software development practice and infrastructure management practices into a shared discipline. It is critical then that delivery concepts be considered and weighted just as fully as traditional functional requirements for an as-a-service delivery.

The SaaS provider should look for ways to most effectively

The SaaS provider should look for ways to most effectively deliver their application in a transparent and controlled manner so that prospective regulated customers can have assurance that additional features will not impact legacy functionality.

deliver their application in a transparent and controlled manner so that prospective regulated customers can have assurance that additional features will not impact legacy functionality. Providers must also demonstrate through documentation or artifacts how those features were regression tested and verified so that those efforts may be leveraged in the change management process for the regulated company.

The SaaS provider should take the time to provide prospective customers with clear definitions of version changes, patches, emergency changes, and hotfixes. Though there will be semantic differences from company to company, it is important that the provider and the regulated company reach agreement about the processes and process outputs that support these activities.

SaaS providers seeking to serve the life sciences market will find both flexibility and adaptability only within the boundaries of a defined and transparent process—anything short of that will likely be seen as a barrier to acceptance for use by a regulated company, and will therefore be a barrier to the sale.

Validation Responsibilities

As noted previously, life sciences companies expect that the SaaS provider will manage a greater proportion of system validation—the assurance that the system functions correctly according to the provider's system requirements. The regulated company's aim is to use the provider's system validation in support of their end user validation for intended use. However, this does not in any way obviate or reduce the regulated company's ultimate responsibility for ensuring that any GxP system is fit for their intended use.

Indeed, data integrity guidance from both the US FDA [8] and MHRA [9] specifically emphasize that validation must be focused on the regulated company's intended use and cannot be purely a vendor or provider process. EMA guidance [10] reinforces a similar concept, stating that the sponsor's responsibility for the conduct of clinical trials extends to the validation of computerized systems used in support of such trials.

To rely on a vendor's or provider's validation and qualification documentation, the sponsor must have knowledge of the vendor's QMS. This knowledge may be obtained through a vendor qualification process, including an in-depth assessment/audit. The assessment of vendor documentation also helps the sponsor company determine what additional qualification or validation or activities they will need to conduct. Software vendors and SaaS providers should be prepared for these assessments and be able to support the sponsors in meeting their regulatory expectations. Some of the activities often requested by sponsors to assist them in meeting these expectations include:

- Sharing of qualification/validation procedures and documentation during sponsor audit/assessment
- Contractual agreements that vendors will support sponsors during regulatory inspections, including the sharing of qualification/validation documentation and procedures

There is currently an initiative within the US FDA via the Case for Quality program [11] to introduce the concept of computer software assurance (CSA). The forthcoming FDA guidance is intended to provide regulated companies with clarity for risk-based software assurance activities. The recent ISPE *GAMP® RDI Good Practice Guide: Data Integrity by Design* has an appendix tying the CSA concepts to the foundations of *GAMP® 5*. Key to the CSA concept is a risk-based approach to testing that leverages all previously performed testing.

Because a major principle of CSA is the leveraging of testing from the software providers themselves, adoption of the CSA approach may create a new focal point for both the regulated company and the regulators. It therefore behooves the successful SaaS provider to ensure that their testing, including exploratory, unstructured, ad hoc, and error guessing approaches, affords sufficient rigor, evidence, and traceability that fulfills the regulated customer's need for system validation. This can, in turn, then be leveraged by the regulated company in support of their user validation and demonstrating fitness for intended use. Robust and traceable provider testing can minimize the impact of software releases and the associated validation burden on the regulated company.

Ongoing Life Cycle

With purchased software, the regulated company has control of what upgrades it implements and when it implements them. In a multitenant SaaS environment, the regulated company is tied to the SaaS provider's application life cycle throughout the life of their SaaS subscription.

Release cadence

The change management and validation expectations of a regulated life sciences company are often somewhat in conflict with the Agile and perpetual change models that SaaS providers usually prefer. Therefore, the regulated consumer of SaaS software

must evaluate whether the application under consideration has a change cycle that presents an acceptable risk profile for its intended use within the regulated company. It is entirely possible that software from an application provider that has an aggressive change cycle coupled with limited documentation is simply not suitable for purchase by a regulated company. When shopping for a cloud-delivered application, regulated companies often look for set change cycles (e.g., semi- or triannually).

A final design review before release for SaaS applications with high GxP impact could provide further assurance to the regulated customer that the final application and delivery checks have been performed.

Support

The support model required for life sciences customers can be similar to the model applied to nonregulated customers. However, SaaS providers wishing to service the life sciences market should have a clear understanding about the level of risk that their applications present to their end customer's data.

For example, if a manufacturing execution system is cloud-delivered (as many currently are), the loss of data or the delay of transaction processing caused by a service delivery problem could affect the regulated company operations with an immediate and significant financial impact.

Additionally, slow provider response times or overly generous service level agreements (days vs. hours of response time) have the potential to add unforeseen risks to product quality and, in turn, patient safety. It is therefore critical that the SaaS provider align their service level agreement response times commensurate with the risk for the workflows they seek to service. Regulated companies should also be prepared to potentially purchase premium levels of service in order to maintain GxP compliance. The regulated company must also ensure that the SaaS provider's help desk understands the boundaries of acceptable change during the resolution of a ticket.

CAPA

SaaS providers seeking to support the life sciences industry must understand that although the correction of problems is a necessity, the prevention of their reoccurrence is equally valued. The corrective and preventive action (CAPA) expectations of life sciences companies are aligned with the CAPA provisions of both SOC 2 and ISO 27001. Therefore, attaining one or both of these certifications gives confidence that the SaaS provider uses a CAPA program subject to a regular third-party assessment cycle.

Exit Strategies

The regulated company is ultimately responsible for the integrity of the data supporting their regulated products, and so must consider the full data life cycle.

Extracting and retaining data

The SaaS provider must plan for cancellation of the regulated company's subscription to the SaaS offering that includes a means to extract the company's complete regulated data from the SaaS application. Where the data are dynamic, it will be essential that the data can be extracted and passed to the regulated company in a dynamic format. Following the successful extraction, the data should no longer be present in the SaaS application. This may require a documented and authorized manual deletion process.

Readable data for the retention period

Irrespective of the software deployment model or data format, data should not only be retained but also human-readable for a specified retention period, as determined by applicable regulations. When the regulated company has exited the SaaS application, methods to ensure they can read the extracted data must be established. Options include the following:

- If the SaaS provider offers a purchased software version of the application as an alternative to the SaaS subscription offering, the regulated company may be able to install the purchased version on-premise to read the data.
- The data could be converted to be read in an alternative application. However, this approach brings with it the risk of loss of metadata or functionality (especially for dynamic data) and would require data migration verification.
- If there is no other alternative, the regulated company may need to keep a reduced subscription to the application for the purposes of readability of their existing data through their retention period.

Deleting data

Data may need to be deleted from a SaaS application (a) when a regulated company ends their SaaS subscription (after first extracting the data and passing it to the regulated company), (b) when data reach the end of their regulated retention period, and (c) in the case of personally identifiable information, when required to do so under the EU's General Data Protection Regulation [12] or other similar regulations.

Consideration should be given as to whether data will be deleted by the regulated company's authorized personnel or the SaaS provider's personnel under written authorization from the regulated company.

Data must be deleted not only from the live instance of the application but also from any archive areas and from backup copies residing in storage. It is unlikely that the regulated company personnel will be able to access and delete backup data; therefore, this task will probably require intervention from the SaaS provider. The SaaS provider may be required to provide an audit trail entry or other record of the deletion to the regulated company as evidence of the deletion.

CONCLUSION

The life sciences market offers SaaS providers a unique opportunity to positively impact public health and patient outcomes. Many nascent SaaS providers have enjoyed something of a honeymoon in this space, as a desire to adopt their technology has driven

many regulated companies to offset inherent compliance weaknesses through internal remediation efforts. As regulated companies' understanding of "as-a-service" delivery rapidly matures, providers must implement GxP processes or demonstrate that their processes are compatible with GxP to be competitive and maintain legitimacy in the regulated market.

Many of the regulatory requirements for computerized systems and software in the life sciences industry have their foundations in good engineering practices for IT controls. As we have shown throughout this article, the need to meet regulatory expectations should not, and need not, be viewed as an impediment to market. Rather, SaaS providers have an opportunity to increase product quality, ensure data integrity, and apply risk-based approaches and critical thinking to technology applications that fully support customers' therapeutic areas and patient safety.

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About the authors

Charlie Wakeham has been a passionate GAMP® volunteer since the early 2000s. She is currently Secretary of the ISPE GAMP Global Steering Committee and a member of the GAMP Data Integrity Special Interest Group Leadership Team. Charlie was awarded ISPE Member of the Year in 2019 for her volunteer activities within GAMP and for her training of health authority inspectors across Asia Pacific. Charlie is the APAC GxP Compliance Manager for Waters Corporation, where she leverages her industry knowledge to enhance Waters product positioning, marketing strategies, and technical collateral. She applies her computerized systems validation and data integrity expertise to drive continual improvements in the delivery of Waters CSV projects for Empower, NuGenesis, and UNIFI customers in the APAC region. Charlie has been an ISPE member since 1999.

Stephen R. Ferrell, CISA, CRISC, CDPSE, is Managing Director, Americas and Asia for CompliancePath. A recognized expert in regulatory compliance in the pharmaceutical, medical device, and biotech space, he was cofounder of CompliancePath, a Scottish and US compliance services company that supports regulated global clients. Stephen has held executive and senior level management positions with a number of technology firms in the life sciences. He has implemented quality management systems at several companies at both the corporate and divisional level and has hosted and conducted many audits across the GxP disciplines, ISO 13485 (inclusive of IEC62304/ISO14971), ISO 27001, SOC 1 & 2, EHNAC, HITRUST, and FEDRAMP. He is a member of the ISPE GAMP Steering Committee, former Chair of the Cloud Special Interest Group, and was the project lead and main author of the ISPE *GAMP IT Infrastructure Control and Compliance Guide*. He has been an ISPE member since 2008.

Loretto Vuolo-Schuessler is Senior Director of Computer Systems Quality at Syneos Health. This team provides support and consultation to internal and external business partners to assist them in meeting global regulatory and data integrity requirements for computerized systems. CSQ conducts internal and external computer system audits and supports audits and regulatory inspections that focus on computer systems. Lorrie has been involved with ISPE and the GAMP Community of Practice leadership since 2002. She is currently Chair of the GAMP Americas Steering Committee and a member of the GAMP Global leadership team. She has been driving the data integrity efforts within GAMP as the Co-Chair of the GAMP Data Integrity Special Interest Group that developed the ISPE *GAMP Guide: Records and Data Integrity*, *GAMP RDI Good Practice Guide: Data Integrity–Key Concepts*, *GAMP RDI Good Practice Guide: Data Integrity–Manufacturing Records*, and *GAMP RDI Good Practice Guide: Data Integrity by Design.* She has been an ISPE member since 2002.

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Name: Susan Sandler
Addr 1:6110 Executive Blvd.
Addr 2:Ste. #600
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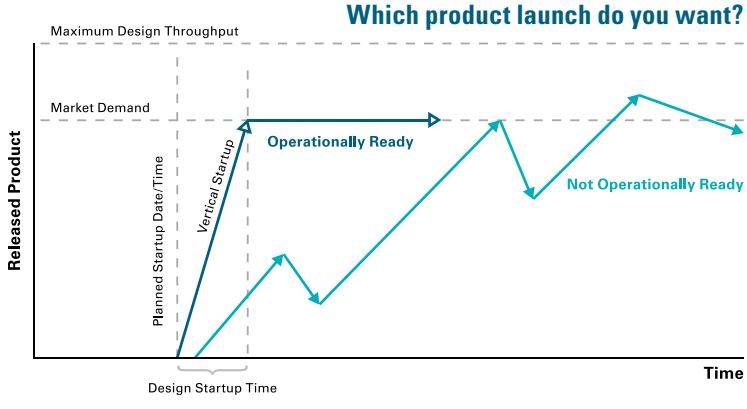

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