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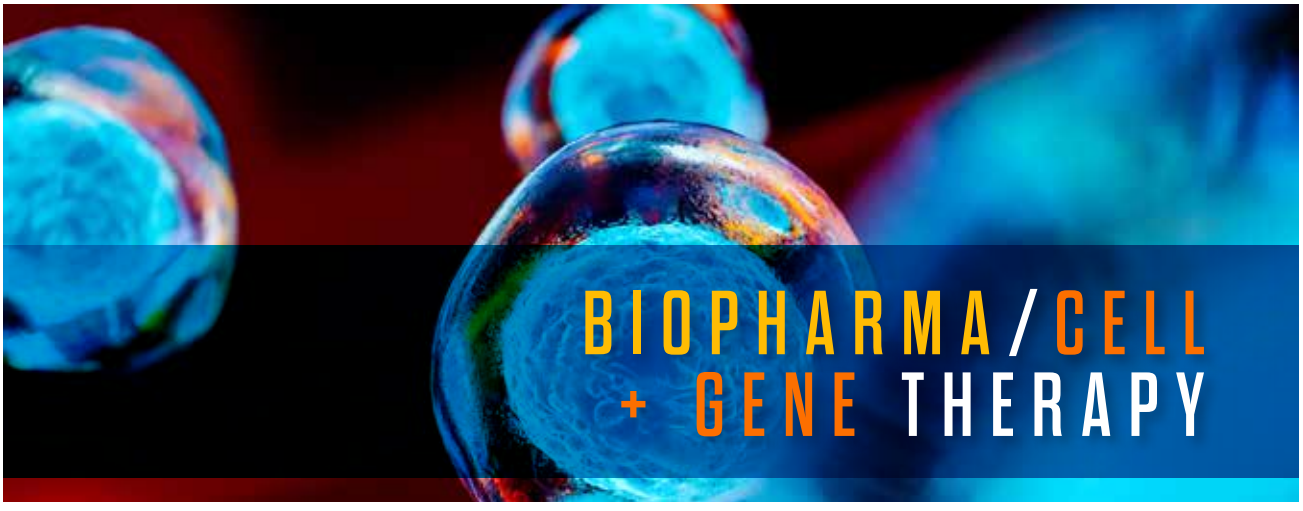

ON THE COVER A colorful rendering of embryonic stem cells illustrates the bright future of gene therapy.

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PHARMACEUTICAL ENGINEERING

Volume 40, Number 6
Published since 1980

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

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ISSN 0273-8139

Pharmaceutical Engineering is published six times a year by ISPE and is online at ISPE.org/Pharmaceutical-Engineering

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Stock Photography and Illustration
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Art Direction and Graphic Design
THOR Design, Inc., www.thor.design

Printing
Royle Printing

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Periodicals postage paid at Tampa, Florida, US, and additional post offices

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By Frances M. Zipp


Frances M. Zipp

That Was The Year That Was

Given the events that have transpired over the last 12 months, I have penned the title of my final column as ISPE Chair to reflect the temperament of our times. Coincidentally, and please pardon my digression, the title also happens to be the name of a hit album of topical songs by Tom Lehrer, recorded live in July of 1965 at the "Hungry I" nightclub in San Francisco, California.

As the album title implies, the songs were commentaries on events that transpired during that particular year. There were many. And they had profound impact. For the record (no pun intended), "That Was the Year That Was" peaked at number 18 on the Billboard Top 200 Albums list on January 8, 1966, and stayed on the charts for almost a year—51 weeks to be precise.

Ironically, 55 years later, it often seems like, as many of Tom Lehrer's songs acknowledge, the more things change, the more some things tend to stay the same. Our world has continued to see its share of dramatic changes over that time span, most notably in the last 12 months. And during my year as ISPE Chair, change has certainly impacted our organization.

ABOUT THIS YEAR

As I prepare my last column as Chair of the Board of Directors of ISPE, I reflect on our activities as well as some of the things at ISPE that have changed during my time as Chair, and some that remain the same.

As one of my first initiatives, I achieved a personal objective to spend "quality time" with our Chapters and Affiliates. In all, I participated in 10 of their meetings, from the end of 2019 and up to March 2020. I greatly appreciate the vision of the international group and to have learned of the good work of these many Chapters and Affiliates. I had the opportunity to get to know their teams and to gain perspective from their thoughts and comments on the life sciences in general and, more specifically, about ISPE and the role we all can play in keeping it vibrant and relevant. These visits, our interactions, and the information they provided helped me gain a greater understanding of how ISPE can continue to add value and, most importantly, thrive during these most challenging times and in the years ahead.

I am pleased to report that one thing that has not changed is our members' outstanding dedication and ongoing contributions to the future success and growth of our organization. We remain as strong today as when I first assumed my responsibilities. In many ways, even stronger.

THE NEW NORMAL

Then, in early 2020 our world changed… and virtually all travel stopped. Our ability to deliver against our plans was challenged, but our commitment remained steadfast.

We regrouped and learned that reaching out to each other and to our community was of paramount importance. In offering support to our colleagues, we learned how to connect remotely, and although our skills were put to the test, we learned how to be

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part of a broader community and grew stronger as a result. We continued to advance our efforts on the Workforce of the Future and our Strategic Plan and realized, now more than ever, the vital need for robust programs to address the rapidly changing way we work.

Additionally, many of us relied on some of our basics—those we learned over the years as ISPE guidance document contributors and recipients of the insights they contain. We worked on adjusting our manufacturing processes to meet the needs of accelerated availability of key product to the market. We applied our knowledge of quality systems and risk mitigation, and systems configurations and controls, to assure that speed to market was much more than a business imperative—it was a matter of quality of life.

With ISPE acting as our unifying "family," we joined together to support each other in addressing the issues our industry faces. Via webinars, we have shared ways to develop work plans remotely and focused on innovative technologies, turning our attention to vaccine development and commercialization in order to combat the current pandemic. We worked within our regulated network and reviewed the many recently published guidance documents issued by our local regulators to assist industry and healthcare providers during this time. The efforts and ingenuity of our pharmaceutical sector came together to provide diagnostics, vaccine candidates, and therapeutics to help the many healthcare systems combat and control the spread of the SARS-CoV-2 virus.

Over the last 12 months, we have also experienced a number of changes to our team—the appointment of an interim President and CEO, a new President and CEO leaving a reduced Executive Committee of ISPE, and the need to elect both a Secretary and Treasurer to the Executive Committee of the Board of Directors. Our members supported this challenge and we again have a complete and dedicated Executive Committee and Board of Directors, representing our diverse and dynamic membership.

Finally, a most heartfelt "THANK YOU" to everyone who I have had the opportunity to work with during my tenure, to those who have generously supported my efforts, and to the many who have helped advance our organization through these most challenging of times. It has been a testament to both our strength as a team and our commitment to our industry. This pandemic has brought us together, reenergized our mission, and proved to be influential to each of us in a most personal way. Everything about business is personal—2020 reinforced this in so many ways.

My, what a year it has been.

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

By Alice Redmond, PhD


Alice Redmond

A YEAR OF Mentoring, Education, and Collaboration

2020 has been a super-busy year for ISPE Women in Pharma® (WIP). We started 2020 with aggressive goals, including to set up global Mentor Circles; start a monthly WIP newsletter, *The Bridge*; and begin a column in *Pharmaceutical Engineering*®. WIP has met and exceeded goals across all the key initiatives.

I am going to reflect on a few goals that really resonate with me. I am passionate about many things: mentoring is very high on the list! WIP met its 2020 goal of developing 20 Mentor Circles in 2020. Mentoring is fundamental to personal and career development. It ensures important skills and knowledge are passed on within the Mentor Circle. Supportive relationships and friendships are formed. Mentors give objective advice and constructive feedback, are usually well connected within their arena, and the mentorship becomes mutually beneficial and personally rewarding for both parties.

Mentor Circles are a fantastic way to promote growing relationships and career development. They consist of about 10 women and men who meet four to six times each year, either face-to-face or virtually. These small groups spend half of their time together networking and the remaining time discussing relevant technical and career advancement topics. Guest speakers and subject matter experts support the circles. Mentor Circle participants are encouraged to network outside of official meetings and use tools such as LinkedIn groups to support friendship, collaboration, career development, and relationship growth. We estimate we will have five more Mentor Circles by the year's end: hurry up and join! The WIP page on the ISPE website (ispe.org/women-pharma) has more information.

WEBINARS AND NETWORKING

Our WIP webinars and networking events have had a global transverse impact in a way we could not imagined. This would have not happened if we did not have the torment of COVID-19!

The ISPE United Kingdom Affiliate's WIP webinar series has provided some very interesting topics, including "Fear, Focus, and Fruitfulness," "Tips to Keep Focused in Challenging Times," and "The Three Pillars of Structure, Trust, and Communication." The ISPE Carolina–South Atlantic (CaSA) Chapter's WIP group has had a busy few months with a number of virtual Lunch & Learns on our changing work environment during COVID-19, including "Leadership & Strategies for Teams" and "Transform and Empower Yourself." A CaSA webinar focused on diversity, inclusive behaviors, and mentoring. It was a huge success, with more than 100 global attendees.

The ISPE Brazil Affiliate hosted two webinars on "Neuroscience and the Return to Work Post-Crisis" in Brazil's native language, Portuguese, and "Clinical Trials and COVID-19"; the latter had more than 70 attendees. We had great collaboration between the ISPE Los Angeles Chapter WIP and Young Professionals (YP) groups to host a very lively webinar on "Navigating a Career in Pharma During COVID-19." The ISPE Ireland WIP group has hosted a number of sessions, including "Navigating the Virtual World in Business," "Building Your Personal Brand and Executive Presence," and "Single-use Technology," with attendees from both Ireland and elsewhere in the EU.

GETTING INVOLVED WITH WIP

The ISPE WIP Community of Practice (CoP) is a great venue for sharing information, asking questions of your fellow WIP members, and posting items of interest to the WIP community. If you have not yet joined, be sure to do so today! We challenge those who are engaged with WIP to spread the word: reach out to colleagues and friends who may not be aware of this initiative.

We have had a year of connectivity. Our July event, Sunrise to Sunset, was amazing and truly connected our ISPE community. Our Chapter and Affiliate events have more global attendees at each one. Our ISPE WIP brand and community have grown from strength to strength. and we should be very proud of this ISPE initiative. Let's make sure we plan to innovate, grow, and expand further in 2021.

Alice Redmond, PhD, is WIP Steering Committee Chair for Europe, a member of the ISPE International Board of Directors and the ISPE Foundation, and Vice President, Europe Operations, at Commissioning Agents, Inc.

By LeAnna Pearson Marcum


LeAnna Pearson Marcum

FROM YOUNG PROFESSIONAL to Emerging Leader

As this is my last Young Professional (YP) column for *Pharmaceutical Engineering*®, I wanted to start with a quote from Winston Churchill that I feel summarizes my two-year journey as the International YP Chair: "Success is not final, failure is not fatal: it is the courage to continue that counts."

When I started this role two years ago, I thought that I would run the YP Community of Practice (CoP), attend the International Board of Directors meetings, keep quiet, and just absorb all that was going on around me. Was I way off base! This was a deeply personal and professional learning and leadership opportunity that was disguised as an ex offico board member role. I will answer some of the questions I have received during these two years.

What was it like being on the board?

The ISPE Board of Directors is possibly one of the most selfless sets of individuals I have ever had the pleasure of working with. They got to where they are in life by working hard, sacrificing their personal and family time, and consistently pushing new initiatives and ways of thinking. When I first started working with the board, it was a bit intimidating, but I quickly realized that they are people and they are there to provide help and guidance, and push me to be better. I can never thank them enough for all they have taught me.

Being on the board taught me lessons that many do not have an opportunity to learn or even witness until they are in the C-suite level of their career. I was supported and welcomed from the start. Many assume it is all just budgeting and patting each other on the back for a job well done, but it is so extremely far from that. ISPE is a large multinational, complex, and hard-working organization. The board discusses the hard topics and the topics that push ISPE to grow, evolve, and be the go-to organization for the pharmaceutical industry. To be a small part of that and to witness it was a growth opportunity I could never put a price on.

> My role was to be an advocate for the YPs worldwide.

What was it like be in an international leadership position?

In one word: humbling. My role was to be an advocate for the YPs worldwide, to bring their issues to the larger stage, and ensure that I pushed initiatives that would allow this CoP to continue to evolve and grow long after I am gone. I have had the honor of working with YPs from around the world. They have shown me new approaches and ways to think. I learned how to take an initiative and apply it to an international audience, take cultural roles into account, and tailor items to fit for all, which is not an easy task.

How do you have time do this?

You make time for what is a priority in your life at that time. I made the time, early mornings and late nights, and missed time with my family to be at conferences or meetings. I have zero regrets about any of this. I had to balance this role with my job, because ISPE is not my job nor is it anyone's full-time job on the board.

Advice for future leaders

Take the leap, and jump in with both feet! You might have some small failures along the way, but the growth will far outweigh any bumps. The individuals you will meet will become your friends, family, and mentors throughout life, and that is a value you cannot ever put a price on.

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

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CELL AND GENE THERAPY FACILITY DESIGN

Using Simulations

By Niranjan S. Kulkarni, PhD

Designing new facilities for cell and gene therapy manufacturing is a challenging task given the many uncertainties in this industry sector, including varying potential demand for any given new therapy, evolving platforms and technology, questions about equipment reliability, learning curves for analysts and operators, possible sourcing issues, and variable lead times for key raw materials. All these factors influence facility sizing, equipment quantities, required head count, and the flow of people and materials. One approach to managing these uncertainties at the facility design stage is to develop operational models and perform computer simulations. The information generated via these simulations enables management to make data-driven decisions.

The number of cell and gene therapy treatments in development has increased exponentially in recent years. While cell therapy had a larger market segment than gene therapy in 2018, gene therapy products are likely to replace or outpace several cell therapy products and account for more than 50% of market share by 2024 [1]. The global gene therapy market size in 2019 was estimated at USD 1.2 billion. It is projected to register a compound annual growth rate of 16.6% from 2020 to 2027 [2]. These therapies are mainly driven by the potential exhibited by chimeric antigen receptor (CAR) T cell usage and have gained significant attention from commercial and noncommercial sponsors.

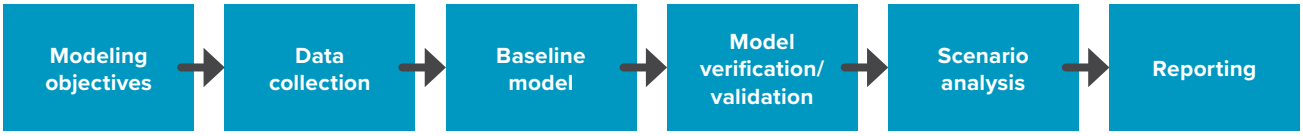
These therapies are produced in a range of settings, from laboratory-scale to full-scale facilities, with most processes involving highly manual operations. As these therapies move toward commercialization and volume demands increase, current practices and technologies will need to be modified. New facilities will also be needed to implement larger-volume manufacturing.

OPERATIONAL MODELING AND SIMULATIONS

Computer modeling and simulations from an operational perspective improve general understanding of the manufacturing process and support the development of optimal facility designs. The field of computer modeling and simulations is broad and can include discrete event simulations (DESs), process modeling, computational fluid dynamics, building information modeling, augmented reality and virtual reality, and other approaches. This article focuses on the use of DES only. A list of commercially available computer modeling and simulations tools is provided in reference 3.

Figure 1 shows the overall methodology for a discrete event modeling and simulation study. The first step is to define precise modeling objectives and identify both the metrics supporting these objectives and potential scenarios to be analyzed. Though this step may seem trivial, it is very important and can influence the study duration and budget.

Figure 1: Typical modeling and simulation study methodology.



For a facility design effort, the primary objective is usually to "right size" the facility to help satisfy patient demand in the most cost-effective manner. Right-sizing involves estimating equipment, personnel, utilities, site logistics (material/personnel movement), and spaces for production, raw material, intermediate and finished goods staging, and support functions (e.g., warehousing, quality assurance [QA] and quality control [QC], maintenance, and administration). These operations and functional areas influence and are influenced by the facility footprint.

For facility design problems, simulations should ideally be performed at the concept or even the feasibility stage to determine whether the right type and size of facility is being considered. Companies looking to modify existing facilities also need this information to make the right decisions when evaluating their options.

After the objectives and metrics are established, relevant supporting data must be gathered to develop a baseline model. As with any simulation, the model will only be as good as the data inputs used to build it (garbage in = garbage out). Because most cell and gene therapies remain in clinical stages and are yet to be produced at commercial scales, data collection efforts will rely on inputs from subject matter experts and laboratory research data. Assumptions must be established. To characterize the uncertainties involved, it is highly recommended to use a range of values instead of using average values or point estimates. Whenever possible, actual data should be used and fit to statistical distributions to capture the variability influencing operations.

Models developed using the DES technique, a special case of Monte Carlo simulations and the time-advance mechanism, are best suited to capture these variabilities and uncertainties because they can randomly select input data from a predefined statistical distribution, run multiple replications, and perform "what-if" analyses. Since the inputs are probabilistic, the outputs will also be stochastic in nature. This allows end users to make decisions based on their appetite for handling risk.

Recent advancements in computing power and graphics have improved visualization capabilities of these models. Figure 2 shows a screenshot of a DES model. Appropriate animation and visualization help in model verification and improve communication and stakeholder buy-in. The 3D animations can help designers better visualize traffic within key corridors, any congestion points, adequacy of intermediate staging spaces, appropriate adjacencies needed, and other factors.

Figure 2: DES models help characterize uncertainty and variability inherent to the operations, while helping visually communicate the results. (Source: CRB.)

The baseline model results must be verified and/or validated to ensure the model is behaving as intended. At this step, assumptions may be fine-tuned, or additional data may be required to more accurately mimic the process that is being modeled.

After completing the verification/validation phase, the model can be used to perform scenario analysis to determine how changing different variables affects the modeled metrics. Sensitivity analysis can also be performed to identify variables or assumptions that influence the design metrics.

These verified/validated models can serve as excellent tools for identifying bottlenecks and key areas of concern. This information can then be used to develop risk mitigation plans to help manage the uncertainties associated with the design and construction of facilities in an emerging field.

CASE STUDY

The study objective was to design a facility to satisfy a desired throughput rate while achieving an optimal cost of goods (COGs). To meet the desired demands, it was important to estimate equipment and direct (and indirect) labor needs for manufacturing, QC, and support functions. Additionally, logistic plans and warehousing and storage needs had to be established. As mentioned earlier, all these attributes influence facility sizing. Although raw materials and labor are the highest contributors to the COGs, followed by equipment, the study focused only on labor and equipment because in most cell and gene therapy production, the facility must scale out rather than scale up.

Figure 3: Output of the sensitivity analysis to establish the number of platforms per suite.

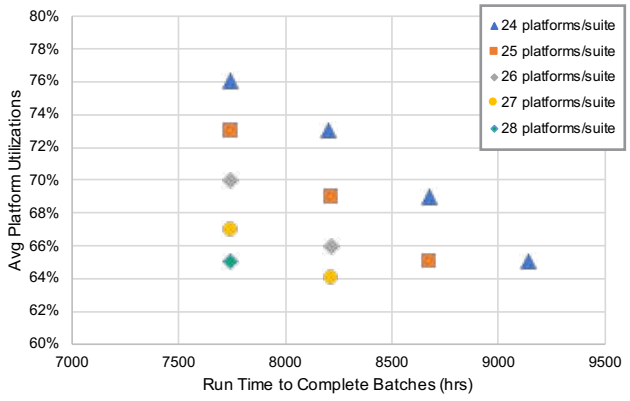


Table 1: Total gowning time per employee versus capacity per area.

Capacity (no. of people in the space)			Performance Metrics (minutes)	
Locker Room	Grade D	Grade C	Average Lead Time	Maximum Lead Time
8	10	10	17.1	20.7
9	5	9	16.6	19.3
10	5	9	16.3	18.4
10	5	8	16.5	18.8
10	4	8	16.5	18.8
10	4	7	16.9	20.2

To make the most-effective facility decisions, key workflows and relevant data were collected for manufacturing operations, QC, and supply chain requirements. Assumptions were carefully documented, and a baseline model was developed using these inputs and assumptions. The model was used to make key decisions regarding the number of suites as well as the number of platforms (sets of specialized pieces of equipment and technology) to be installed per manufacturing suite. The platform is considered critical in the value stream based on the cycle time and the equipment cost. Given that the technology is new and not fully vetted, expecting higher production utilizations would also be unrealistic. Time had to be allotted for training and other (unforeseen) events.

Sensitivity analysis was performed to identify the best combination of acceptable utilization, batch cadence, and quantities of equipment needed to meet the target demands within the given time frame. Figure 3 shows the graphical output of this analysis. The sensitivity analysis revealed that the annual demands cannot be satisfied if the run time exceeds approximately 8,500 hours.

The model was also used to simulate several scenarios, such as simulations to:

- Level load work and understand the extent of cross training required to avoid additional head count
- Assess waste handling strategies
- Justify certain automation in QC to reduce turnaround time, head count, and equipment needs

While the study looked at optimizing equipment and head count, key space types (e.g., gowning areas) were also right-sized. Though gowning is essential, time spent in gowning should be considered as essential non-value-added time, and reducing this time is recommended [4]. However, adding more gowning space and maintaining it can be cost prohibitive. Thus, it is important to strike the right balance between gowning time and the investment and operating expenses for maintaining large gowning spaces. Table 1 shows the results from the simulation analysis that aimed at reducing the overall lead time for operators (i.e., the time spent per operator to change from street clothes to gowning requirements to enter Grade C space) as a function of room occupancy.

CONCLUSION

Operational simulations are a powerful tool to help estimate the resources required to influence space needs and facility size. Though it is important to study the main production systems, the study should also include support functions, such as QA/QC and warehousing. In addition to equipment, head count, and space needs, these models can also help right-size intermediate staging spaces, develop waste handling strategies, ensure adequacy of utilities, and so on. Operational simulation studies should be undertaken at the early stages of design.

Because models can only be as robust as the data used to construct them, excellent communication with subject matter experts and accurate documentation of inputs/assumptions are critical components of operational simulation. The right questions must be asked to ensure that the right data are obtained and that the model will address the users' needs. It is essential to translate and communicate the underlying algorithms in a manner that can be understood by the people providing the data on which the model will be based. Communicating the results generated by a simulation in a manner that the stakeholders and end users understand is equally important.

As mentioned earlier, operational models built using the DES technique help characterize the impact of variability and uncertainty. However, running multiple replications is the key to success with these models. Each replication selects unique values from the statistical distribution, allowing the model to capture the entire range. Selecting the correct number of replications is also important to avoid increasing the overall model run time.

Like quality documents, simulation models should be considered as living documents. These models can also be viewed as digital twins of an actual facility. Before making one or more significant changes to a facility or an operation within it, simulations can

be run to determine the impact of the changes and develop strategies to overcome any adverse situations.

Once any change is made to a facility design, it is important to modify the model to reflect that change (i.e., create a new baseline). The simulation can then be rerun to confirm that the desired result was obtained. Updating the model is also essential so that it continues to reflect the current state of the facility. Whenever additional actual data that can inform the model are obtained, the data should be added to the model. This ensures that the model's performance and prediction accuracy improve. For instance, once the facility has been constructed and is in operation, actual data on the process cycle time for a particular step can be fitted to a probabilistic distribution and used to rerun the analysis.

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Acknowledgment

Sincere thanks to all the reviewers who helped enhance the content of this article.

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FLEXIBLE FACILITY DESIGN

for Multiple Cell Therapy Processes

By Daniel L. Swanson, PE

In many critical ways, the design of facilities for multiple cell therapy processes is unlike the design of conventional pharmaceutical facilities. This article surveys several of the key issues to consider when designing facilities capable of manufacturing multiple cell therapies, including regulatory definitions, product life cycles, processing systems, relevant cell therapy technologies and equipment, biosafety, cross contamination, facility automation, and layout options. A case study is used to illustrate flexible cell therapy facility design.

The field of cell and gene therapy has come quite a long way since Friedmann and Roblin authored the paper "Gene Therapy for Human Genetic Disease" in 1972 [1]. The first approved gene therapy clinical research took place in the US under the direction of William French Anderson at the National Institutes of Health (NIH) in 1990 [2], and the field has only accelerated since. Through the 2000s and 2010s, numerous advances were achieved in the treatment of cancers and other genetically driven diseases. Most recently, US FDA approvals of cell therapies from Kite Pharma (YESCARTA) and Novartis (KYMRIAH) have shown the power of cell therapies to treat cancers [3]. Reading through the history of cell and gene therapy in the context of manufacturing facility design, it becomes increasingly clear how important it is to understand what these therapies are and how they are defined. Common questions for those new to the field are: What are cell therapies? Why do people refer to cell and gene therapies together? The answers are everyone's least favorite response, "Well, it depends!" In this case, it depends on who you are asking.

The US FDA and the EMA define cell and gene therapies differently. The EMA calls them "advanced therapy medicinal products" (ATMPs) [4], and the FDA calls them "human cells, tissues, and cellular and tissue-based products" (HCT/Ps) [5]. Each regulatory body then provides more precise categorizations (Table 1).

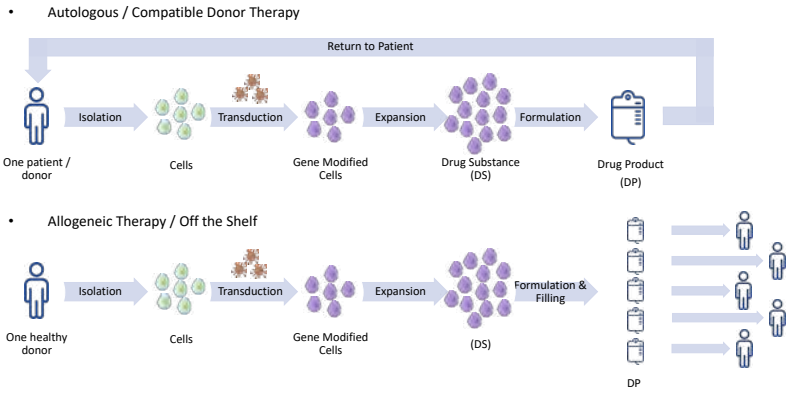
Generally, cell therapies grow cells outside the body and implant whole live cells for a therapeutic benefit. These cells can either be taken from the patient (autologous) or from a donor (allogenic). Cells used for cell therapy are often stem cells (cells that can mature into different types of specialized cells), and they may or may not be genetically altered.

Gene therapies, on the other hand, modify the genes of cells for a therapeutic benefit. This can happen by replacing a disease-causing gene with a healthy copy of the gene, inactivating a disease-causing gene that is not functioning properly, or introducing a new or modified gene into the body to help treat a disease [6]. Gene therapy can be either in vivo (inside the patient) or ex vivo (outside the patient).

Table 1: Key FDA and EMA definitions related to cell and gene therapies.

Agency	Term	Definition
US FDA	Gene therapy	Modifies the genes or cells for a therapeutic benefit.
	Cell therapy	Grows cells outside the body and implants whole live cells for a therapeutic benefit.
	Autologous	The source of the cells is the same as the subject to be treated.
	Allogenic	The source of the cells is different than the subject to be treated.
EMA	Gene therapy medicines	Contain genes that lead to a therapeutic, prophylactic, or diagnostic effect. They work by inserting recombinant genes into the body.
	Somatic cell therapy medicines	Contain cells or tissues that have been manipulated to change their biological characteristics or cells.
	Tissue-engineered medicines	Contain cells or tissues that have been modified so they can be used to repair, regenerate, or replace human tissue.

Figure 1: Cell therapy life cycles.



Cell and gene therapy technologies are lumped together because they are linked by commonalities of scientific procedure. For example, several of the leading cell therapies use gene editing methods to make the cells have therapeutic value. In the US, an engineered cell product such as a chimeric antigen receptor T cell (CAR-T) therapy would be called a cell therapy because cells are what is administered to the patient. In the EU, CAR-T therapy is considered a gene therapy because genetic engineering provides the activity to the cells.

CELL THERAPY LIFE CYCLE

Understanding the life cycle of a specific cell therapy is essential when taking a holistic approach to facility design. In the case of genetically modified autologous therapies, such as CAR-T therapies, there truly is a cycle (see Figure 1). First, cells are isolated from a single patient in a clinic through apheresis (similar to a red blood cell donation). Next, the patient materials are tagged clearly with patient information and either chilled or frozen and shipped from the clinic to a manufacturing facility. Upon arrival, the patient material is washed and select cells are isolated and then genetically modified. The genetic modification is typically performed using a viral vector (e.g., adeno-associated virus [AAV] or a lentivirus); however, other technologies—such as mRNA (or other RNA), cleavage enzymes (e.g., TALEN or CRISPR), and others (e.g., Cas-CLOVER, zinc finger)—are being explored. Once the genetic modification has been performed, the cells are expanded to a therapeutic quantity, concentrated, formulated, filled, and shipped back to the clinic for administration to the same patient.

This is obviously a complicated supply chain and requires close attention to track specific patient materials [7]. Cold chain and traceability should be considered as part of the facility design, and special precautions should be taken to avoid the mixing of autologous materials. Many patients who are receiving these autologous treatments are incredibly sick, and they may only have time for one cycle that could last from three to four weeks. In this scenario, patient cells essentially become the patient. To drive that point home, some companies put the patient's name on the cells throughout the process. When designing a cell therapy facility, it's important to keep this larger picture in mind as well.

In the case of allogenic therapies, the process is similar, but the source materials vary. The major difference is that the starting cells come from donors or, in some cases, a cell bank. The therapy is not necessarily individualized to a single patient, and the same lot can potentially be used to treat a number of patients. The process resembles more of a straight line than a cycle, but cold chain and traceability remain important.

CASE STUDY

For many emerging cell therapy companies, a popular strategy is to use a contract manufacturing organization (CMO) to handle the product through clinical trials in one facility and then transfer operations to a newly built manufacturing facility for commercial production. On a recent project, IPS worked with a CMO that was looking to expand and improve their cell therapy manufacturing spaces. CMOs need to be able to adapt to changing markets, customers, and customer needs. As such, the CMO project team had three major facility design goals:

- The facility will be flexible enough to handle multiple products.
- The facility can handle both autologous and allogenic products.
- The facility can handle both open and closed processing.

These goals are important aspects of designing a single facility for multiple cell therapy processes. Relevant questions include "What specific aspects of the unit operations need to be considered?" and "What process risks need to be considered?" To answer these questions, a strong understanding of what the processes might look like is needed. In this case, most processes likely fall within one of the following three categories:

- Straight cell expansion: A sample of cells, whether it be autologous or allogenic, is grown to a therapeutic dose. An example could be a stem cell therapy.
- Cell processing and filling facility: This operation is similar to a straight cell expansion, but there are some extra processing steps along the way. Considerations also need to be made for aseptic filling on site.
- Multistep aseptic microbiology process: This process involves intensive manual manipulation, with most steps performed within a biosafety cabinet (BSC).

OPEN VERSUS CLOSED PROCESSING

With regard to facility design, one of the biggest considerations of the manufacturing process is whether it operates in an open or closed fashion. Cells in an open process are exposed to operators and the surrounding environment, and high-grade air supply is required. Cells in a fully closed process are never exposed to the surrounding environment. On the other hand, functionally closed systems are routinely opened and then returned to a

closed state via sanitization, cleaning, or sterilization prior to product contact. Closed processing is typically achieved with single-use pathways. However, isolators can be used where a single-use option does not exist.

Open Processing

According to US FDA guidance [8], open aseptic processing should be performed in a Grade B environment (e.g., a BSC), which is typically in a Grade C surrounding environment. Concurrent open processing of different batches may occur in different workstations in the same suite by dedicated operators [9], but only under strict operational controls:

- The use of a suite must be based on campaigns (same viral vector).
- Work spaces must be operationally segregated.
- Operators must be dedicated to a workstation (no patient material cross flow).
- Only one patient batch can be used in each BSC.
- Proper line clearance/changeover procedures must be followed after each processing step.

These requirements cause big challenges in scaling the process out. The facility is limited by the number of BSCs and the segregation methods employed. While scale-up is an issue, open processing does come with a major advantage: there is little need for change between the laboratory-scale and commercial-scale processes.

From a facility design perspective, the following challenges need to be considered:

- The need to design processing suites for a Grade B background.
- The volume of material movement between BSCs, incubators, and other operating steps.
- Operator quantity and variability. With largely manual processes, the techniques of different operators vary enough that consistent product quality can be difficult to achieve.
- The difficulty of defining a boundary for cleaning and decontamination.
- Additional environmental monitoring (EM) requirements at the BSCs and for personnel and surfaces at the end of operations, batches, and/or campaigns.

Fully Closed Processing

Closed systems typically utilize single-use equipment and tubing sets; all material transfer is through presterilized tubes connected by sterile aseptic connectors, or with connections made by a tube welder. Safeguards such as HVAC design and room changeover procedures must be in place for operator safety and cross-contamination mitigation in case the system is breached. Scale-up to commercial scale is typically much easier in closed systems than in open ones, and closed systems are less reliant on operator technique. Although closed systems certainly involve a higher initial investment in terms of development time and equipment costs, they may reduce manufacturing costs because they have lower room classification requirements, require fewer operators, and have a smaller cleanroom footprint.

Functionally Closed Processing

Functionally closed systems operate in much the same way as fully closed systems, but they have one or more routine operations that require the process to be opened (installation of a filter, making a connection, etc.). Once the open operation is complete, the system is returned to a closed state by sterilization, sanitization, or cleaning before any product contact occurs. A risk assessment can be used to determine if and when open steps are at an acceptable risk level to be considered appropriate within a given environment.

CELL THERAPY TECHNOLOGIES

The next part of the process that needs to be considered is what technologies are being used. This decision will drive whether the system will be open or closed. There are numerous suppliers for each unit operation, with some of the many vendors listed in Table 2.

One of the first considerations is whether an end-to-end cell processing platform will be used, or whether separate unit operations will be selected. End-to-end systems have advantages such as being closed and modular, but they can be relatively expensive, and, in some instances, having all unit operations combined can cause bottlenecks.

If separate unit operations are required, additional questions must be posed:

- Is an adherent or suspended cell culture being used?
- What is the scale of the cell culture process? This decision will drive whether a T-flask, cell stack, cell factory, or bioreactor makes sense.
- What transfection technologies are being employed? Certain technologies, such as flow electroporation, are currently incompatible with closed processing.
- Is a stabilizer added before product filling and freezing? If so, will it necessitate a quick formulation, filling, and freezing operation?
- Is a filling step required as part of the process? Will an open vial or closed vial technology be used? How many containers need to be filled? Will it be a robotic filling operation or a manual operation?

These decisions will drive containment and facility segregation requirements. Understanding the process equipment intricacies and limitations is essential to ensure the facility is designed with enough flexibility to handle each scenario. Bear in mind that this list of questions is not all encompassing, and each process must be examined thoroughly to determine specific requirements.

MANAGING RISKS AND BIOSAFETY

Many traditional biologic therapies, such as monoclonal antibodies or recombinant proteins, are small enough that they can be sterile filtered (0.2 µm) prior to filling. That is not the case with cell therapies, as they cannot be terminally sterilized. Because of the relatively large size and fragility of cell therapies, typical sterilization techniques such as filtration, heat, or ultraviolet light are not options. It is easy to forget these therapies are living cells. Therefore, aseptic processing is required to ensure product safety,

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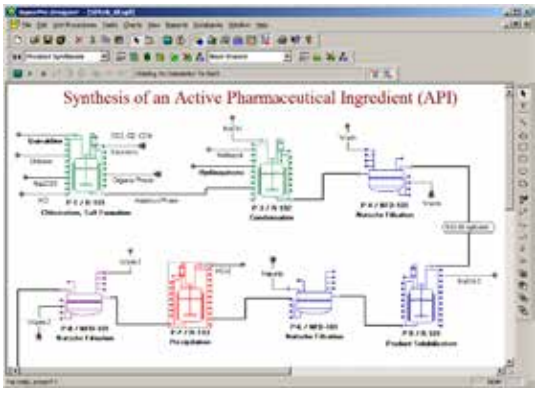

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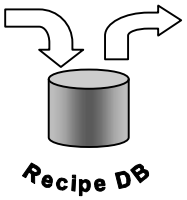

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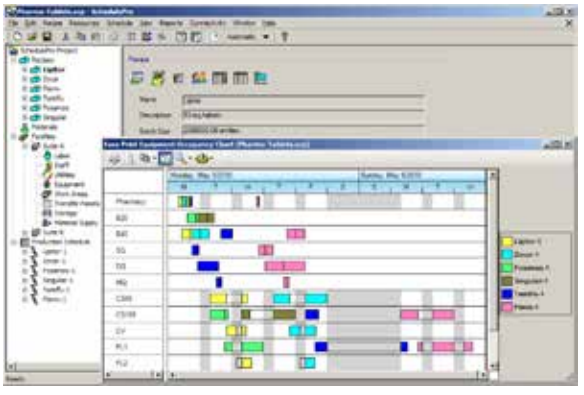

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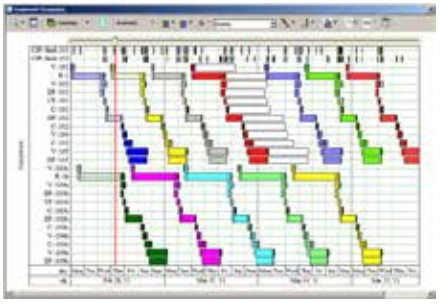

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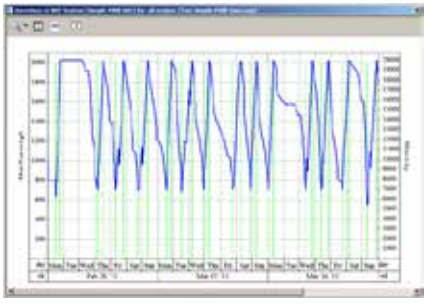

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Table 2: Cell therapy technologies and equipment.

Area of Operations	Technology/Operating Principle	Vendor/Technology Examples
Leukapheresis/apheresis	Centrifugation	Terumo BCT: Spectra Optia Blood Bank Equipment
Cell processing	Immunomagnetic	Miltenyi Biotec: CliniMACS Plus Miltenyi Biotec: CliniMACS Prodigy AdvaBio: Adva X3
	Microfluidic	GPB Scientific: Curate
	Centrifugation	Cytiva: Sefia S-2000 Cytiva: Sepax 2 Cytiva: Sepax C-Pro Fresenius Kabi: Lovo Terumo BCT: ELUTRA Terumo BCT: COBE
	Electroporation	MaxCyte: GT, STX, or VLX Lonza: Nucleofector
	Acoustic cell retention	Draper (system name to be determined) FloDesign Sonic (Millipore Sigma): ekko
	Immunodensity cell separation	Reagent based with centrifugation
Adherent cell culture	2D	Corning: Cellcube Corning: HYPERStack ThermoFisher: Nunc Cell Factory Wilson Wolf: G-REX Terumo BCT: QUANTUM Pall: Xpansion Cytiva: Xuri
	3D matrix	Octane Biotech: Cocoon Pall: iCELLis
	Microcarriers	Pall: SoloHill Cytiva: Cytodex
Freezing/thawing	Controlled rate freezing/thawing	Cytiva: VIA ThermoFisher: CryoMed Sexton Biotechnologies: Cell Seal Thaw
Filling	Open	Sexton Biotechnologies: Cell Seal AF-500 Sexton Biotechnologies: Cell Seal SAFS-100 Aseptic Technologies: M1 Aseptic Technologies: L1/SL1
	Closed	Terumo BCT: FINIA Sexton Biotechnologies: Signata CT-5
Cell storage	Liquid nitrogen	Cryotherm Brooks Life Sciences

especially for injectable drugs, and the use of closed manufacturing systems is encouraged wherever possible [8].

Cold and cryogenic shipment, receiving, and tracking are very important to maintain starting material viability. The expression and nature of biomolecules and factors that are present in apheresis collections for cell therapies are not currently well defined and measurable; as a result, these materials are fragile and sensitive to changes in cold chain procedure. Other dangers include humidity, shock, and carbon dioxide ingress, which, in addition to temperature, could all have an effect on cell metabolic function during transportation. Traceability is also essential to ensure that products are supplied and administered to the correct patients. Facility automation and integration can help alleviate some of these challenges and reduce supply chain risks.

Table 3: Biosafety levels.

BL	Practices	Primary Barrier and Equipment	Facilities (Secondary Barriers)
1	Standard microbiological practices	None required	Laboratory bench and sink required
2	BL1 practices plus: • Limited access • Biohazard warning signs • "Sharps" precautions • Biosafety manual defining any needed waste decontamination or medical surveillance policies	Primary barriers: • Class I or II BSCs or other physical containment devices used for all manipulations of agents that cause splashes or aerosols of infectious materials Personal protective equipment (PPE): • Laboratory coats; gloves; face protection as needed	BL1 facilities plus: • Autoclave available emergency eyewash
2-Plus	BL2 practices plus one or more of: • Controlled access • Decontamination of waste • Decontamination of laboratory clothing before laundering	Primary barriers: • Class I or II BCSs or other physical containment devices used for all open manipulations of agents PPE: • Protective lab clothing; gloves; respiratory protection as needed	BL2 facilities plus: • Physical separation from access corridors • Self-closing double-door access • Exhausted air not recirculated • Negative airflow into laboratory

Biosafety of the facility needs to be evaluated during a biological risk assessment [10]. The risk assessment evaluates agent risk to both personnel and the environment, procedure risk, and appropriate risk management measures. Risk groups are an assessment of the agent, and biosafety levels (BLs) are the appropriate methods to control the risk (see Table 3). The NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules [11] state, "The institution shall appoint a Biological Safety Officer if it engages in large-scale research or production activities involving viable organisms containing recombinant or synthetic nucleic acid molecules." In this instance, large scale is defined as volume greater than 10 liters.

The agents that need to be considered with regard to biosafety are donor materials, cells from cell banks, and viral vectors. Donor materials need to be prescreened for bloodborne pathogens, or the facility must be designed to handle biohazardous materials. Cell banks need to be evaluated for biohazard level because some cell lines may contain carcinogenic materials. Additionally, if any viral vectors will be used during cell processing, the vectors must be assessed for biohazard level. It is common for cell therapy facilities to be designed to a BL2-plus level. However, BL2-plus is not actually a prescriptive safety level in the NIH guidelines [11]; rather, BL2-plus meets more than the elements of BL2, but less than those of BL3. These improvements are usually with regard to facility directional airflow or additional containment, which are not requirements to meet BL2.

CROSS CONTAMINATION

The single greatest driving factor for cell therapy facility design is the mitigation of the risk of cross contamination. What constitutes cross contamination? During cell therapy processes, the goal is to grow a single cell line. Contamination of another cell or viral vector from a different process or source could cause major problems in culture mediums, and these contaminations could seriously compromise the quality of the therapeutic product, potentially causing tumorigenic and immunogenic risks in patients if the contamination is not discovered. This is different than the other contamination risks considered in aseptic operations, such as bacterial and fungal contaminations.

As touched on previously, some of the major ways to prevent cross contamination are closed systems and single-use technologies. Other preventive measures involve risk mitigation associated with personnel, materials, waste, and product flows. The gold standard is unidirectional flows in a facility, where raw materials start at one end and products and waste come out the other. This is not always achievable because of the orientation of an existing space or economic constraints. Expenses such as a separate entrance and exit airlocks for processing suites, separate supply and return corridors, and so on can add up quickly. If perfect unidirectional flow is not achievable, a risk assessment is required to determine where the risk of deviating from unidirectional flow is small enough to be acceptable.

Another essential aspect of cross contamination that needs to be considered is HVAC design. Although the number of air changes present in Grade B cleanrooms (ISO 5 in operation) is higher than in Grade C cleanrooms (ISO 7 in operation), that does not necessarily mean that cross-contamination risk is lower in a Grade B environment. There are two major concepts to address: (a) isolation, where the focus is on keeping all the process components and materials within one architectural suite, and (b) segregation, where the focus is on separating facility air-handling units (AHUs) depending on risk assessment.

Isolation

First, considering isolation, potential contaminants are likely coming from outside the processing suite, so the room boundaries, which are airlocks, need to be considered (see Figure 2). Traditionally, the goal of airlocks is to keep cleanrooms clean, so clean air cascades across an airlock flowing from the clean side to the dirty side. In a multiproduct facility, a cascade design could potentially lead to the contamination of a shared hallway with the cellular or viral particles of a process. For this reason, a bubble and sink design is the best airlock design for multiproduct facilities. Bubble airlocks are pressurized to provide clean air to both sides of the airlock at the entrance of a cleanroom. Sink airlocks, on the other hand, pull air from both the cleanroom and shared hallway at the exit. The goal of this configuration is to isolate processing suites from one another. This is necessary for two reasons:

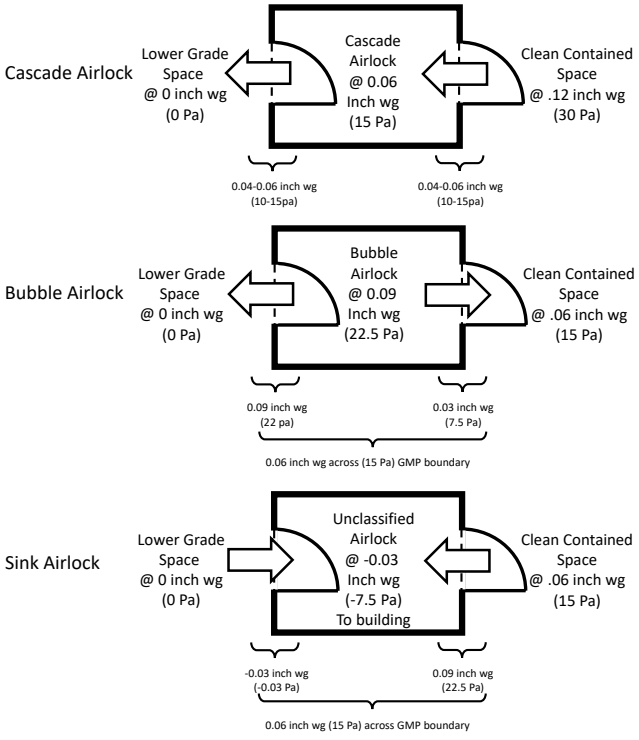
- To contain products, media, and components of a product, preventing them from contaminating any other suite.
- To prevent any bioburden outbreak that might occur in one suite from traveling into another suite, whether it is used for a similar product or not. Isolation facilitates quick identification and remediation and prevents plant-wide contamination.

Segregation

When considering process segregation, the risk assessment centers on how the failure of any single AHU affects the rest of the facility. Designs should ensure that failure of one AHU only affects a single product/processing suite. This means multiproduct facilities should not share supply and return air ducts between the suites so as to prevent cross contamination between suites in the event of a spill or bioburden excursion. Cleanroom designs are thus pushed to use smaller, less-expensive variable frequency drive-based AHUs, rather than the larger, more traditional style [12]. An alternative is the consideration of once-through air supply. Although once-through air designs are costly in terms of energy efficiency, a return on investment calculation should be performed to determine if the reduced capital expenditure and increased environmental impact for a once-through design outweighs the energy savings of a recirculated design.

Room changeover and cleaning methods need to be considered when changing from one product campaign to the next. One method that is being used more frequently is vaporized hydrogen peroxide (VHP). Although other sterilizing vapors such as chlorine dioxide have been considered, VHP is the most commonly applied because of its lower relative humidity required. This method is frequently used in isolators to kill potential contaminants, and it can also be used to change over rooms using fixed or mobile equipment. VHP tends to stick around, absorbing into plastics, only to be off-gassed slowly over time. This could potentially lead to lower product yields for cell therapy processes if the VHP is not sufficiently removed from the room after the decontamination cycle. It is for this reason that careful attention must be paid to HVAC design and target residual VHP levels.

Figure 2: Airlock configurations (arrows indicate airflow path).



FACILITY AUTOMATION

There are three major challenges that cell therapy companies face with regard to manufacturing and delivering their products to patients:

- Manufacturing productivity
- Achieving compliance
- Scalability

Specially designed facility automation platforms can help address these issues. Manufacturing productivity can be improved by integrating clinical treatment facilities, delivery logistics, manufacturing execution systems, enterprise resource planning, and customer resource management systems. Rather than relying on disjointed manual processes, integration allows for a trackable, digital workflow allowing for easier scheduling [13]. Additionally, materials and products could be tracked by barcodes or wireless radiofrequency identification technology throughout the process. Facility automation can also limit particulate generation in aseptic processing, where an operator's manual manipulations would normally take place. In the same vein, integration allows for stronger compliance as well.

It is possible that a record of continuity throughout the process may become a requirement for compliance. While compliance reviews for traditional therapies can last a month or more, processing for autologous therapies must be completed in days. The need for expedited batch record review and approval is obvious.

In addition to the aspect of improved compliance, reliability of the logistics supporting the cold chain and traceability are strengthened, minimizing the risk of mix-ups (e.g., delivering the wrong cells to a patient). Scalability is the biggest issue facing many cell therapy processes, and logistics is the biggest hurdle with regard to scalability. Automation integration can help with this aspect of the facility as well [14]. Having a cloud-based platform that provides accessibility of data not only to the manufacturing facility operations team but also to cell therapy customers and partners allows for better communication and can reduce logistics development and deployment time.

LAYOUT CONSIDERATIONS

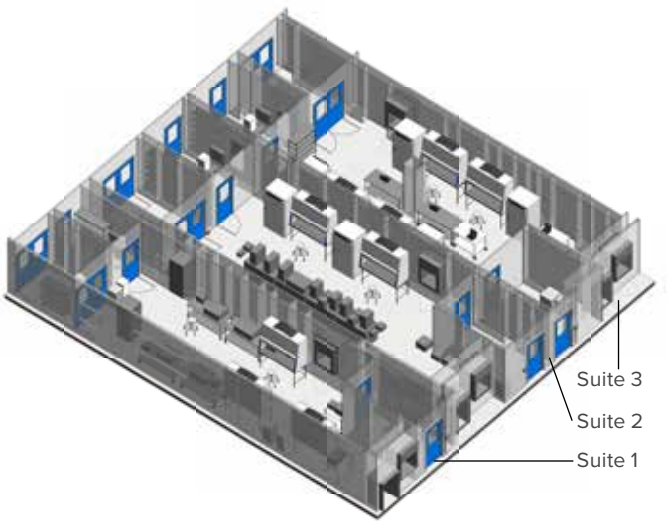
There are a multitude of options and opinions on how cell therapy facilities are organized and laid out. Flexibility and modularity are universal concepts in designs, but how these aspects are approached can differ. Modules are typically designed as "ballrooms" where a series of suites may lead to one large multipurpose room, or all of the processing may take place in the single ballroom. Many cell therapies have separate upstream and downstream modules. While the ballroom design is more typical of research and development and clinical production, a modular approach allows for scale out. As incremental production demands change over time, from clinical trials to commercial production, additional processing modules are added. Traditional design and building methods are able to meet the basic requirements of the cell therapy facilities, but other methods, such as modular wall construction or prefabricated modular delivery, are often better choices to meet highly compressed project timelines.

Flexibility is key when designing modular layouts, especially for a CMO that will be hosting different customers with different needs. Figure 3 shows different configurations for multiple cell therapy suites that were designed for Grade B operations and flexible enough to handle multiple process configurations. Specifically, process gases and chilled water were provided to support many different equipment configurations. Process gas utility panels are typically supplied on the ceiling for maximum flexibility, while the chilled water is supplied at the walls.

Special considerations should be made for equipment selection with regard to structural elements. For example, some incubator designs require a penetration through an architectural wall, so maintenance access is available from a mechanical space adjacent to the cleanroom. This type of incubator design is not amenable to a flexible suite layout because of the architectural changes required. Suites 1 and 3 are configured for a two-dimensional (adherent) cell culture operation that uses open operations in T-flasks and cells stacks and heavily relies on operator manipulations in BSCs and incubators. Suite 2 is configured for a three-dimensional (suspended) cell culture operation that utilizes closed single-use bioreactors. For a closed system, a Grade B background is not required; therefore, designing flexibility into the HVAC system so that it can be requalified to a lower grade should be a consideration.

Figure 4 is an example of a zoning and transition diagram showing the personnel flows, material flows, and airflows for several

Figure 3: Flexible suite layouts.



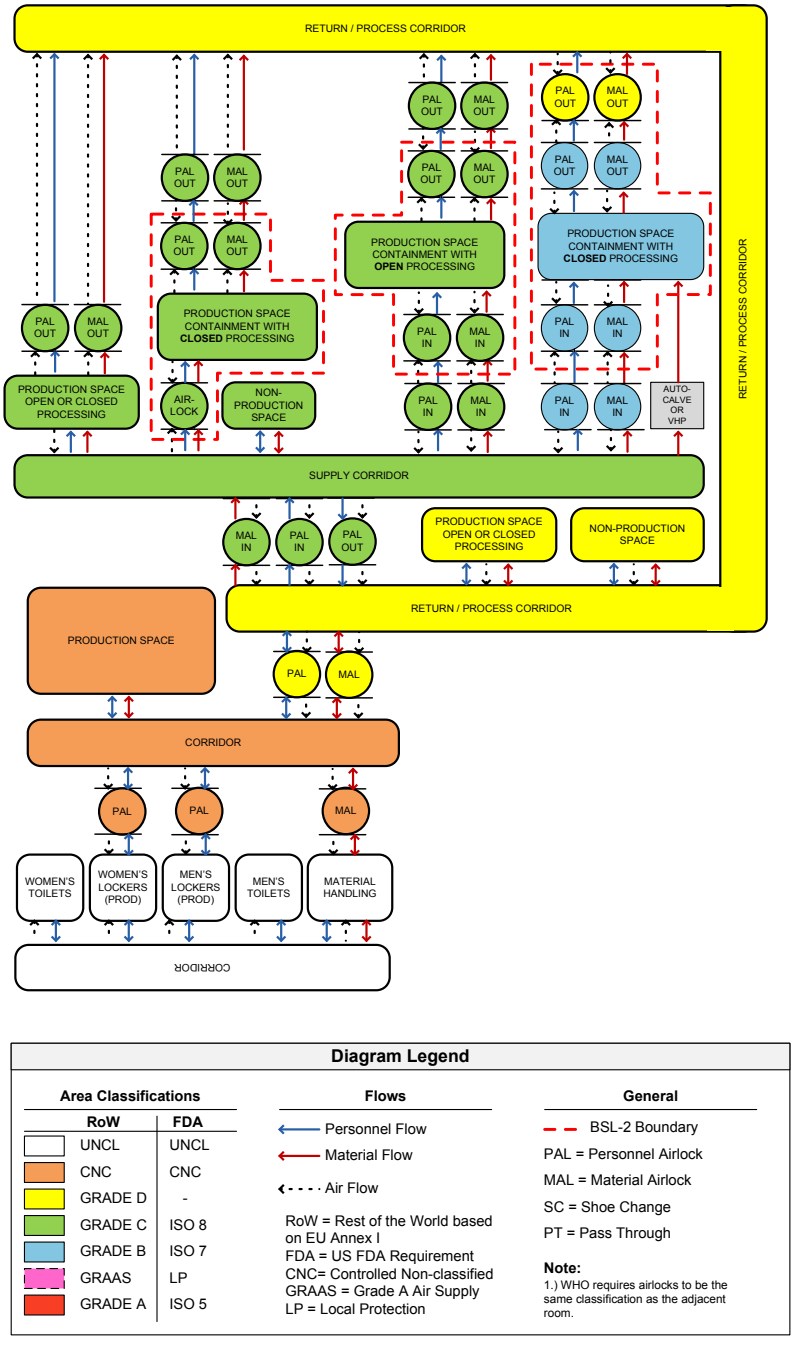
processing suite configurations within the context of a facility. Looking at the diagram from left to right, both flexibility and cost to build increase. A strong undertanding of the underlying requirements of the facility and potential processes is necessary to choose a layout that has the right amount of flexibility while minimizing unncessary expense. Note the "bubble" airlock entrances and "sink" airlock exits to the production suites and how these line up with potential biosafety boundaries (dashed red lines).

CASE STUDY REVIEW

Now that layouts that fit within the context of the rest of our facility have been established, it's time to review the goals established in our CMO case study and how they have been addressed.

- The facility is flexible enough to handle multiple products:
  - Biosafety has been considered in the HVAC design, waste flows, and decontamination steps.
  - Cross contamination has been addressed with the use of closed process technologies, single-use equipment, HVAC design, and room changeover procedures.
  - Utility panels are provided in optimized locations to support future flexibility.
- The facility can handle both autologous and allogeneic processes:
  - The automation designs considered make robust traceability and cold chain possible for autologous products.
  - Materials flows have been considered and are optimized for unidirectional flow as much as possible.
  - Support rooms are designed in such a way that they allow for optimized material and personnel flows.
- The facility can handle both open and closed processing:
  - A Grade B suite is capable of working with both open and closed processes and can be designed to be requalified to

Figure 4: Example zoning and transition diagram.



Grade C, if necessary, in the future. If optimum flexibility is required, as in the case of our CMO, the suites must be designed to Grade B. If less flexibility is acceptable, a mix of Grade B and Grade C suites can be considered.

Although not every cell therapy process is amendable to this type of flexible facility design, the principles are still applicable in most situations, and especially in those cases where multiple products are manufactured in the same facility.

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Current State of OLIGONUCLEOTIDE THERAPEUTICS

By Xianglin Shi, PhD, and Charles C. Tong, PhD

Oligonucleotides are a relatively new class of drugs, composed of natural and synthetic nucleotides, which primarily include small interfering RNA (siRNA), micro RNA (miRNA), and antisense oligonucleotide (ASO). These molecules achieve therapeutic effects through RNA interference, degradation, or splice-modulating pathways [1–4]. Other oligonucleotide therapies include messenger RNA (mRNA, single strand, >500 mers) [5], small activation RNA (double strand, ~20 mers) [6], antagomir (single strand, ~20 mers) [7], and aptamer (single strand, >30 mers) [8]. This article focuses on synthetic ASOs (single strand, 16–22 mers) and siRNAs (double strands formed by hybridization of a pair of complementary sense and antisense strands, 19–25 mers).

Several ASO drugs have been approved (Table 1) [9, 10], including SPINRAZA (nusinersen), which has become the standard care for spinal muscular atrophy, a rare genetic disease [11]. A customized ASO drug, milasen, has also been developed to treat the genetic disorder Batten disease, which is unique to a single pediatric patient [12]. The therapeutic potential of siRNAs via gene-silencing mechanisms was proven for the first time by approval of the lipid nanoparticle-delivered siRNA drug ONPATTRO (patisiran) in 2018 for the treatment of the rare disease hATTR amyloidosis. GIVLAARI (givosiran; approved in 2019), a siRNA conjugate of a liver-targeting delivery system N-acetylgalactosamine (GalNAc), further opened opportunities for siRNAs to treat liver-expressed diseases. For example, the GalNAc-conjugate drug inclisiran, which targets PCSK9, shows great promise as a transformational medicine for atherosclerotic heart disease and familial hypercholesterolemia in chronic cardiovascular disease patients at higher risk of cardiovascular events due to high low-density lipoprotein cholesterol levels [13].

Strong interest in oligonucleotide therapy is evidenced by the 386 compounds being investigated in various research and

Table 1: Approved oligonucleotide drugs.

Drug	Year Approved
Fomivirsen	1998 (US FDA) and 1999 (EMA)
Mipomersen	2013 (US FDA)
Eteplirsen	2016 (US FDA)
Nusinersen	2016 (US FDA) and 2017 (EMA)
Inotersen	2018 (US FDA and EMA)
Patisiran	2018 (US FDA and EMA)
Volanesorsen	2019 (EMA)
Givosiran	2019 (US FDA)
Golodirsen	2019 (US FDA)
Viltolarsen	2020 (US FDA)

Figure 1: Oligonucleotide compounds under investigation for the treatment of diseases. (Data are from reference 14.)

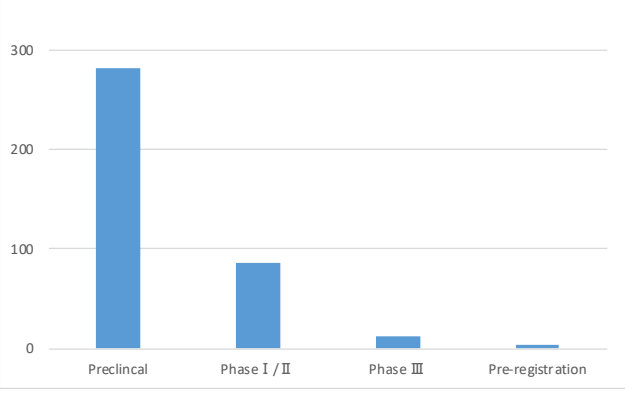
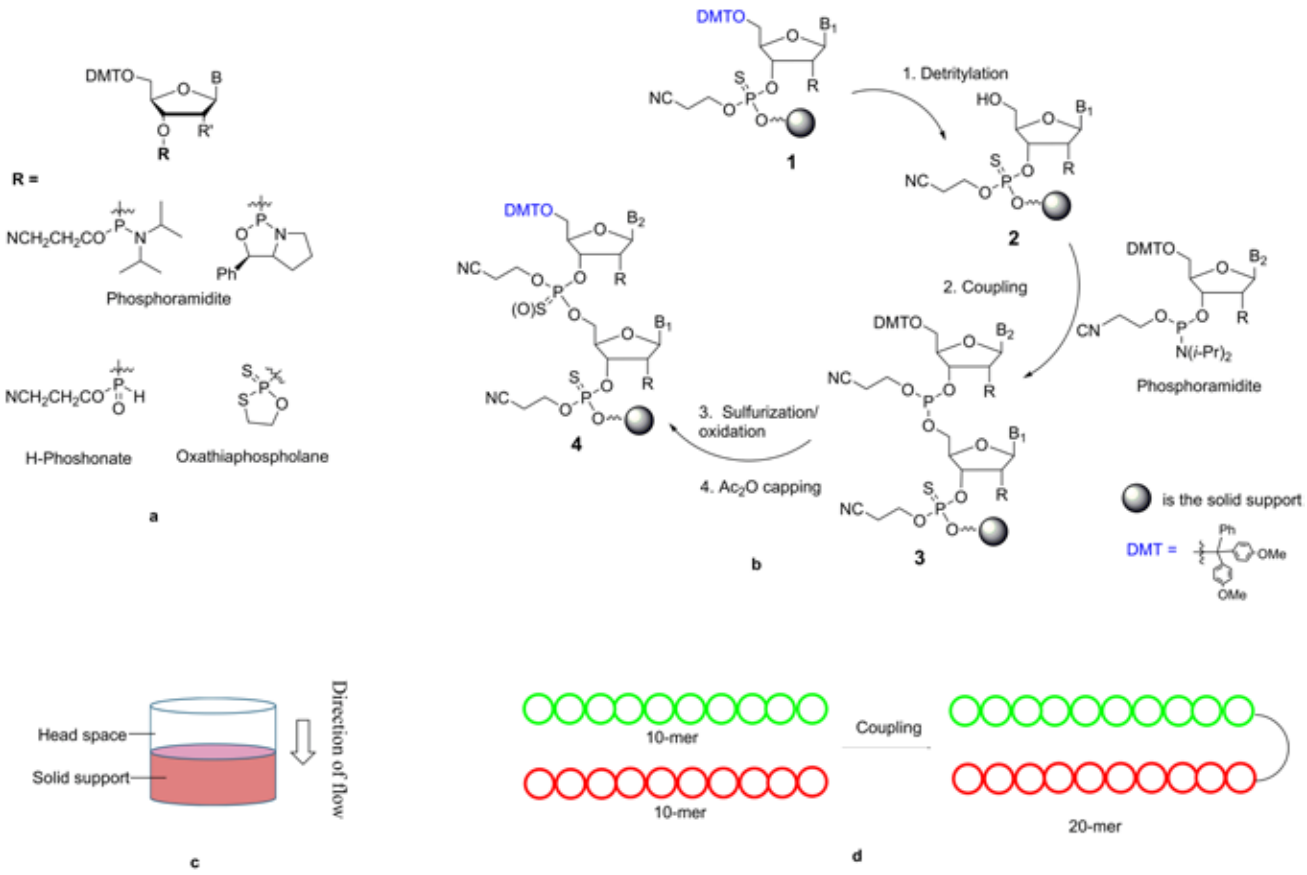


Figure 2: Solid-supported synthesis of oligonucleotides: (a) common building blocks; (b) chemical reactions; (c) diagram of a column showing the resin bed, head space, and flow of reactant solutions; (d) convergent liquid-phase synthesis.



development stages (Figure 1) [14], of which 76% are chemically synthesized oligonucleotides. They cover rare and common infectious (e.g., chronic hepatitis B), cardiometabolic, and central nervous system diseases.

The clinical development of these complex molecules poses challenges and opportunities from a chemistry, manufacturing, and controls (CMC) perspective. The drug substance manufacturing operations that present the most difficult challenges involve the chemistry, process, and impurity characteristics.

OLIGONUCLEOTIDE SYNTHESIS TECHNOLOGIES

The chemical synthesis of oligonucleotides is based on the iterative coupling reaction of nucleotide starting materials (SMs), which contain both a 5′-DMT protecting group and a 3′-reactive phosphorous linking group. The phosphorous linking group is typically a phosphoramidite, H-phosphonate, or oxathiaphospholane (Figure 2a) [15–17]. The phosphoramidite is most widely used in the synthesis from nanomole to molar scales. Both phosphoramidites [16] and oxathiaphospholane [18] have been developed for the synthesis of stereochemically pure phosphothioate linkages.

A repeating synthesis cycle is employed to build an oligonucleotide chain by chemically connecting the nucleotide SMs, one at a time, to a solid support, such as resin (see steps 1–4 in Figure 2b). Operationally, each reaction is carried out by pumping a solution of the SM or reagent through a column packed with the solid support (Figure 2c) and then washing the resin-bound product with a suitable solvent. After the four-reaction cycle is completed, the single nucleotide is added, and the growing chain (step 4) has the same 5′-DMT functional group as step 1. Therefore, the same four-reaction cycle can be repeated to add the next nucleotide, until the desired chain is assembled. Note that step 4, capping with the acetic anhydride, is used to control deletion impurities (n-1) by converting the unreacted 5′-OH to acetate.

This elegant synthesis has been automated. A synthesizer equipped with a computer can carry out an oligonucleotide synthesis without human intervention. A parallel synthesizer can produce hundreds of oligonucleotides each at milligram quantity in as little as 3 hours, and the synthesis of a single oligonucleotide up to 7 kg per batch can be accomplished in less than 24 hours. Parallel synthesis of long-chain oligonucleotides (150 mers) is also possible [19].

The synthesis reactions occur when a solution of an SM or a reagent flows through the column. The reaction times (i.e., the duration of the solution deliveries through the column) and volumes of the reactant solutions can both be controlled precisely by the computerized synthesizers. Though it is true that the dynamic contact of solutions with the resins can vary with change in column size, particularly with swellable resins, extraordinarily similar results can be obtained from syntheses carried out at a broad range of scales (e.g., from 2 to 600 mmol), when the reaction conditions and the resin bed heights are kept the same. This phenomenon indicates that possible changes in mass transfer in the range of scales has no impact on reaction efficiency, despite more than 10-fold differences in column diameters and the constant swelling changes of the resin bed throughout the synthesis.

For solid-supported synthesis to work, the reactions must be high yielding with little side product generation, and the SMs must limit the levels of impurities that are reactive and can be incorporated into the growing chain. This is because the reaction cycle is repeated many times and impurities are generated on the growing chain in each cycle. Similarly, an impurity in an SM that can be incorporated into the growing chain generates one impurity every time the SM is used. Most of these impurities cannot be removed from the desired full-length product in the purification process. Therefore, the small quantities of impurities generated in each reaction and from SM add up to a high level of total impurities. For example, one impurity at 1% incorporation into a 20-mer product in each cycle would result in about 20% impurity. For the same reason, a small change in quantities of process and SM impurities can result in a large change in total impurities. Fortunately, most of the oligonucleotide therapy platforms are based on SMs with chemically stable substituents on the sugar ring [20] and well-established supply chains. The synthesis process is well optimized, and most of the process-related impurities are adequately controlled.

Oligonucleotides can contain many structurally related impurities that cannot, at present, be separated and quantified individually. In practice, the oligonucleotide impurities are grouped and quantified as groups, mostly based on their structure characteristic [21]. For example, deletion impurities such as n-1 are a group of impurities in which one of the nucleotides is missing from the full-length oligonucleotide. This deletion can happen at any position in the sequence where a repeated individual nucleotide is supposed to be present. Despite the current limitations of specificity, highly sensitive analytical technologies such as high-performance liquid chromatography with ultraviolet and mass spectroscopy (HPLC-UV-MS) methods are indispensable for developing a manufacturing process and establishing a control strategy to ensure acceptable product purity across each stage of clinical development.

LARGE-SCALE SYNTHESIS

Solid-supported synthesis will remain the mainstream production method for oligonucleotide drug discovery, early-stage clinical studies, and even late-stage clinical investigations and commercialization to treat rare diseases. However, with the anticipated success of oligonucleotide drugs to treat diseases affecting large patient populations [3], a cost-effective and sustainable large-scale synthesis process is needed. For example, over a metric ton of a single drug may be needed per year to treat Alzheimer's disease or cardiovascular disease. To meet such a demand, around 200 batches of the synthesis are needed at the current maximal scale of approximately 1 mole and approximate 55% yield. To gain economies of scale, it is conceivable that the synthesis unit operations may be scaled up further, on the basis of the remarkably similar results obtained from 2- to 600-mmol scales, despite the technical challenges foreseen with even larger columns and flow rates topping hundreds of liters per minute [22]. Furthermore, the cost to build synthesizers and related facilities is high. Clearly further scale-up is a formidable undertaking. Alternatively, increasing the yield—for example, to 90% from the current approximate yield of 55%—could substantially reduce the cost by eliminating roughly 90 of the 200 runs. This is not impossible, considering the fact that about 75% yield was obtained by removing the capping step [23].

Large-scale solution-phase manufacturing of small molecule pharmaceuticals has existed for decades, and spare capacity is available around the world. Consequently, processes suitable for these facilities have considerable advantages financially and environmentally.

Investigators have extensively explored synthesis that uses soluble instead of solid anchors and can be performed without synthesizers and columns, although only synthesis of a morpholino oligonucleotide has been demonstrated at the 10-kg-per-batch scale [24]. However, it is not far-fetched to expect that this approach can be scaled up further. More recently, proof-of-concept studies focusing on separation of intermediates using membrane filtration at laboratory scale have been reported [25]. Synthesis using template-dependent [26] or independent [27] enzymatic reactions has been investigated. Nevertheless, many technical obstacles must be overcome, particularly for oligonucleotides containing unnatural nucleotides and phosphorothioate linkages [20].

Most issues in the linear synthesis employed in solution-phase synthesis could be alleviated by developing convergent processes. Figure 2d illustrates a convergent synthesis of a 20-mer from two 10-mers. Such an approach has been used in peptide manufacturing [28]. This strategy minimizes impurity generation and yield loss by reducing unnecessary exposure and burden to carry the growing oligonucleotide through many reactions and isolation steps, and it reduces the impact of failure because the synthesis of two 10-mers is independent. The few studies on convergent synthesis reported include the synthesis of a 6-mer by a 3 + 3 [29], trimers for gene libraries [30, 31], and ASOs using a template-based ligation of fragments [26]. A promising convergent template-free synthesis of double-strand siRNAs from short oligonucleotide fragments using enzyme catalysis was disclosed at the September 2020 US TIDES: Oligonucleotides and Peptide Therapeutics

Conference. We believe convergent chemical synthesis can provide cost-effective and sustainable manufacturing processes in the near future.

CONCLUSION

Solid-supported synthesis fulfills the need for early-stage development and commercialization of drugs for rare diseases. Multiple production lines may be built to produce hundreds of kilograms of drugs to treat common diseases. However, we foresee that successful clinical development of drugs to treat diseases that afflict millions of patients will create demands for metric tons of drugs. In our opinion, such demands can be met only by developing large-scale solution-phase convergent synthesis due to its intrinsic advantages for multistep synthesis, such as in the synthesis of a typical oligonucleotide, which requires at least 54 reactions to prepare.

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Acknowledgments

The authors thank William F. Kiesman, PhD, and Firoz D. Antia, PhD, of Biogen for their feedback in the preparation of this article.

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2019 ISPE Europe Biotechnology Conference: INDUSTRY TRANSFORMATIONS

By Thomas Zimmer, PhD

As biopharmaceuticals have become a major part of the pharmaceutical industry, we have witnessed significant transformations in product development, strategy, technology, and operations. This ongoing transformational process was the main theme of the fourth annual ISPE Europe Biotechnology Conference, 25–26 September 2019, in Brussels, where featured tracks included Gene and Cell Therapy, Regulatory & Quality, Digitalization and ISPE Pharma 4.0™, and Operational Innovation.

Emmanuel Amory, GSK (left), and Paul McKenzie, CSL Behring

Although the 280 attendees were excited about innovations such as gene and cell therapy, which are making promising advances in regenerative medicine and disease remission, conference participants also acknowledged that there are considerable operational and technological challenges to overcome. For example, reproducing large molecules reliably at an industrial scale requires manufacturing capabilities of a previously unknown level of sophistication. The starting materials used to produce recombinant therapeutics are genetically modified living cells that must be frozen for storage, thawed without damage, and made to grow in a reaction vessel. The molecules must then be separated from the cells that made them and the media in which they were produced, all without destroying their complex, fragile structures.

Also, biopharmaceutical manufacturing involves distinctive GMP- and quality-related challenges. For example, when working with a nonsterile starting material in a sterile and aseptic manufacturing process, it is necessary to prove that the microorganisms in the biopharmaceutical product are from the starting material only, and not from processing.

Presenters at the conference addressed these topics, often offering insightful industry case studies, and attendees also had opportunities to take part in plant tours. Some of the excellent presentations are covered here.

EMMANUEL AMORY, GSK

Emmanuel Amory, Vice President of International Operations, GSK Vaccines, and Conference Chair, opened the conference by talking about the future of the biopharmaceutical industry. He addressed operations management, industrial excellence, project management, business development, and international leadership as key success factors in the biopharma world of tomorrow.

He identified the competing driving forces in the industry as demand agility versus constrained environment, cost of compliance versus price erosion, liquid generation versus rigid organization, and long-term investment versus short-term return.

Table 1: Comparing traditional and advanced process controls.

Traditional Process Control	Advanced Process Control
Fixed controlled input parameters	Flexible input parameters
Offline analysis	Process analytical technology (PAT) used for online analytics
In-process tests primarily for go/no-go decisions	Real-time automatic control with appropriate feed forward/backward controls
Drug product quality controlled by process intermediates and end-product testing	Drug product quality controlled by real-time release testing (RTRT) with more limited end-product testing

Plenary session at the 2019 ISPE Europe Biotechnology Conference in Brussels in September 2019.

According to Amory, enablers of success in this environment are collaborative culture, advanced capabilities, and agility by design.

When defining optimization parameters, industry stakeholders should add predictability alongside the usual ones, such as replenishment frequency, speed, and release frequency.

PAUL MCKENZIE, CSL BEHRING

Paul McKenzie, Chief Operating Officer, CSL Behring, showed innovation by the numbers in his presentation. When the 2019 ISPE Europe Biotechnology Conference took place, there were approximately 800 gene therapies in clinical trials, about 130 cell therapies in trials, and almost 800 regenerative medicines being tested. In 2018, global investment volume was about USD 172 billion, nearly half of which was focused on oncology and immuno-oncology.

McKenzie also outlined three pivotal ways that leadership can drive innovation: find the intersections where innovation can happen, reward and recognize innovation across the organization, and foster a culture of diversity and inclusion. He explained that corresponding obstacles to innovation include failing to look ahead and take advantage of change, lacking focus on transformational innovation, and not engaging stakeholders early and often.

Where can engineers create intersections for innovation? McKenzie identified modeling/analytics, operations intensification, design to value (DTV), and scale-down and prototyping as key areas. Engineering sciences provide opportunities for innovation in computational fluid dynamics modeling, process modeling, dynamic facility modeling, statistical modeling, and advanced analytics. For example, these methods can support transitions from traditional process control to advanced process control (Table 1).

McKenzie further explained that DTV strengthens the connections among the development, supply chain, and commercial sectors, to the benefit of patients. In fact, DTV means investing in value throughout the product life cycle:

- Design attribute decision-making guided by marketplace input
- Integration of customer input into product and supply chain design
- Platform-based development, robust process capability, and knowledge management
- Deep understanding of critical quality attributes
- Real-time control and release, clinically based specifications
- Right first-time approval
- Speed to launch and stabilization
- Reliable supply and proactive customer-driven product roadmaps

Manufacturers of the future will have multiple factors to consider: market size and cost as a function of throughput; initial capital outlay as a function of the likelihood of clinical success; network size and use as a function of the uniqueness of the product and process; and price as a function of the company's market segment.

McKenzie proposed a systematic approach to development of the optimal design space that includes the creation of subspaces for stability, bioavailability, and processability. In general, future development in the industry will focus on prototyping, finding the means to receive rapid feedback on prototypes and workflows, and continuous improvements.

UWE GOTTSCHALK, LONZA

Uwe Gottschalk, PhD, Chief Scientific Officer, Lonza Pharma Biotech & Nutrition, presented "Applying Old Know-how to New Challenges: The Manufacturing of Emerging Therapeutic Modalities." He addressed five technologies that will disrupt healthcare in the near future:

- Artificial intelligence
- Immunotherapies (checkpoint inhibitors)
- Liquid biopsy, which has the potential to monitor tumors noninvasively
- Three-dimensional (3D) printing
- Clustered regularly interspaced short palindromic repeats (CRISPR)

The biggest disruptor is personalization.

The therapeutic modalities considered by Gottschalk are antibiotics, vaccines, proteins, cell therapy, and gene therapy. The enabling platforms are single-use technologies, mammalian cell cultures, centralized large-scale facilities, and high-throughput screening. Onto these, the following disruptors will have an impact: microbiotics/phages, RNA/nucleic acids, mRNA/gene therapy, exosomes, gene editing, integrated process chains, synthetic biology, GMP in a box/point-of-care manufacturing, and predictive in silico tools.

However, he noted, the biggest disruptor is personalization. The cell and gene therapeutic market is a dynamically growing segment, with more than 500 companies developing over 1,300 products. The compound annual growth rate was 27% between 2014 and 2017, with growth driven by key macro factors such as:

- The population over the age of 60 will double by 2050.
- The middle class will become a larger proportion of the global population.
- Sequencing cost is dropping rapidly, making personalized treatments increasingly practical.
- The chance of successful drug development with personalized medicine is increasing, as exemplified by the leap in orphan drug indication approvals with relatively small/less-expensive clinical tests.

Personalized medicines will still be costly for patients, but in some cases these therapies will still be less costly than the total cost of care. Gottschalk said the industrialization of cell and gene therapy manufacturing involves two types of scale-up strategies: centralized scale-up or decentralized scale-out. As an example, for centralized scale-up, he showed the development of human pluripotent stem cells (hPSCs). Contributing and enabling factors to achieve quality, quantity, consistency, and efficiency are:

- High fold expansion to meet cell quantity demand for clinical indications
- A closed process to comply with cGMP requirements and reduce contamination risk
- Automated, scalable, controlled, and monitored stirred-tank bioreactors
- Enhanced in-process control
- Reduced labor requirements and cost
- High-quality hPSCs

Another example discussed by Gottschalk was commercial exosome manufacturing strategy. Exosomes are surrogates of their parental cell and contain genetic material representing the parental cell (RNA, DNA, and protein). They are communicators between cells, intervening in horizontal gene/protein transfer with preferential delivery sites and acting as valuable, well-conserved sources of biomarkers representing the parental (live) cells. When exosomes are used in regenerative medicine treatment, they are commonly made by growing stem cells in culture and then taking the media in which they grow while getting rid of the stem cells by ultra-centrifugation. These products are used to treat orthopedic injuries or combat the effects of aging. The idea is that they will promote tissue repair.

Finally, for the decentralized scale-out strategy, Gottschalk reviewed the complexity of manufacturing of chimeric antigen receptor (CAR) therapies. CARs, which are receptor proteins that have been engineered to give T cells a new ability to target a specific protein, are used for cancer therapy. Manufacturers of these therapies must focus on robustness of process to avoid product failure, efficiency to achieve commercially viable therapies, scale-out to meet commercial demand, proximity to patients to resolve logistical challenges, and key components to reduce complexity in the supply chain.

SONJA WILLEMS, JANSSEN BENELUX

In a presentation titled "The Future of Health Care and the Role of Pharma," Sonja Willems, Managing Director, Janssen Benelux, addressed three trends: disease elimination, meeting serious unmet needs, and technology.

She said disease elimination will involve three steps: *prevention*, where disease-specific approaches to warding off disease onset/initiation are the goal; *interception*, where the target is to stop disease before clinical manifestation; and *disease management*, where the target is to potentially eliminate disease after it manifests and possibly reverse damage to restore full health. According to Willems, there is a clear trend toward prevention strategies.

The next trend is addressing serious unmet needs. Goals include:

- Achieving a world without tuberculosis
- Ending HIV transmission and reducing the burden of living with HIV
- Ensuring access to quality mental healthcare and promoting well-being for those living with mental illness
- Controlling soil-transmitted helminths as a public health problem

The third trend, technology, is enabling individuals to participate in their own healthcare and disrupting the status quo in research. For example, apps are changing clinical trials by connecting patients with trials they may be eligible to join. These apps have the potential to help patients find trials, get trial information and educational materials, and even offer input about trial design. During trials, apps can be used to conduct experience surveys, promote in-trial engagement, and provide data access for patients. And after a trial, the same apps can be used to distribute plain

language summaries, conduct additional experience surveys, and establish long-term connections (an alumni community).

JACOB HARTTUNG, SANOFI

Jakob Harttung, Head of Digital for Sanofi, presented the Sanofi Digital Factory 4.0. In this model, there are five pillars of digital transformation and target outcomes:

- Integrated industrialization will shorten the time to launch and improve robustness of processes and yield.
- Connected plants and equipment will improve capacity utilization and plant cycle time.
- Smart quality will improve operational outcomes and the batch release process.
- Connected teams and operations will enhance training efficiency and support paperless work.
- A real-time, data-driven supply chain will enhance service levels and optimize inventory levels.

From a management point of view, the digital factory is achieved in three phases. It is initially introduced via so-called lighthouse projects and sites that pilot the new approach, followed by early adopters in phase 2. Phase 3 is the scale-out across all sites.

Major plant investments are driven by the digital-by-design concept. In practical terms, this means zero paper, zero destructions, zero runs that cannot be sold due to GMP failures, zero inspection issues, zero deviations, zero delayed releases, and zero supply chain delivery failures.

Harttung said one of the key strategies is to overcome a silo mentality that separates manufacturing and R&D by accelerating feedback cycles and learning from other industries. Sometimes, scale-out avoids the risks associated with scale-up and might result in better processes.

About the author

Thomas Zimmer, PhD, is ISPE Vice President, European Operations. He previously was Senior Vice President of the Corporate Division, Safety, Quality & Environmental Protection at Boehringer Ingelheim, where he worked from 1981 to 2000 and held several positions in pharmaceutical development and pharmaceutical manufacturing and in the area of management operations for the Americas and Europe. He was also Head of the Project Production Alliance Europe and later Head of Pharma Operations at Boehringer Ingelheim France. Thomas is Chair of the Anti-Counterfeiting Ad Hoc Group and a member of the Scientific, Technical and Regulatory Policy Committee at the European Federation of Pharmaceutical Industries and Associations. He is Chair of the Industry Advisory Board for the Institute for Packaging of the University of Applied Sciences in Berlin, a member of ISPE's International Leadership Forum, and a board member of the Pharmaceutical Security Institute. He studied pharmacy at the Johann Wolfgang Goethe University in Frankfurt/Main, where he wrote his doctoral thesis in pharmaceutical technology.

VISION INSPECTION

Using Machine Learning/Artificial Intelligence

By Vijay Yadav and Conor Kennedy

Pharmaceutical companies rely on automated vision inspection (AVI) systems to help ensure product safety. Although these systems overcome challenges associated with manual inspection, they can be hindered by limitations in their programming—if the system is programmed to consider every variation in inspection conditions, it is likely to falsely identify defects in safe products. This article discusses a project that explored how artificial intelligence (AI) and machine learning (ML) methods can be used as business tools to learn about the ejected product images, understand the root causes for the false ejects, trend the true defects, and take corrective actions.

The United States Pharmacopeia (USP) Convention requires visual inspection of all products intended for parenteral administration [1, 2]. Pharmaceutical products must be essentially or practically free of observable foreign and particulate matters. Additionally, any product, container, or closure defects potentially impacting the product or patient must be detected and ejected.

Although 100% manual inspection is the standard for detection of visible particulate matter and other defects, it is a slow, labor-intensive process, and not a match for high-volume production. Therefore, to meet visual inspection requirements, pharma companies have turned to AVI systems, which use arrays of cameras paired with image processing (vision) software to automatically inspect sealed containers using the image visuals. The high throughput of these machines is achieved by machine vision engineers who develop, qualify, and implement the vision recipes on AVI machines for the relevant products.

The AVI method of inspecting products in containers is a well-established process; however, it is not yet perfect when it comes to handling variations in lighting conditions, physical containers, product appearance, environmental factors, camera position, and other contributors that may change continuously. Generally, AVI systems come with vision software that uses heuristic/rule-based methods to differentiate good products from defective ones. Defects range from missing components of the final product, such as caps and stoppers, to purely visual ones, such as dirt or scratches on the outside of the container, and critical defects like cracks and particles. The challenge is that heuristic methods cannot be programmed to account for every variation. It is nearly impossible to tune machines to cover all variations while ensuring true defect detection; the result is false ejects. To address this challenge, we investigated how AI and ML technologies can help overcome AVI system limitations.

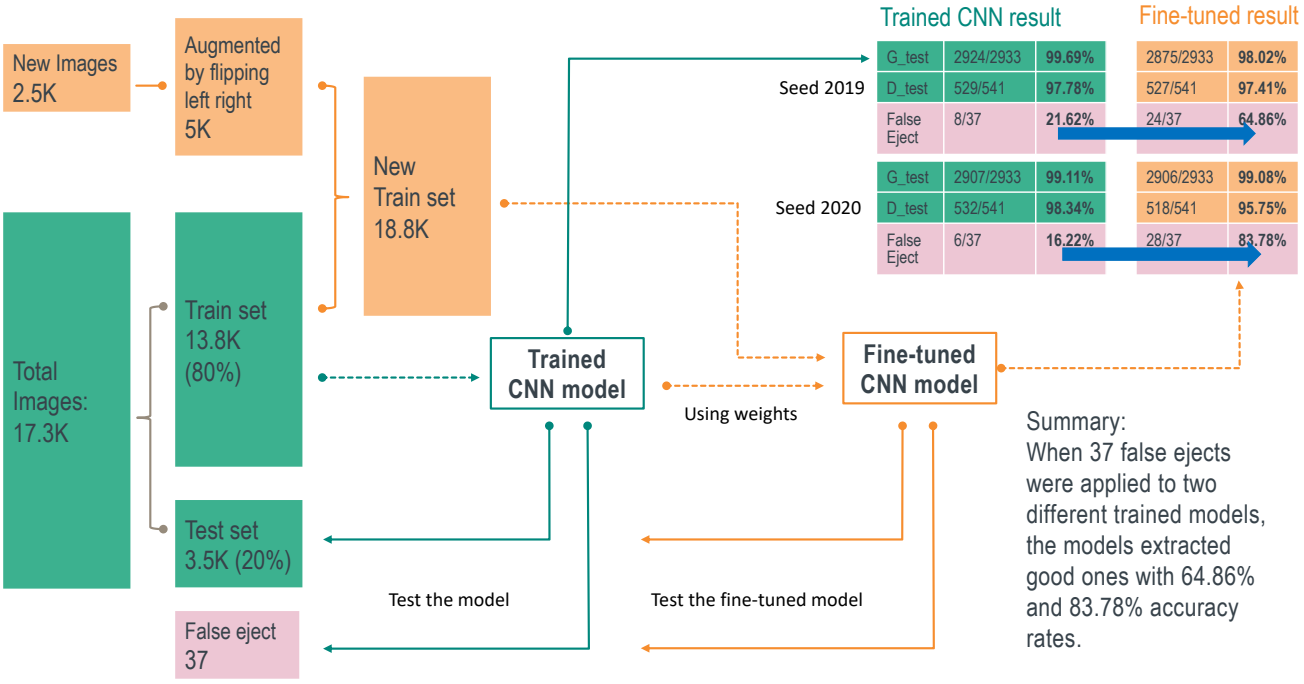
PROJECT INCEPTION

Before any data analytics work began, our team focused on building a good data set that included drug product images and process data. Because the machines inspecting the lyophilized products were already designed to retain all ejected images, the team used those data to develop its first AI/ML models. Initially, the team selected a small set of cameras that are used to detect specific defect categories to focus their modeling efforts.

To confirm, classify, and monitor true defect occurrences, the vision team developed a data collection method to pull and organize all the eject images that the machines use for decision-making. These images were from both the machines and the manual inspection of the AVI eject population, which is done to confirm, classify, and monitor defects via process control limits. Once the data repository was created, the team created dashboards that gave near real-time eject insights about which components and associated suppliers were the potential source of the ejects.

As part of the exploratory phase for using the AI/ML for AVI, our team conducted two proof-of-concept experiments:

Figure 1: CNN model training process and validation results for a lyophilized vial AVI system. (Legend: G = good product; D = defective product.)



- Experiment 1 tested the hypothesis that ML/AI can help vision system experts tune AVI machines by identifying and sorting false ejects from large image data sets.
- Experiment 2 tested the hypothesis that ML/AI can facilitate a streaming analytics platform for the AVI process. This streaming analytics platform will support the vision system experts with rapid identification and remediation of both true and false ejects from the upstream drug product unit operations.

For both experiments, the vision inspection team collaborated with the data science team to explore whether advanced techniques could be used to further improve the capabilities of inspection. Immediate value was seen in developing the AI/ML algorithms to classify the defect images. The team then set out to develop a prototype convolutional neural network (CNN) to test the ability of AI/ML models to identify true versus false ejects.

The first step was to assemble data sets of relevant images to develop the CNN model. The vision inspection team began labeling ejected images that had been saved from lyophilized vial AVI machines. After the eject- and acceptable-image sets had been assembled, the team collaborated with data science team to develop a deep learning model that could classify the images. Using Python, OpenCV, Keras, and TensorFlow, the team developed a RESNET 50 CNN architecture for classifying the images.

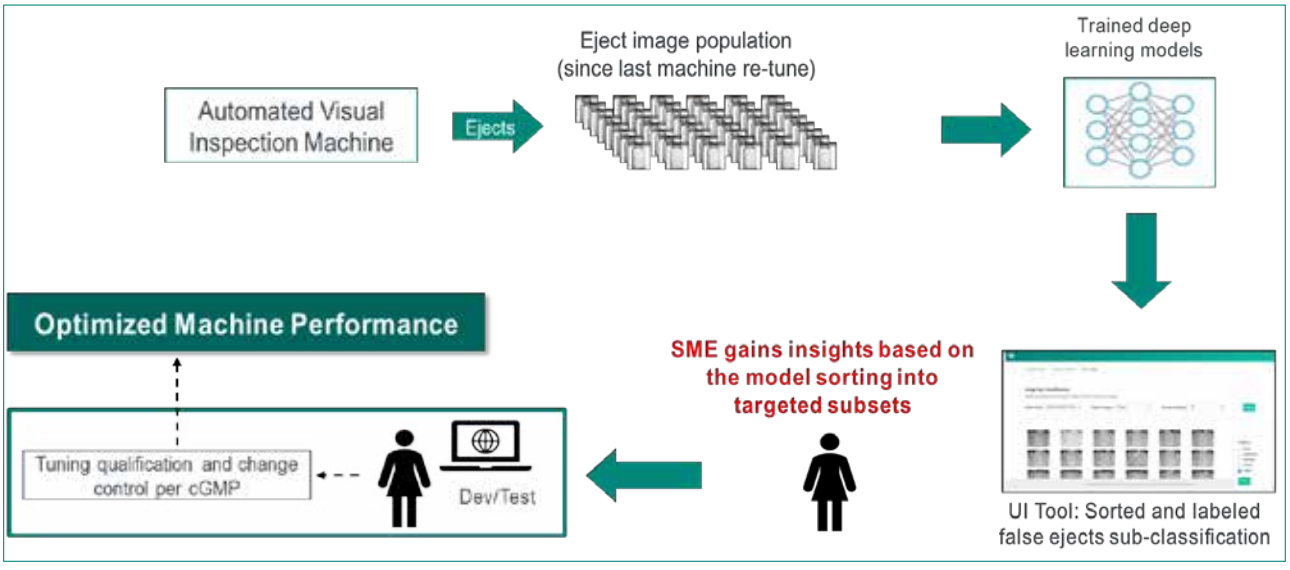
Figure 1 presents the performances of two sample models in multiple validation tests that evaluated how closely each deep learning model could replicate the automated vision recipe developed by the vision engineers for cameras. The team used a binary classification model to separate good units (G) from defective units (D).

In Figure 1, the teal-colored path and boundaries mark the first (initial) trained model. When this model was fed unseen 37 false ejects from the current AVI system, it was only able to identify eight of them as good. The key reason for the low performance was that the training data set did not contain the hard-to-classify variations.

The team then augmented the training data sets with more variation (refer to the yellow and orange parts of Figure 1). The fine-tuned model showed much improved potential to reduce the number of false ejects. For example, when 37 false-eject images (previously unseen by the model) were input in the model for inference, the model was able to identify 24 (65%) as good units.

The results from the prototype CNN were extremely promising. In developing the model, the team used 2,500 images that had been manually inspected to determine whether they were ejects or acceptable product, plus 17,300 images that were not manually labeled but used the current AVI system's classification. Because the current system was shown to eject acceptable units, the training set of images contained units that would be acceptable by

Figure 2: Deploying a user interface tool to subclassify false ejects for machine retuning support.



manual classification. The current system's overly cautious nature of ejecting good product was learned by the CNN because the neural net is dependent on having correctly labeled data to train on. The ability of the neural net to extract the features of defective images, while also improving the detection of acceptable products, showed the team the potential of using deep learning for AVI.

If a CNN could be developed to identify signals buried within images, it could reveal insights into the process that cannot be seen by humans. Given the breadth of analysis possible with AI/ML, existing vision recipes could potentially be drastically improved by incorporating models developed from large classified sets of images instead of relying on the traditional inspection window techniques currently in use. Using a large set of images, the CNN model was trained to provide a highly accurate classification of images that was not possible using a traditional rule-based AVI system.

The outcomes of both experiments demonstrated the ability of AI/ML learning models to provide a rapid and thorough root-cause analysis of eject rates, leading to eject-rate reduction. It should be noted that none of the images used in these experiments were from drug product units that were released for human use.

PROOF OF VALUE

Given the successful outcome of the initial proof-of-concept experiments, the AVI project team launched a formal project with an expanded scope to show proof of value. For this project, the team adopted an agile delivery approach that focused on specific user stories to determine the user requirements for a minimum viable product. As part of this process, the team held workshops to bring together different user personnel and capture their user stories to make sure the solution addresses their needs.

The team selected three use cases and focused on two goals for this proof-of-value project:

- Goal 1: To create an image catalogue and contextualize data into a centralized data repository to (a) enhance intra-batch troubleshooting and decision-making and AVI machine tuning through a deeper understanding the ejected images; and (b) provide enterprise data for the component performance associated with ejected units that will enhance negotiations between procurement and component suppliers
- Goal 2: To use ML/AI to determine trends and generate insights about root causes of false ejects in drug product unit operations, leading to reduced false-eject rates

Use Case 1

The first use case considered a user interface tool to subclassify false ejects for machine retuning support. Figure 2 shows how AI and ML can be used as business tools to sift through the pool of ejected images and group them into different defect and false-eject categories. A vision inspection team member can then quickly review specific categories and follow the cGMP process to retune the vision machines.

Use Case 2

The second use case involved a rapid-response tool for an upstream drug product process. Figure 3 shows how an AI/ML–trained model can be used as a business tool to sift through the pool of ejected images and classify them by different attributes (defect

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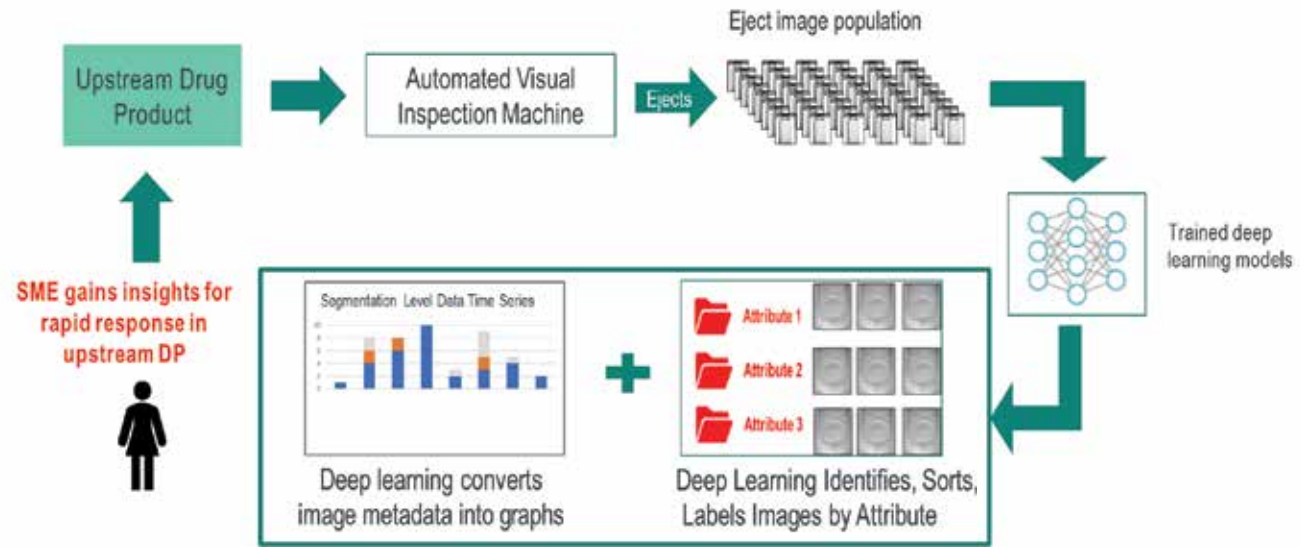
Figure 3: Deploying a rapid-response tool for an upstream drug product process.



and false-eject categories). An upstream process team can then compare the ejects over multiple batches, analyze the defect trends, perform root-cause analysis, and follow the cGMP process to make changes to address the true defects or false ejects.

Use Case 3

When using AVI systems to inspect liquid products, differentiating between nondefect bubbles and true particulate matter in solution is a common challenge. In the third use case, the team explored the abilities of AI/ML models to improve the new liquid vial inspection system.

Whereas capturing images from the AVI machines in the lyophilized vial manufacturing area was relatively simple, the team found it difficult to get images to develop the CNN model for liquid vial inspection. Specifically, limitations to the image-saving capabilities of the first vision systems used by the team made it challenging to collect a sufficient number of images to encapsulate all the variance needed to effectively predict whether a unit was defective or acceptable.

Once the images were collected from the liquid product camera stations, the team decided to try and improve particle versus bubble classification using morphological image-processing methods instead of a CNN. The method used information on pixel colors within the image to form the basis for detecting a bubble or particle. The method also captured the size, location, and number of bubbles/particulates found in the vial. Figure 4 shows the techniques used to distinguish between a particle and a bubble.

Once it was possible to distinguish between the bubbles and particulates in the images, a user interface was developed to execute the algorithms in the background. The team built a dashboard showing the trends for bubble counts versus time. The goal was to identify a step change in the process that caused bubbles to be generated. However, once the tool was developed, the vision inspection group saw that the number of bubbles the tool was identifying was much higher than the number bubbles historically seen. The data the team presented were useful for showing general bubble trends, and the ability to differentiate images of bubbles and particles with high throughput provided new insight into the process for the vision team. Therefore, the team refocused their efforts to use ML to develop AVI solutions.

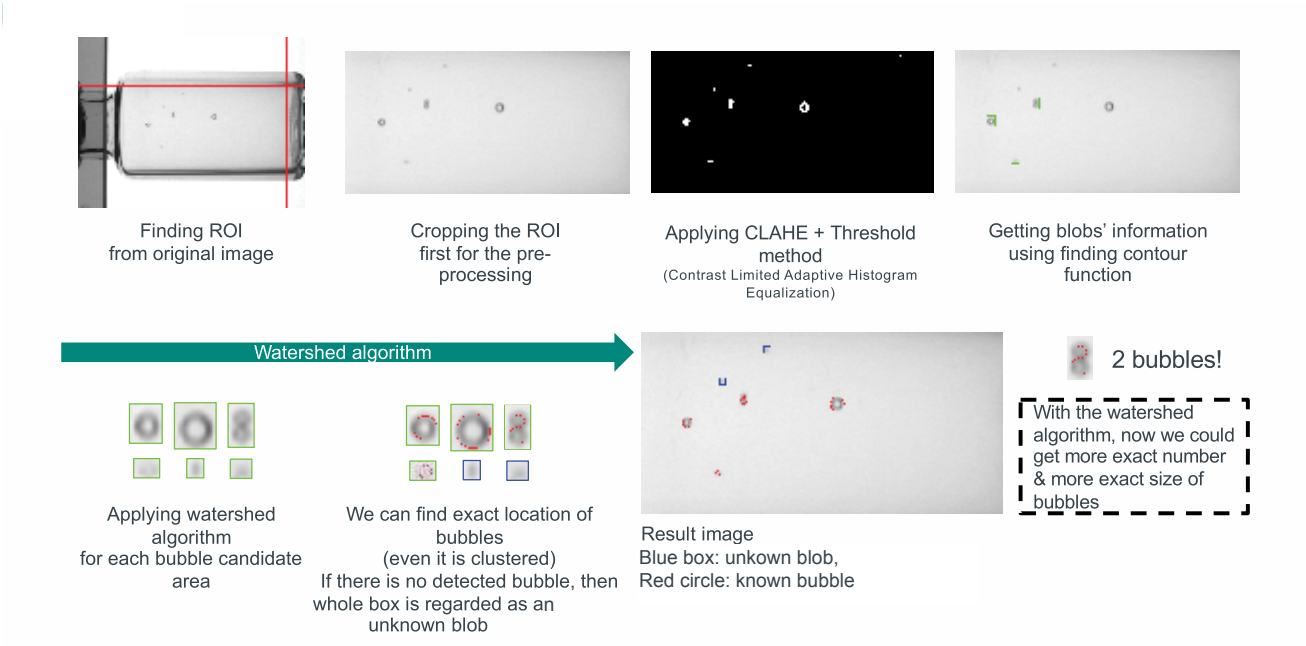
LESSONS LEARNED

Because of technical limitations, some AVI systems do not retain images permanently on the computer where the vision software is running. Acquiring and saving (ingesting) the ejected-image data set is critical to building AI-driven advanced analytics insights. We recommend that pharmaceutical companies invest in AVI machines that are capable of retaining eject images on an ongoing basis.

Other lessons learned include:

- It is important to invest in the IT infrastructure to build a scalable solution that can ingest, pre-process, train, test, and deploy large sets of images for near real-time insights, model inference, and image query.
- The current approach to maintaining and improving performance with AVI machines is effective; however, continuous improvement opportunities exist. There are opportunities to use AI/ML models as business tools is to learn about ejection

Figure 4: Image processing to Identify bubbles and particles.



rates, root causes of defects, and defect trends. It may also be possible to facilitate rapid response/adjustments to the upstream process issues and to verify the effectiveness of corrective and preventive actions.

- Advanced analytics and AI (deep learning) applications in AVI machines have the potential to improve productivity in the factories of the future. It is imperative that AVI vendors seek to embed these capabilities in their future products.
- A speed-to-value, agile delivery model offers incremental value to businesses while keeping morale high during the adoption of transformational changes.

NEXT STEPS

The AVI project team is continuing the process of developing models to identify all known defects for both lyophilized and liquid products. The team is also building an automated image-ingestion capability to go along with the AVI systems within our company's manufacturing network. The team's success so far in the project has been directly correlated with its ability to retain and label images to build the models. If a CNN model is going to account for the variation in each process and product, large numbers of images for every known defect in that manufacturing process/product are needed. Developing the data sets to build accurate models cannot be done without automated image saving and contextualization, as well as a method to tag each image with metadata that identifies associated site, product, inspection machine, and camera numbers for deeper-level insights.

Finally, the team would welcome collaboration with other pharmaceutical companies and AVI system manufacturers. Working with other large manufacturers provides opportunities to develop best practices and share the lessons learned from industrializing AI/ML (deep learning models) for visual inspection, helping the entire industry move forward.

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About the authors

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Conor Kennedy works for Merck's Global Engineering Solutions group on installing new AVI machinery for vaccine manufacturing. He joined Merck with the West Point vision inspection group and supported their suite of inspection systems at that site as well as the packaging vision inspection team. He was a founding member of the Merck Machine Learning for Automated Vision Inspection project. Conor graduated from the Pennsylvania State University with a BS in mechanical engineering; he conducted research with the Penn State Intelligent Vehicles and Systems Lab and Multiscale Thermal Fluids and Energy Lab. He is currently attending Drexel University, where he is studying for a master's degree in electrical engineering.

OPERATIONAL RISK MANAGEMENT

in Global Supply Scenarios

By Klaus Finneiser, PhD

The current regulatory framework in the pharmaceutical industry places pressure on marketing authorization holders (MAHs) to demonstrate quality oversight, and a systematic risk management process is a prerequisite for avoiding compliance and productivity pitfalls. This article focuses on options to improve day-to-day operations and to ease decision-making by integrating operational risk management into a company's quality system.

Key risk management concepts were introduced to the pharmaceutical industry about 20 years ago when, for example, the World Health Organization recommended that the food industry's hazard analysis and critical control point (HACCP) methodology also be applied to pharmaceuticals with a focus on monitoring critical control points (CCP) [1]. Various industry stakeholders and regulatory institutions now seem to issue new risk management guidelines nearly every year. In particular, the US FDA initiative for cGMPs in the 21st century [2] and ICH Q9 [3] triggered a broader discussion of risk management requirements.

Risk management is mentioned in many ICH guidelines (specifically, ICH Q8 [4] and ICH Q10 [5]) and is part of the EU GMP regulations [6]. ICH E6 (R2) [7] situates risk management in the Good Clinical Practice (GCP) scope. In the medical devices industry, both ISO 13485, which concerns the quality management system [8], and ISO 14971, which addresses risk management [9], are required for market approvals.

Risk management is also an important element of the ISO 9000 series, which addresses quality management [10]. ISO 31000 has a broader focus on risks in organizations [11]. This standard may influence future directions in the pharma industry as it applies to the whole organization, rather than just quality.

Despite this range of regulations, the pharma industry has not made much progress implementing risk management strategies in recent years. The methodologies listed in Annex 1 of ICH Q9 can be widely applied [3, 12]. However, a single approach—failure mode effects and criticality analysis (FMECA) in combination with spreadsheet applications—predominates. As Greene and coauthors have stated, the value of quality risk management in the industry "has not yet been realized" [13]. Moreover, there are reports of companies applying risk management in situations where it is inadequate or inappropriate—for example, to justify noncompliance situations or as a proxy for proper root-cause investigations. This results in the industry facing increasing risks rather than getting existing ones under control [14].

These observations align with perceptions that the pharma industry has made less progress toward continuous improvement and innovation compared to other industries [15]. In sum, although risk management tools are applied here and there in daily quality operations, a systematic approach to risk management is missing and there is room to improve.

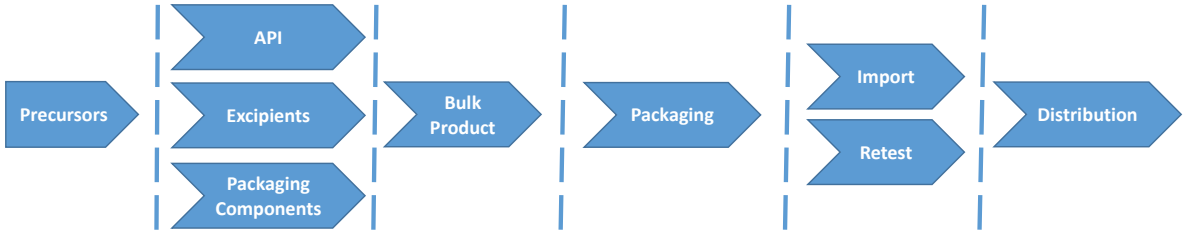
GLOBAL SUPPLY CHAIN CHALLENGES

The pharmaceutical industry underwent remarkable changes in the 1990s. Mergers and acquisitions, new launches of blockbuster drugs, the growing number of older adults, and a high demand for drugs to manage hypertension, cancer, and diabetes indicated a bright future for pharma. In this era, supply chains were fully integrated from API synthesis to finished product market delivery.

Later, the supply chains became more and more diverse and complex as certain drug patents expired. Generic manufacturing, first in the US and Europe and later in Asia, together with price pressures from buyers, led to more risks [16–19].

Though every step in a supply scenario can be performed by someone else, the MAH remains in charge. In the view of regulators, the MAH cannot delegate the responsibility for the products it markets.

Figure 1: A global supply scenario with cross-country and cross-cultural interfaces.



The consequences of this requirement are not always clear. MAHs are often just sales organizations without the resources to oversee all the activities along the value chain. GDP regulations brought a bit more clarity about what is required, but these regulations were not definitive. European inspectors have recognized a lack of quality oversight, and the EMA issued a reflection paper [20] on the topic for public comments in January 2020. It is obvious that processes must be developed for MAHs to gain complete oversight. These processes must be integrated into the quality management system. In addition, the MAH is also responsible for pharmacovigilance. Small organizations often neglect these requirements and outsource pharmacovigilance services, which again diminishes the MAH's oversight. Finally, regulators expect the MAH to maintain its ability to supply its products. Risk management is probably the only concept that can address risks impacting quality, patient safety, and deliverability. The whole organization must be involved to reduce and manage risks. Risk management ultimately concerns the freedom to operate.

Figure 1 illustrates the complexity of a supply scenario with manufacturing in Asia and, export to Europe and the US, with retesting, batch certification, and final distribution. Each group of chevrons belongs to a different site and country. A dashed line indicates an interface where errors may occur and miscommunication may happen. If errors slip through, they can adversely affect patients. Unavailability of drugs due to challenges in foreign countries is a serious problem in Europe, particularly during the COVID-19 crisis. The tendency to "insource" (i.e., bring in house) services that were previously outsourced is now evident in the European sector, despite the huge effort this requires for technical transfers and the expenses of re-registration fees. New risks will likely emerge if competencies and industry knowledge need to be reestablished in Europe as part of this trend.

Some quality professionals believe that MAH oversight can be achieved by service-level and quality agreements [21]. The expectation is that everything will run smoothly once these documents are in place with shared responsibilities defined. Practice, however, shows that communication between contract partners tends to cease shortly after paperwork is done. At this point, risk management strategies are critical.

To gain oversight, the MAH must know what can go wrong. Long before the specific risks of the manufacturing process are addressed, it is important to understand the interfaces. The dashed lines in Figure 1 represent points of control, but they also represent points where the flow of goods and data can become blocked, or information can get lost. People in charge must establish and maintain their communication channels. This ensures a state of control and initiates continual improvement.

Products are endangered by temperature, humidity, and mechanical influence. These risks are nowadays quite well under control. However, successful batch release decisions depend on reliable document exchanges. Unfortunately, the required documents may be missing, wrong, or unclear. Documentation errors are early warning indicators or proxies for underlying weak points in the organization of work. When data transfers from one IT system into another occur in conjunction with miscommunication and negligence, the results may include data integrity problems, human errors, and wrong decisions; ultimately, the MAH may lose the necessary control of situations and become incapable of delivering products.

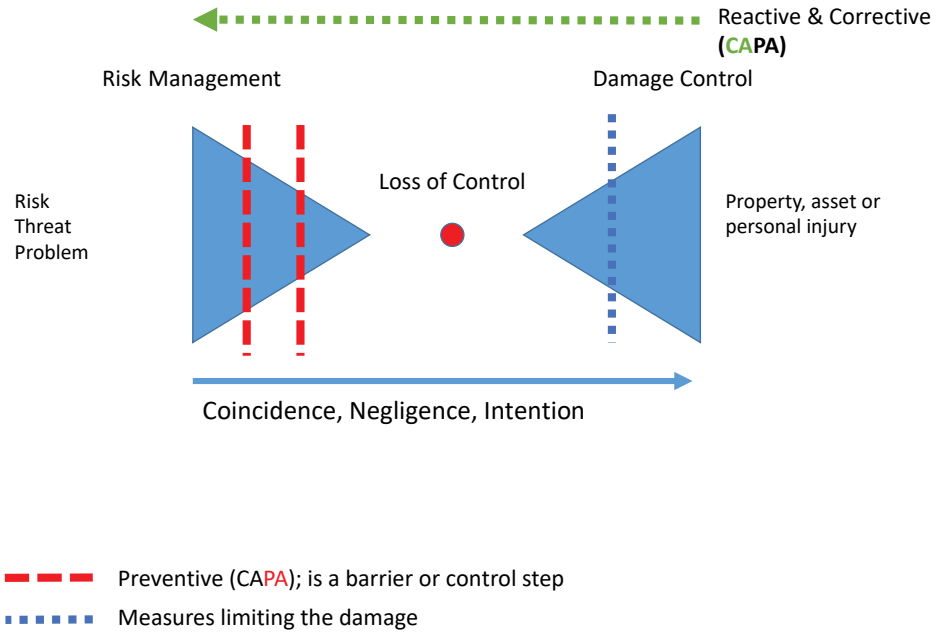
Furthermore, complex transportation routes may also be at increased risk for fraudulent activities. The answer to this is serialization. Modern enterprise resource planning systems allow companies to collect the requisite data. Managing risks involves detection of anomalies, from end to end, in data transfer processes.

The division of labor, price pressures, and a lack of communication between the individuals have led to serious violations of GMPs. The high number of US FDA warning letters issued to manufacturers in China and India in recent years is a symptom of serious inherent risks in global supply chains [22]. In some cases, European MAHs have not received important information promptly and have been surprised by emerging problems. Recalls are required if an unsafe product is already on the market.

Risk management focuses on risk prevention. Pitfalls can be avoided when the appropriate controls are in place. These controls must cover the entire product life cycle.

In manufacturing, risk management must focus on technology and process robustness. Solid oral dosage forms are the largest

Figure 2: Bow tie diagram of relationships among corrective and preventive action (CAPA), risk management, and controls.



category of pharmaceutical products. Nevertheless, progress in risk management in this field came late. Risk management and quality by design (QbD) are the essential elements in the quality system, which is the right approach to develop scale-up processes and increase robustness. Good indicators for process robustness are content uniformity of blends, reliable particle size distributions of granulated material, and reproducible dissolution rates. Control charts clearly show any adverse trends and illustrate whether the manufacturing process is robust enough (i.e., is under control).

Annual product quality reviews help stakeholders analyze the centricity of a process between the lower and upper specification limits. Data from these reviews can be used to calculate the process capability index. Descriptive statistics are a central element in risk management. It is in the interest of the MAH to verify that contract manufacturers have the requisite competencies to react early to trends and to continuously improve processes that ensure robustness.

Another area for risk management is cross contamination. For APIs, key risk factors for cross contamination can be attributed to synthesis routes; use of recycled solvents and catalysts; material storage and flow in factories; and multipurpose equipment, transfer tubes, and containers, and their cleaning operations.

HVAC design has shown to be troublesome in production facilities. The accumulation of dust and dried-out coating residues in parts of the equipment and in filters, together with pressure variations, may lead to the release of contaminants into fresh blends. Traces of other chemicals may not be detected by routine testing. It is easy to claim that cleaning validation prevents this problem. However, warning letters show that these risks are not always under control. This must be addressed in the planning phase, and risk management is the tool of choice.

Process robustness, predictive maintenance, and effective barriers to prevent cross contamination are assets at every manufacturing site.

To manage risk at the interfaces, further measures are required up front. Risk management and quality planning must include training of employees and communication management in global supply scenarios before adverse trends lead to nonconformities. A "person in the plant" strategy (i.e., an employee of A works at site B, and vice versa) is one promising approach to manage such risks.

For countries with nonharmonized GMP regulations (countries without mutual recognition agreements), a retest of imported material is required. If both the process and the testing methods are robust, a loss of control it is extremely unlikely (see Figure 2).

To recap, risk management must trigger process robustness, prevent cross contamination, and ensure communication crossing interfaces. With these key factors in mind, it becomes obvious that risk management embedded into the quality system can offer a lot of advantages.

ORGANIZING OPERATIONAL RISK MANAGEMENT

Organizing operational risk management into modules and phases can be an effective approach. Figure 1 may be useful to define modules/work packages to implement risk management across all operations. It is advantageous for the MHA to create a

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Asking "What is the risk here, and how do you want to manage it?" is the starting point in day-to-day operations and decision-making of a mature organization.

risk assessment package for each chevron and its input and output factors shown in the figure.

Following ISO 31000 [11], the whole organization is involved in managing risk. The organization's top management is in the driver's seat, and the project starts with assigning the responsibility on a high level. No management commitment means no progress. Asking "What is the risk here, and how do you want to manage it?" is the starting point in day-to-day operations and decision-making of a mature organization.

To set up and maintain a risk management system, the organization will require a few skilled risk management ambassadors for training, support, and internal communication. These ambassadors must spread the seed for a company's risk management ambitions. As discussed by Gigerenzer [22], increasing the risk savviness of individuals and, finally, the whole organization takes effort.

Assuming that management is committed, and the ambassadors have some credibility in the organization, a risk-based system to manage operational quality and supply risks can be achieved in three phases (Figure 3).

The first phase provides the foundation for the system. Its outcome is an operational risk management report, which is the basis for the risk register or risk library. This phase is described in greater detail in the next section (Risk Identification).

In the second phase, selected remediation activities can be initiated to directly address specific risks identified in phase 1.

For example, if the report generated in phase 1 shows many problems with documentation, a corrective and preventive action (CAPA) project could be triggered to change instructions that are unclear, too long, error inducing, or otherwise problematic. Improved (modular) templates designed to help operators follow a process can reduce errors in daily operations.

In another example, CAPA might address missing data in handwritten batch records, erroneous yield calculations, and missing controls. One option might be to make the right place to document data more obvious. This basic change may lead to fewer documentation errors and less need for retraining. "Nudging" is a current buzzword in this context.

When teams work together, data control and data integrity (i.e., adherence to ALCOA+ principles) are put at risk by sharing, storing, and retrieving documents on shared drives. Changes such as establishing a directory plan defining a process-oriented filing system or using a cloud-based document management system may help reduce these risks.

All such phase 2 remediation projects must be appropriately staffed and executed. With a few projects like those described here, the organization harvests low-hanging fruits. Employees and contractors will see that there is something in these efforts for them and will likely accommodate new ways of working. However, individual CAPA measures typically deal only with single deficiencies and are therefore inadequate to fully manage risk.

In the third (routine) phase, the organization uses risk management in daily operations. When new risks are discovered, they are routinely processed and remediation actions are endorsed by an operational quality (risk) review board or similar entity. As noted previously, the risk ambassadors must look beyond single events and ask what is wrong with the system.

In this phase, continual improvement, risk management, and quality review come together, and the organization can control quality issues quickly and effectively. A defined improvement project is much easier to handle than checking long CAPA lists and wasting time with "number of CAPA overdue" key performance indicator tracking.

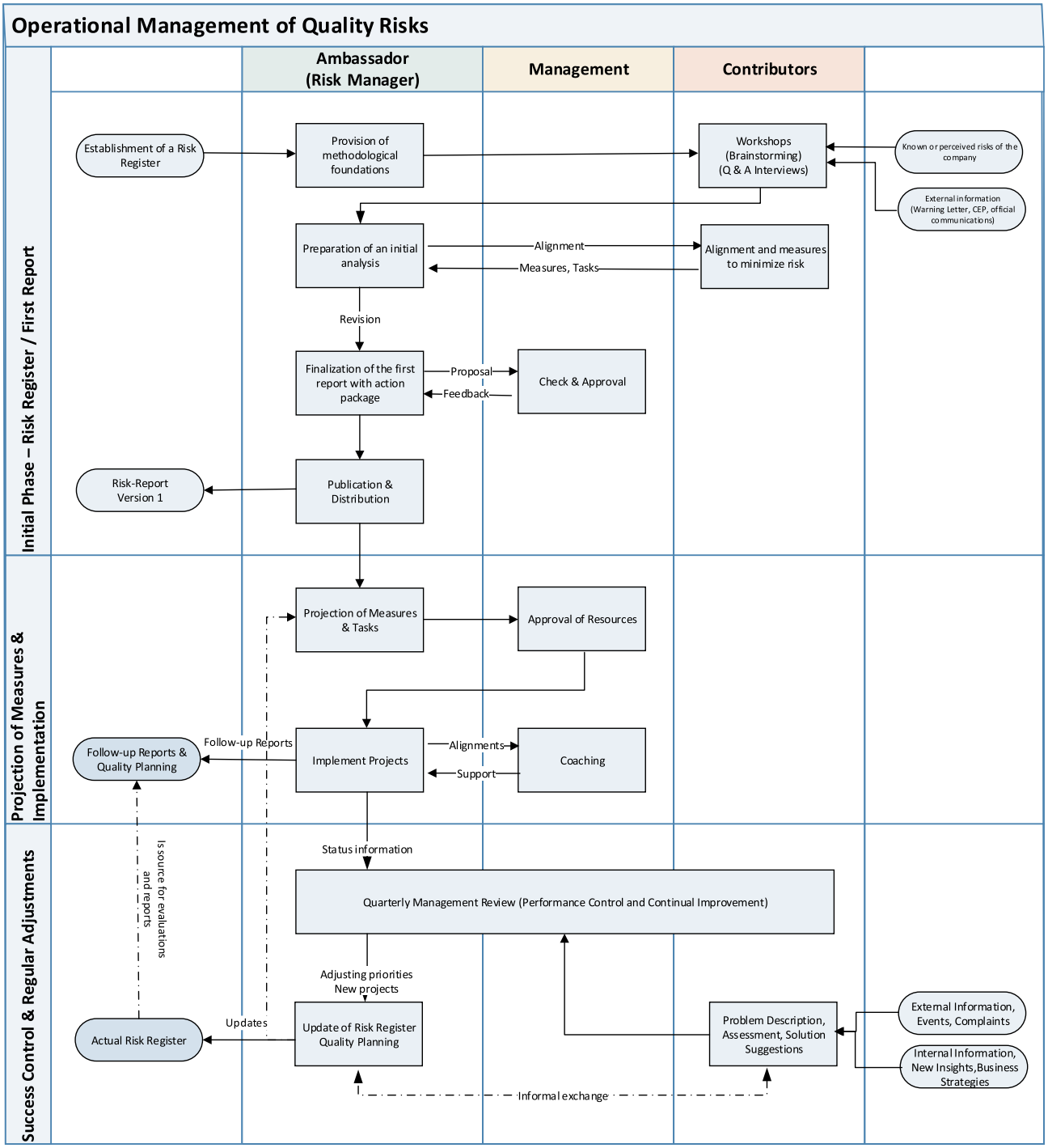
RISK IDENTIFICATION

To implement operational risk management, it is important to get the big picture first. Risk management depends on fast and complete knowledge of potential risks. This is related to the concept of availability. Even if a risk is known, it may not be present and documented in a certain situation. It might be identified and documented later, but in a completely different context. It is therefore important to follow a systematic approach to identify risk (i.e., potential nonconformities). Information sources include:

- Electronic common technical document (eCTD) Modules 1 and 3 [23]
- Commercial contracts and technical agreements
- Contact partners (regulatory support, logistic services, laboratory operations, etc.)

It is also important for the risk management team to get in touch with other stakeholders and employees directly involved in related manufacturing and supply operations to determine what they know about risks. For example, shop floor operators may have tacit and undocumented knowledge. They know the details and can contribute to risk identification and management.

Figure 3: Process to establish a risk-based system for managing operational quality and supply risks.



For each operational module (Figure 1), the risk management team should start by collecting as much data as possible. This involves:

- Studying the module in the registration dossier
- Looking into master batch records and recent product quality reviews
- Consulting audit reports
- Calling people identified in the contracts and asking questions like:
  - What happened previously?
  - What kind of deviations are observed?
  - Which changes have been made in the process and why?
  - What risk management efforts have already been implemented?
  - What kind of risks are perceived?
  - Are there hidden flaws or weak points in the process?

Risk managers should use keywords like those used in the hazard and operability study (HAZOP) methodology. They should also think in scenarios and ask, "What happens if…?" or "What can go wrong here?" It is always better to overestimate a risk than to be surprised later.

It is also helpful to query for public information, such as warning letters or reports published by competent authorities, and raise the question, "Can similar things happen in this unit operation as well?"

Controls and checks must be identified, agreed upon, implemented, and communicated. Quality oversight and communication through the interfaces are essential. Open communication on trends and near misses must be shared. Regular contacts between the risk management team and the people in charge are crucial. The risk management ambassador (or a subject matter expert in relevant unit operations) therefore plays a key role in facilitating risk identification.

The next step is to put together a list of the information received—the risk register or risk library. In the modular approach, the lists established for each chevron shown in Figure 1 will not be long—maybe 30–50 line items that are shared among similar unit operations.

The risk management team may hold brainstorming sessions to narrow down the line items by looking for common root causes, synonymous expressions, and redundancies in the issues they have collected. If the risk managers feel something is missing or contrary to their own experience, they may arrange a second round of interviews or closely examine specific issues discovered.

It is not required to collect and document complete investigation reports. Instead, the risk management team can move one level up and investigate root-cause summaries, or judge intuitively what the problem might be. Auditors typically have a good sense for operational flaws. Simply asking them can yield good information.

The final step in collecting data is to identify appropriate categories. Use a classification that suits the organization's needs, such as 8M (machine, management, material, measurement, men, methods, mindset, mother nature) or 5P (people/personnel, processes, product, performance). to prioritize where the quality system needs to be improved.

Accurate classification of documentation errors is crucial. Useful designations include missing, wrong, not clear, misplaced, and lost. All aspects of a document's life cycle must be addressed.

Categorizations help establish a structure, but issues can sometimes be categorized in multiple ways. The key is to be comprehensive and to clarify how categories are defined. For example, "management" could mean the style of direction or might be focused on budgeting or staffing. "Process" might be defined as "dealing with performance issues, such as drifting or unstable performance, with too many deviations."

Another way to classify risks is by their impact. Risks may lead to personal injuries (e.g., hospitalization of a patient); damage to assets (e.g., loss of a customer or buyer); property damage (e.g., material loss due to a quality defect); GxP violations and inspection challenges; and lost productivity.

RISK EVALUATION

For FMECA, which is the most frequent method of analysis used in pharmaceutical risk management, risks are described in the three dimensions: impact, likelihood, and detectability. Words like low, medium, and high, or minor, major, and critical, are used to rank risks by each dimension on an ordinal scale.

The risk manager should make a choice about how to rank risks but should not lose sight of the bigger picture.

A practical hint is to omit the valuation of likelihood from the first rankings. It is difficult to assign a likelihood to a single event, and it is not easy to identify the number of conforming events that will be appropriate to use for later rankings. It is easier to think initially about risks in terms of prevention and control measures.

With the dimensions of impact and detectability in mind, the risk manager can group and prioritize risks. If there are many risks, a simple (3 x 3) matrix can be used to cluster them. Risks with a higher rank cluster on the upper right, and the ones with lower values on the lower left. Different diagrams can be established—for example, there might be a diagram for each unit operation, diagrams for the interfaces being considered, or one diagram for each impact category.

The clusters may show different patterns, and pattern recognition can be advanced through artificial intelligence. Mighty tools such as multivariate statistics, cluster analysis, principle component analysis, and data mining are infrequently used, but they can help stakeholders make better decisions.

RISK CONTROL

In phase 3 of risk management, barriers or controls can have a broad meaning. Detectability of an error mode is not always related to sensors and technologies. Organizational measures are

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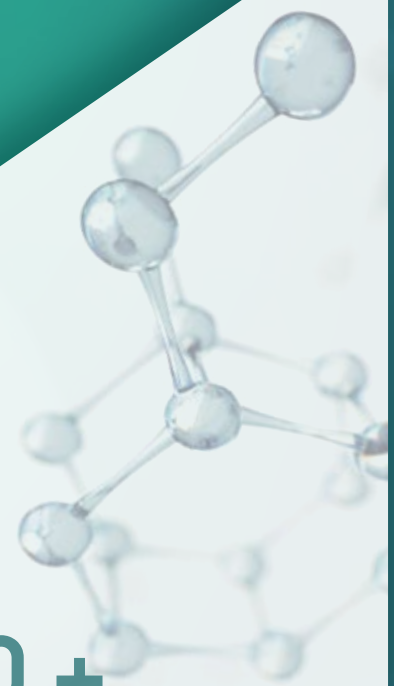

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equally important, so that coincidence, negligence, or intention does not lead to a loss of control (see Figure 2).

To maintain momentum in operational risk management, a quality risk review board brings risk assessment, review, and communication together. The board can also facilitate the use of new risk management tools and training for risk managers in their use. The organization will recognize their benefits as soon as the first effects become visible.

After implementation of operational risk management, regular ad hoc reviews should take place to ensure that improvement projects are on track. The role of the risk manager is to manage the risk portfolio and to prepare decision-making by the risk management committee or team. Applying a plan-do-check-act cycle ensures a constant stream of information, acknowledgment, and risk mitigation actions is maintained.

CONCLUSION

A risk management system can be embedded into a pharmaceutical quality system by first identifying the elements in a complex supply chain. Unit operations and interfaces are the primary work packages to be considered. Risk assessments on a unit operation level result in a risk register or risk library, which is maintained by risk ambassadors. A single process for risk management embedded in the quality system integrates project controls, management, and product quality reviews. Modern technology can be used to present the right metrics, allowing the organization to make timely, fact-based decisions about operational risks.

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About the author

Klaus Finneiser, PhD, holds a PhD in chemistry (15N-NMR spectroscopy) from the University of Siegen, Germany. He started his career in the chemical industry where he gained experience in analytical chemistry, worked with universities to develop methods for monitoring enzyme fermentation processes, and supported other development and pilot projects. He then worked for five years in the dyestuff and chemical division of Ciba-Geigy before moving into the pharmaceutical branch (now Novartis) in Switzerland. During his 20 years in quality control and global quality operations he was involved in many quality initiatives and improvement projects. As a delegee in the EFPIA group for ICH Q9, he came across quality risk management. After leaving Novartis, he joined Ferring and later Acino, where he established a modular quality management system based on ICH Q10. Since 2017, he has supported industrial clients in quality improvement and remediation projects.

FOCUSED ON THE MISSION:

Joydeep Ganguly

By Paul J. Cumbo, MS, MLitt

Joydeep Ganguly, who is currently Senior Vice President, Corporate Operations, at Gilead Sciences, Inc., places a premium on working for a mission-oriented company. "If you choose the right company with the right ethos and a deep, tangible commitment to the patients, the mission is not just rhetoric," he said. "You see it in the way they do things. If you work for a company that makes that central to its value proposition, you have that moral compass. That's one of the ways I've been able to find meaning and inspiration in what I do on a daily basis at work."

Prior to joining Gilead in 2016, Ganguly spent 10 years at Biogen. He holds an MBA from North Carolina State University and an MS in electrical engineering from Notre Dame University. He is proud of his industry achievements but also humbly acknowledges that many other people contributed to them.

A FAMILY COMMITMENT TO CARE

Ganguly comes from a family deeply committed to the medical profession. His father, grandfather, uncle, and father-in-law were all physicians and graduates of the same medical school in India, and Ganguly firmly believes that his work in the pharmaceutical industry honors these family roots in the medical world. "I pursued engineering because of the encouragement from my father—he was insistent that someone in our family not be a doctor. I wanted to find a way to contribute to the healthcare industry, and biotech was an obvious choice. It allowed me to work in a meaningful space that leveraged my love of engineering and mathematics."

The unexpected loss of his father two years ago, at the relatively young age of 66, served to further galvanize Ganguly's commitment to his profession. "While I continue to grieve his loss, working close to the science at a patient-centric company assures me that disease states that have taken the lives of loved ones will continue to be studied and prevented," he said.

INDUSTRY CONTRIBUTIONS

Joydeep Ganguly

Ganguly's contributions to the biotech industry have been notable. "My passion early on was applying automation and controls systems concepts, grounded in advanced mathematical principles, to meet productivity and efficiency risk imperatives within operations," he recalled. "And I feel some of my major industry contributions have been redefining the role of advanced analytics in areas such as biological process monitoring, design and engineering of new facilities, and risk management within operations."

Citing his tenure at Biogen, he explained how the application of multivariate algebraic algorithms to data gathered in process facilitated "a paradigm shift in how we monitored batches of product, how we course-corrected and controlled process." These innovations supported the move from reactive to adaptive control, improved methods for process transfer and scale-up, and democratized data access and availability. This work led to multiple patents and is featured in book chapters and other publications.

Ganguly's accomplishments at Biogen in the early 2000s were arguably ahead of their time. Well before the Fourth Industrial Revolution and digital transformation were trending concepts, he was able to apply multivariate algebra to build mathematical modeling directly into production processes. This work "took something super esoteric, really just in the province of mathematicians, and brought it to the factory floor," he said.

"It collapsed a lot of data into something useful. It allowed you to look at how things are going in the moment—this provided intelligence on the production floor, which allowed you to take immediate action instead of doing so retroactively or based on investigation."

To illustrate the magnitude of this change using an everyday example, Ganguly compared it to going from weighing oneself once a month to using a smart watch to monitor fitness. As it turned out, the story of these developments, "Process Analytical Technology (PAT) and Scalable Automation for Bioprocess Control and Monitoring–A Case Study" (*Pharmaceutical Engineering*, January-February 2006) authored by Ganguly and his colleagues, received the Roger F. Sherwood Article of the Year Award for 2006.

LEADERSHIP IN SUSTAINABILITY

Sustainability is a major priority for Ganguly, and his role at Gilead is deeply integrated with the company's sustainability strategy. "I see sustainability as more than a program or a project. I see it works best when it is embedded within the fabric of an organization's way of operating. Organizations serious about sustainability often take a holistic view, incorporate it within their goals, and incentivize eco-friendly behaviors," he said. The more integrated and focused a sustainability plan is within the operating plan, the more effective it is, he explained.

He identified three interwoven objectives for successful sustainability plans: growing operations sustainably, reducing a company's environmental footprint, and increasing business resiliency. Plans need to have "an integrated framework. Sustainability is not a thing unto itself," he said.

As part of its master plan, Gilead's ambition is to reduce greenhouse emissions by 25% by 2025. This goal will not be achieved by "any one big, shiny thing," he said.

"It will be achieved by making some big commitments, sure, but also through many small initiatives. For one thing, we've incentivized people. We've augmented that with a very analytical approach to efforts, relying on technology, sensors, and data to reduce the impact of energy-intensive operations. Sustainability requires a good scientific temperament."

According to Ganguly, influential companies must lead by example for the industry as a whole to embrace sustainability. "The way to do this is to make it a team sport," he said. "Companies in a position to incentivize sustainability have to reward those who do so."

Moreover, "we have to redefine 'sustainability' and get away from everything that has constrained the term." Though sustainability includes environmental consciousness and activism, Ganguly believes the concept has to be more holistically applied and broadly incentivized. "We have to make it a 'business value stream,'" he explained.

How can this be done? "You don't want to focus on transient things. You have to look beyond the myopic view of short-term achievements that will be heralded in one moment," Ganguly said, referring both to high-profile eco-friendly initiatives and cost-saving measures made in the name of sustainability. "I've seen that big initiatives often don't last beyond the half-life of the leader who had them in mind. We have to ingrain and incorporate sustainability into the framework or 'DNA' of how we do things."

As an example, he outlined how Gilead has taken a long-term view with regard to contracting relationships. "When we look at RFPs for engineering firms that want to work with us, we look at things beyond just cost. We put an equal emphasis on the company's sustainability efforts. We want to reward those firms who have prioritized this." In this way, Gilead makes building relationships a key part of its holistic approach to sustainability.

"It's a position of privilege to be able to direct business to the companies that are taking the risk and making the investment to do this," he said. "Yes, we are financially disciplined, but we'd rather go for the right company that shares our values because, in the long term, that's more cost effective. People who share our values typically work better for us because they share the long-term priorities.

"In my world in operations, when there is a choice between two firms and one outpaced the other in terms of values—even if at a higher bid cost—I'd always go with the first. And we've never been disappointed. Integrity matters."

DIGITAL TRANSFORMATION AND ENABLING WORKERS

Like other senior executives in biotech, Ganguly is keenly aware of the digital transformation currently underway. He explained that the digitalization efforts at Gilead—especially within operations—are centered around enabling workers and driving digital dexterity. The technology leadership team focuses on building skills in a culture of values-based leadership emphasizing empathy, caring, and listening. Additionally, he noted the company's embrace of social responsibility, collaboration across the ecosystem, and a commitment to seeking and responding to employee feedback.

Industry Leaders: A Year of Excellence

This profile is the latest in the Industry Leaders series started in January-February *Pharmaceutical Engineering*®. Other profiles:

"An Advocate for Quality: Ranjana Pathak" (January-February)

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Ganguly believes in a "goodness chain," across which individuals and companies can support the common good.

"The Fourth Industrial Revolution is meant to inspire us, not to turn us into robots. And people get inspired when we have an egalitarian way of working," he said. "It's values-based leadership to focus on the workforce and then design the workspace—not the other way around. There's a lot to consider from an empathetic perspective."

Ganguly stressed that firms have a responsibility to put people first as they work toward technological transformation. "Lead with empathy, appreciate the diversity within the workforce, and find ways to create value through the different skills and perspectives that exist within the team," he suggested. "Invest heavily in learning and development—not just in technology areas, but in areas of core fundamental leadership. Finally, don't let the technology become the only driving force behind decisions in your overall strategy."

ISPE AND ADVICE TO YOUNG PROFESSIONALS

ISPE has been an invaluable resource for Ganguly, and he emphasized its importance for everyone in the industry. In the earlier years of his career, the Society served as an education portal, providing access to thought leaders and a network of colleagues who shaped his way of thinking. Eventually, as he began contributing more to conferences and forums, ISPE afforded him a platform to vet, discuss, and stress-test ideas that needed critical peer review.

"As we now enter a new era—technologically and socially—I continue to be impressed by the efforts of ISPE to drive discussions and plans to inspire the next generation. ISPE and its Foundation are doing important work to further inclusion and diversity efforts within our profession. It has informed the way I look at hiring, retaining, and developing talent within my own team and has created a greater sense of resolve to ensure our profession continues to find ways to lead in this space."

Asked what advice he'd offer to Young Professionals, Ganguly said, "It's a great time to be in this industry. The pace of change has never been higher, and the opportunities have never been as exciting. Be curious, continue to learn about new areas, and don't be afraid to take risks. Focus equally on soft skills, leadership values, how you get things done, and what you can achieve. Look outside your job description to find ways to contribute to society and embrace a bigger mission for yourself. Give back to the community and your profession. Get a mentor, and when you've reached a position where you can mentor, pay it forward and support other professionals. And have fun! There has never been a better time to be an engineer in the biotech world than today."

STRENGTHENING THE "GOODNESS CHAIN"

Ganguly believes in a "goodness chain," across which individuals and companies can support the common good. "We should not measure ourselves on capital budget or how many buildings we have. We should be looking at ourselves in social purpose, and accelerate innovation that would not otherwise see the light of day. We have to drive a 'different phenotype.'"

For Ganguly, a long-range, forward-looking perspective is crucial to sustain the industry. "We have to focus our strategy on recruiting the next generation. If we don't, they will want to go work in a different industry," he said.

"If we don't inspire kids to come and learn cool things, we're lost. At Gilead, our employees help teach students about careers in science, technology, engineering, and math (STEM) at a variety of events each year. We also invite them to come to our Foster City campus for STEM career days. Additionally, we have to focus on the workforce and keep it future focused."

Nurturing the next generation of industry leaders involves inclusion efforts, Ganguly said. "We have to drive a more inclusive and diverse culture within our discipline. We need to attract, develop, and retain talent within our profession, and create the requisite framework and ecosystem to address the disparities that do exist today. This is where ISPE is doing a great job through the Foundation and the educational programs, but there is more work to be done."

That kind of future-oriented focus, in Ganguly's view, all comes back to values-based operations and the importance of good leadership by those in positions of high influence. "Not everyone has the license to make values-oriented decisions. But if you pick the right company, it puts the mission into action and this connects to the bigger picture of care—and the greater good. When you look for a company that not only gives you the license to be a good community citizen but also encourages and eventually expects you to be one, you'll never have a question about being part of the goodness chain."

For Ganguly—a husband and father—the opportunity to serve as a strong, resilient link in that goodness chain is as much a personal vocation as it is a professional achievement. Moreover, living this vocation has connected him with a family legacy of patient care that now spans the globe from India to California.

About the author

Paul J. Cumbo, MS, MLitt, a veteran high school teacher and administrator, is a freelance writer, editor, and communications consultant serving a variety of industries. He has collaborated with some of the world's most well-known Fortune 500 manufacturers, consulting firms, and global nonprofits, including the World Economic Forum, on projects ranging from internal documents to major white papers and other publications. His work for *Pharmaceutical Engineering* began with the July–August 2018 cover story on the Fourth Industrial Revolution featuring Enno de Boer of McKinsey & Company. He is a Principal and Cofounder of the Camino Institute, which offers service-oriented travel and retreat experiences for families and organizations.

Validation 4.0: Shifting Paradigms

By William E. Bennett II, Hans Heesakkers, Stefan Horneborg, Gilad Langer, Line Lundsberg-Nielsen, Anthony Margetts, PhD, and Fritz Röder

As Pharma 4.0™ increasingly becomes reality, our validation practices must change. We can no longer apply 20th-century thinking to 21st-century technology and resources. Validation must adapt to industry shifts from iterative to disruptive innovation, from batch to continuous processing, from bulk processing to personalized medicine, from centralized systems to the Internet of Things (IoT), from controlled data to distributed data, and similar changes.

What does validation in the context of Pharma 4.0™—i.e., "Validation 4.0"—look like, and why do we as validation professionals care? Just as validation practices and paradigms shifted throughout the industry's prior evolution, so must they change to keep pace with future evolution. Adoption of quality risk management (QRM) and quality by design (QbD) principles and practices in validation lagged behind industry adoption. Unless we prepare now, the adoption of validation practices for Pharma 4.0™ innovations will lag behind industry adoption, and this could jeopardize implementation of industry innovations. This challenge applies to all validation, not only computer system validation.

LESSONS FROM OTHER INDUSTRIES

The 20th century was the era of blockbuster pharmaceuticals, during which the pharmaceutical industry unsurprisingly adopted the principles of mass production. As we enter the era of product differentiation and personalized medicine, we should learn from other industries that started this journey before us.

After the 2001 recession, the semiconductor industry went through a fundamental transition through which it was transformed in a matter of 10 years from high-profit, high-waste operations to one of the world's most highly automated, lean industries. This astounding rate of adoption was facilitated by what we know as Industry 3.0 computer technologies.

In the 1990s, the aerospace industry embarked on an initiative to digitize product information to alleviate costly and burdensome regulatory and customer documentation requirements. Each F-16 jet fighter delivered was rumored to require a volume of documentation sufficient to fill a 747 jumbo jet. This initiative resulted in the product life-cycle management (PLM) systems that are now commonplace in the aerospace industry.

The automotive industry delivers, with a few hiccups, a very high level of quality with little regulatory oversight, because quality is understood to be a competitive advantage, and therefore a critical business goal, in this industry. The relevant concept that the automotive industry has adopted is QbD, an integrated product design approach, which is also the cornerstone of the Pharma 4.0™ holistic control strategy [1].

Since the 1990s, the automotive, aerospace, and defense industries have used concurrent engineering principles that are enabled by digital product models, or model-based design. At the heart of this process are structured data models of the product aided by software tools that allow multiparty collaboration on product design, production, and testing.

These industries are already primed to be able to adopt artificial intelligence/machine learning or augmented reality/virtual reality because these tools can build on the data foundation they already have. In contrast, most of the pharmaceutical industry lags behind other industries in applying concepts such as digital maturity, digital twins, PLM, and QbD.

VALIDATION AND PHARMA 4.0™

What does this mean for validation? Ultimately, the community of validation professionals must ask ourselves two questions:

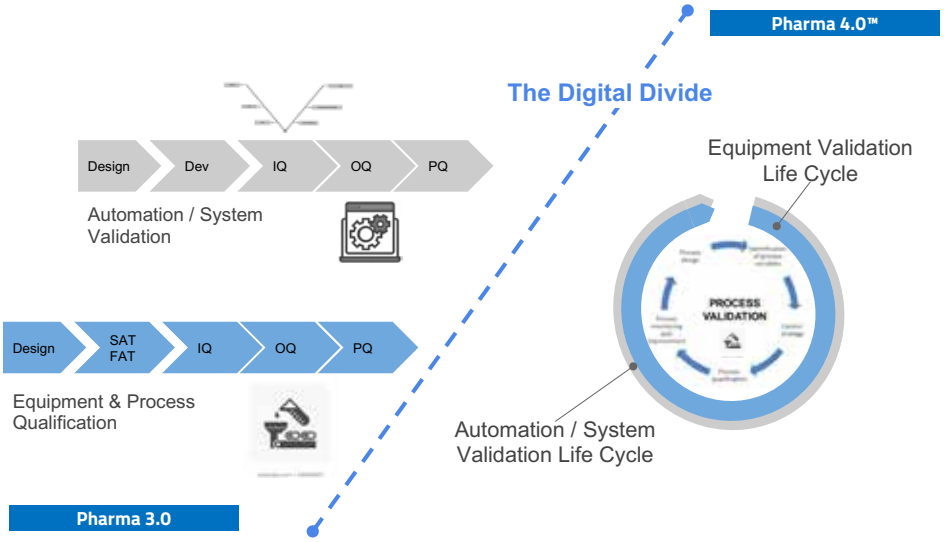
- Can we adequately deal with the pace and complexity of pharmaceutical evolution and paradigm shifts by applying current methodologies?
- Can we build on our current methodologies, or must those methodologies change to accommodate industry evolution and paradigm shifts?

Enablers and Challenges

There are three key external enablers and trends for a new Pharma 4.0™ approach to validation:

- Regulatory encouragement to help the pharmaceutical

Figure 1: Changing the mindset of validation—from siloed automation, system, and equipment qualification to integrated process, automation, and system validation for intended use.



manufacturing sector mature to a maximally efficient, agile, and flexible state, in which manufacturers reliably produce high-quality drugs without extensive regulatory oversight (21st-century GMP initiative)

- Advancement of health sciences knowledge to the molecular level, enabling the pharmaceutical industry to evolve from "discovering" medicines to "engineering" the next generation of differentiated, competitive medicines
- Innovative technologies that are smarter and more adaptive in conjunction with software capabilities to handle large amounts of adaptive, self-optimizing data in near real time

In the new digitalized and connected Pharma 4.0™ world, we must be able to adapt to evolution in production, such as from blockbuster to personalized medicine, and respond immediately to changes in consumer demand, supply chain, raw material and product variability, equipment breakdown, and even the way we work (think of the COVID-19 pandemic's impact). Such responses are only possible if we understand and accept the impact of changes from a holistic perspective, looking at the entire value network that covers the controls that must be in place to ensure the product can be manufactured and supplied the patient.

This is the holistic control strategy, which enables us to predict (or simulate) this impact in real time and propose the necessary process adjustments. The science and risk basis of the predicted outcome of the change will provide a statistical basis to estimate the risks to the patient, product, business, operator, environment, and so on, and to use this risk estimate to determine the next step.

However, current validation strategies are not well suited to this new paradigm. If the simulated change is implemented, current validation paradigms would likely not consider such a process to be in a state of control, particularly if this process were not just predictive, but also adaptive.

How will we manage processes that have automated decisions to change or improve? How will we ensure such a process is validated? Perhaps we will require a completely new meaning of validation for these Pharma 4.0™ self-optimizing or self-decision-making systems and processes.

Process Performance Qualification

Current models for initial and continued process validation assume closed manufacturing processes using algorithm-based input-output automation and control. These models need to change across the entire value network to accommodate the holistic control strategy and manufacturing processes that are distributed—even to the point of single-patient/bedside manufacturing/delivery—and that will apply new technology.

Product and process knowledge derived from process development will be refined using real-time process data. Digital twin technology will be used to provide additional understanding and will contribute to the validation process.

The holistic control strategy will facilitate the delivery of process performance qualification and incorporate a range of innovative technologies. Validation will be built in, and the various groups involved in validation will have to work together. A siloed approached will no longer work (see Figure 1).

HOW DO WE GET THERE FROM HERE?

Validation concepts have developed and evolved as the industry has tried to adopt new trends and technologies. However, in Pharma 4.0™ we must integrate these concepts; therefore, it is now the time to rethink the validation strategy and facilitate the

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move to agile processes. The validation strategy must be part of the holistic control strategy, and stakeholders must use critical thinking to ensure lean and robust risk assessment.

Key subject matter experts will require experience to set up lean processes. There is an opportunity here for ISPE to help companies improve their digital maturity and move to lean processes as part of the holistic control strategy.

This transition in validation strategies is facilitated by adopting QRM-based integrated commissioning and qualification principles defined by the revised *ISPE Baseline Guide*, volume 5 [2]; risk-based process performance qualification, as defined in the *Good Practice Guide for Practical Implementation of the Lifecycle Approach to Process Validation* [3]; and the risk-based approach to computer system validation defined in the *GAMP® 5 Guide* [4]. Together, these efforts can potentially help shift validation paradigms to make Validation 4.0 a reality.

CONCLUSION

Current practices lead to silos between computer system validation, facility and equipment qualification, product and process qualification, and the overall quality systems. These silos inhibit innovation within the industry. This is not just a business concern—it is also a risk to the delivery of lifesaving therapies to the patients served by the industry. The goal of Validation 4.0 is to develop a cohesive, harmonized, integrated, holistic, risk-based approach for process performance qualification incorporating computer system validation that builds on the Pharma 4.0™ operating model and includes the holistic control strategy, digital maturity, and data integrity by design. This approach will help support and facilitate current and future innovations in the pharmaceutical industry.

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About the authors

William E. (Chip) Bennett II is Associate Director, Global C&Q, for CAI, where he is a QRM subject matter expert and lead commissioning, qualification, and validation program development subject matter expert. A Project Manager and Senior Validation Engineer, Chip is a PMI-Certified Project Management Professional (PMP) with 20 years of experience in the pharmaceutical and regulated non-pharmaceutical industries. His areas of expertise are risk-based verification, aseptic manufacturing, cleaning validation, quality systems, and owner project management. Chip is responsible for developing and implementing QRM-based commissioning and qualification programs and projects, with a particular focus on assessing and training clients regarding development and implementation of, and transition to, risk-based approaches. He has been an ISPE member since 2020.

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

Stefan Horneborg is a Business Process Management (BPM) Specialist and has worked for more than 15 years in the domain of process and change management in the life sciences industry. He is a certified computer systems validation manager and trainer for regulatory submission management and pharmacovigilance. While working in the life sciences industry, he has been responsible for helping companies around the world with their quality and regulatory processes and with training in these processes. In his positions as Presales and Sales Consultant, he gained expertise in quality assurance, research and development, BPM, and other areas. Currently, Stefan is responsible for driving electronic validation management across Europe as Director, Sales Europe, at ValGenesis EMEA B.V. He has been an ISPE member since 2013.

Gilad Langer is an accomplished business leader with over 25 years of experience in IT, automation, engineering services delivery, technical operations, business development, and sales. He has deep domain expertise in digital technologies and manufacturing business systems and an accomplished track record of digital transformation to drive high levels of operational performance in manufacturing industries, with a specific focus on regulated life sciences industries. He has also served as an advisor and business consultant in the areas of technology directions, industry strategy, and software implementations. Gilad started his career in academia, researching concepts and architectures for agile manufacturing systems using novel technologies such as multi-agent systems and concepts that were the archetype for Industry 4.0 and the Industrial IoT. He has been an ISPE member since 2010.

Line Lundsberg-Nielsen runs her own consultancy business and works as a Consultant for NNE, supporting clients in developing and implementing manufacturing processes for pharmaceutical products. She has spent more than 20 years in the pharmaceutical industry. She holds a PhD in process analytical technology (PAT), and her work focuses on science- and risk-based approaches to QbD, PAT, control strategy, process validation, qualification, technology transfer, and Pharma 4.0™. Line has been an ISPE member since 2001. She is currently the Chair of the Global PAT and Lifecycle Control Strategy Community of Practice (CoP) Steering Committee, serves on the advisory board of the Pharma 4.0™ SIG, and is a member of the Validation 4.0 subgroup.

Anthony Margetts, PhD, has 35 years of pharma experience. He worked for ICI-Zeneca-AstraZeneca, leading teams responsible for technical transfers, new product introductions, and preparations for international, European, and US FDA preapproval and regulatory inspections. He managed the introduction of new medical device products, including setting up global supply chains and ensuring their compliance to international standards. Tony managed compliance-related assignments in many countries, including Australia, Canada, China, Denmark, Ireland, France, Germany, Italy, India, Japan, New Zealand, Puerto Rico, Sweden, the UK, and the US, and recently helped the ASEAN pharmaceutical industry achieve the PIC/S standard for manufacturing, with projects in Indonesia, Malaysia, Singapore, Thailand, and Vietnam. Tony was Chair for the editorial review of the latest version of *GAMP® 5* and has been an ISPE member since 1995.

Fritz Röder has a diploma in environmental engineering and 12 years of industry experience in various positions. He gained knowledge in a broad field of pharmaceutical topics and worked for companies such as Allergan and Bayer. Currently, he is Senior QA Manager at Merck Healthcare, KGaA, Darmstadt. Fritz is involved in the ISPE Pharma 4.0™ Validation Group, the ISPE Utilities Steering Committee, and the ISPE D/A/CH Water and Steam CoP. Fritz has been an ISPE member since 2015.

MEMORABLE MILESTONES:
40 Years of ISPE

ISPE is celebrating its 40th anniversary this year! Here are some of the memorable events from the last 40 years.

1980
- In August six men met to discuss the formation of an engineering society that would primarily focus on education, networking, and the exchange of information. They chose the name "International Society of Pharmaceutical Engineers." A three-person staff was retained.
- *Pharmaceutical Engineering*® published its first issue in November 1980-January 1981, initially publishing on a quarterly basis.

1981
- ISPE's relationship with the US FDA began. In February, the FDA spoke in Tampa, Florida, at the first ISPE seminar, "Upgrading to Meet cGMPs."
- In the first year, ISPE membership reached 430.
- The first Annual Membership Meeting and Awards Banquet was held in November in Philadelphia, in conjunction with PACK INFO '81.

1982
- *Pharmaceutical Engineering* began to publish bimonthly with the July-August issue.

1985
- Bob Best became ISPE's Executive Director.
- The first North American Chapter was formed in New Jersey.
- A member newsletter was launched.

1986
- ISPE sponsored its first International Pharmaceutical Engineering Forum during the Annual Meeting held in November in St. Petersburg Beach, Florida.
- ISPE membership grew to 1,000.

1989
- ISPE's first European venture, the International Congress of Pharmaceutical Engineering, took place in September in Brussels.
- The first two Affiliates were formed in 1989–1990 in the UK and Ireland.

1990
- The Society's name was changed slightly from "International Society of Pharmaceutical Engineers" to "International Society for Pharmaceutical Engineering."
- ISPE staff grew to nine employees.
- The ISPE Editorial Committee unanimously chose *ISPEAK* as the official name of the ISPE newsletter in March.

1991
- The New Jersey Institute of Technology became ISPE's first official Student Chapter.

1992
- ISPE opened a European office in The Hague, Netherlands, with six employees.
- Volunteer leaders from North America and Europe wrote ISPE's first strategic plan and mission statement.

1993
- ISPE implemented strategic objectives by establishing North American and European Operating Committees.
- The D/A/CH Affiliate became ISPE's first multinational Affiliate and organized its first programs.
- ISPE membership reached 5,000.

1994
- Industry leaders developed industry-wide guidance for suppliers to assist in the management and development of computer systems. The result was the first *GAMP® Guide*.

1995
- At the Annual Meeting, ISPE introduced the Pharmaceutical Engineering Baseline® Guide Series with the draft of volume 1, *Bulk Pharmaceutical Chemical Facilities*.

1996

- In response to member demand, ISPE launched its website (ispe.org) in November.

1997

- Sharon Smith Holston, Deputy Commissioner for External Affairs, FDA, presented the FDA Commissioner's Special Citation to ISPE, "in appreciation of outstanding cooperation with the Food and Drug Administration in providing vital support to the industry through educational and special projects, nationally and internationally." Bob Best accepted the award on behalf of ISPE and received the Harvey W. Wiley Medal, named for the father of the Pure Food and Drug Law.
- At the Society's Annual Meeting, Vice President Al Gore's Hammer Award was presented to the ISPE-FDA team that developed a list of "similar equipment" needed for efficient implementation of scale-up and postapproval changes (SUPAC) guidance for products in immediate release–solid dosage form.
- On 21 November 1997, the Center for Drug Evaluation and Research gave ISPE a special Recognition Award.
- ISPE membership reached 10,000.

1999

- The ISPE European Office in The Hague closed.
- The first global edition of *ISPEAK* was published in July-August.

2000

- ISPE staff reached 31 employees.
- ISPE acquired the GMP Institute, effective 1 January 2000, and began ISPE's training division.
- In June, the ISPE Singapore Affiliate, the first Affiliate in Asia, was officially launched.

2002

- The US Department of Commerce chose ISPE to offer a four-week intensive training program jointly led by the GMP Institute, consultant Dale McMillen, and the American Association for the Advancement of Science. The course provided basic knowledge and training to enable former biochemical scientists from Russia's Novosibirsk region to shift from their current manufacturing standards to international cGMPs.

2004

- ISPE membership reached 20,000.

2005

- ISPE celebrated its 25th anniversary.
- Novo Nordisk A/S received the first Facility of the Year Award (FOYA), which recognized the NovoSeven pharmaceutical manufacturing facility in Hillerød, Denmark.
- In September, in cooperation with the US FDA, ISPE released a definition paper on restricted access barrier systems.
- The FDA invited ISPE to play a leading role in transitioning how the industry is regulated and the incentives being offered to companies to innovate. Specifically, the FDA asked ISPE to change its current operating procedure in several ways:
  - Publish a new science-based, peer-reviewed journal.
  - In collaboration with universities and the FDA, develop a training program to be used by both industry and regulators.
  - Establish a certification program that sets a standard for pharmaceutical manufacturing science and technology competency.
  - Work through ASTM International to establish standards that must be referenced by the FDA.
- ISPE began forming Communities of Practice (CoPs), with six CoPs announced at the Annual Meeting in November.
- Also at the Annual Meeting, ISPE received the FDA Commissioner's Special Citation in recognition of ISPE's "outstanding commitment and many years of continued support of crucial initiatives including the drug shortage program, the Process Analytical Technology Initiative, the reform of 21 CFR Part 11, and the Risk Based Inspection Model, as well as significant contributions to preparing for training the pharmaceutical professionals of the future."

2006

- ISPE's Professional Certification Commission (PCC) launched an international job analysis survey, one of the first steps to develop a professional credential for pharmaceutical practitioners.
- ISPE redesigned its website and logo.
- In March, ISPE joined forces with the University of Florida to train workers for Florida's growing biotechnology industry.
- ISPE launched an E-Letter series based on CoPs.
- ISPE published the inaugural electronic version of *ISPEAK* and the premier issue of the *Journal of Pharmaceutical Innovation*.
- ISPE cohosted its first conference with the Parenteral Drug Association about ICH guidances.

2007

- PCC held the first exam for the Certified Pharmaceutical Industry Professional (CPIP) credential.
- ISPE created the Product Quality Lifecycle Implementation (PQLI) initiative and held the first PQLI workshops in Washington, D.C.
- ISPE launched a new web application for its 14 CoPs.

2008

- *GAMP® 5* was launched.
- ISPE membership reached reached over 24,000.

2009

- ISPE reorganized, with staff and cost reductions, due to the global financial crisis.
- ISPE began offering technology-based learning and social media communication with members.

2010

- To strengthen and expand the involvement of global regulators, ISPE introduced complimentary membership for these professionals.
- ISPE started its Young Professionals (YP) initiative.

2011

- Bob Best announced his retirement as President and CEO after 27 years of service to ISPE.
- ISPE launched a redesigned website.

2012

- Nancy Berg became ISPE's President and CEO.
- ISPE held its inaugural cGMP Conference, initially cosponsored by the FDA.

2013

- The ISPE Drug Shortages Initiative began with a global survey of industry professionals about the manufacturing root causes of drug shortages.
- The Patient Initiative launched a global survey of patients to learn about their experiences with clinical trial materials.
- ISPE announced initiatives in the areas of quality metrics and breakthrough therapies.
- ISPE began a partnership with PMMI—The Association for Packaging And Processing Technologies, including developing Pharma EXPO for November 2014.

2014

- ISPE expanded its e-learning.
- John Bournas was named ISPE's President and CEO.

2016

- ISPE and the Pew Charitable Trusts initiated a joint research project into drug shortages.
- GAMP® celebrated its 25th anniversary.
- The "Message from the Chair" column debuted in the September-October issue of *Pharmaceutical Engineering*.
- *Women in Pharma®* held its inaugural session at the Annual Meeting.
- ISPE held its first Biopharmaceutical Manufacturing Conference and first European Biotechnology Conference.

2017

- ISPE introduced a website redesign in August.
- ISPE and Pew Charitable Trusts released their report, "Drug Shortages: An Exploration of the Relationship between U.S. Market Forces and Sterile Injectable Pharmaceutical Products."
- *Pharmaceutical Engineering* covered Pharma 4.0™ for the first time in the May-June issue.
- *Pharmaceutical Engineering* reported on the development of chimeric antigen receptor T cell (CAR-T) therapies.
- The Regulatory Steering Committee was established.

2018

- YP representation was added to the ISPE International Board of Directors with the creation of an ex officio slot. Caroline Rocks was the first YP representative to the board.
- PE Online, the online version of *Pharmaceutical Engineering*, began publishing on the ISPE website.

2019

- Open access for *Pharmaceutical Engineering* was launched.

2020

- ISPE celebrated its 40th anniversary.
- Tom Hartman became ISPE's President and CEO.

ISPE D/A/CH Affiliate: Striving to Lead

By Mike McGrath

The ISPE D/A/CH Affiliate is a leader in many respects, from its ever-increasing size to the invaluable engagement of its members, who contribute to ISPE's growth around the world. Grouping together Europe's German-speaking countries—Germany (D), Austria (A), and Switzerland (CH)—it is currently the second largest ISPE Affiliate or Chapter.

The D/A/CH Affiliate has more than 1,100 members, with approximately 60% of its membership coming from Germany, 30% from Switzerland, and 10% from Austria. "We have been providing good services through conferences and workshops for members in the D/A/CH region," said D/A/CH Affiliate President Gunter Baumgartner. "Over the years, we have always increased membership and have maintained a high retention rate."

BALANCED LEADERSHIP

With ongoing growth as an objective, the D/A/CH Affiliate has elected to organize its board to have representation from the various types of members. "We have a 15-member board with approximately 30% from industry, 30% from suppliers, 30% from engineering companies, and about 10% from academia," said Baumgartner. "It's important for us to maintain this balance so that the Affiliate is not misused by a marketing company or an equipment supplier to sell their products. This is something that is appreciated by our members."

Baumgartner also noted that all three members of the Affiliate's executive board (the President, Vice President, and Finance Officer) must come from the pharmaceutical industry. The term for the President is a minimum of two years, with no maximum. "With a term of less than two years, it would be difficult to be consistent," he explained. "You have the onboarding process and by the time you start on your initiatives, half a year is gone and then you only have a few months before the next election. Our strategy is for a longer term. I'm currently in my fifth year, and the previous President served for five years. Ideally, I'd say a five-year term would be best because then the presidency is not always focused on one person."

Gunter Baumgartner

Each of the 15 members of the Advisory Board is responsible for a specific aspect of ISPE activities, such as Communities of Practice (CoPs), students, Young Professionals (YPs), workshops, or conferences and events.

AN ACTIVE SCHEDULE

Although all in-person events have been canceled for 2020 due to the ongoing pandemic, Baumgartner outlined the activities that would normally be included in the Affiliate's calendar. "Typically, we hold about 10 conferences and workshops per year, plus one bigger event where we generally get 100 to 150 participants," he said. "This year, we adapted to virtual conferences. A key highlight was the digital conference, Pharma's Journey to Digital Manufacturing: OWN It—DRIVE It—WIN It!, with more than 120 participants."

The larger event, he said, is normally held at a manufacturing location, which provides members the opportunity to tour the site. "We try to select a site where there has been a recent investment project so that our members can see a modern facility or a new state-of-the-art process. From the feedback we received, this strategy is attracting many of our members to participate in such a conference."

The various events are held in major cities throughout the Affiliate's region, with a certain percentage in each of its three member countries. Baumgartner said that quick and efficient travel by train, plane, or car to Vienna, Zurich, Hamburg, or Berlin makes attendance relatively easy for members.

The Affiliate has launched a new initiative to pair YPs with experienced members from the pharmaceutical industry at all conferences. Baumgartner explained that this arrangement is popular with the YPs. "It gives them an opportunity to discuss matters with experienced industry leaders, which they would not have in their normal lives as young engineers. This is a good platform for the YPs to develop their own networks, and we have a very active YP team."

In addition, the Affiliate has a committee dedicated to student outreach. Each year, the D/A/CH Affiliate awards a prize for the year's best master's thesis. "The professors at the universities do an internal evaluation and nominate the best thesis at their university," Baumgartner said. "We then do a short evaluation and select 5 to 10 awards. This year, we awarded students €1,000 and a free one-year ISPE membership."

INTERNATIONAL CONTRIBUTIONS

In 2018, while celebrating its 25th anniversary, the D/A/CH Affiliate received the ISPE Affiliate and Chapter Excellence Award in recognition of its success in membership growth and engagement, as well as its contributions within Europe and around the world. Several members are active in international committees and conferences. "We have been a leader in Europe and have contributed a lot to conferences and events like the Hackathon, and members of our team were the first to introduce the Pharma 4.0™ initiative. We are proud of all of these contributions and, as a result of all the activities, receiving the Affiliate Excellence Award," said Baumgartner.

The Pharma 4.0™ initiative, a framework for establishing digital strategies in a pharmaceutical context, was the brainchild of ISPE D/A/CH board members Christian Wölbeling and Marcel Staudt. Wölbeling in particular has been very active in promoting Pharma 4.0™ around the world.

Baumgartner, who has been an ISPE member for 15 years, is serving his second term as a member of the ISPE International Board of Directors and is part of the judging committee for the Facility of the Year Awards (FOYA) and other program committees. "The experience of serving on the International Board has been a great experience, which has also enhanced the work in the D/A/CH Affiliate," he said. "Additionally, it has supported providing a broader knowledge about ISPE operations around the world, especially understanding the different needs of the Affiliates."

He expects, however, to diminish his role in international committees in the coming year so that he can focus on the D/A/CH Affiliate while balancing his day-to-day activities as Head of Global Engineering at Takeda Pharmaceuticals International and as a father of two young children.

About the author

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

Quick facts about the ISPE D/A/CH Affiliate

Founded: 1993

Region: Germany, Austria, Switzerland

Membership: 1,100+

Executive Board

- **President (Chair):** Gunter Baumgartner, Takeda Pharmaceuticals International AG
- **Vice President (Co-Chair):** Marcel Staudt, Bayer Consumer Health
- **Affiliate Finance Officer (Treasurer):** Michael Atzor, PhD, Retired, formerly Bayer AG

Advisory Board

- **Secretariat:** Rolf Sopp, Retired, formerly Sanofi Aventis
- **Strategy/Cash Audit:** Thomas Waldleben, Geistlich Pharma AG
- **Workshop Coordination:** Josef Kriegl, Chemgineering International
- **Aseptic Community of Practice (CoP):** Volker Storn, F. Hoffmann–La Roche AG
- **Containment CoP, Robotic/Cobotic Special Interest Group (SIG):** Richard Denk, SKAN AG
- **GAMP® CoP:** Hartmut Hensel, formerly Harz University of Applied Sciences
- **Water and Steam CoP:** Marcel Zehnder, BWT Pharma & Biotech AG
- **Pharma 4.0™ SIG:** Christian Wölbeling, Werum IT Solutions
- **Project Management:** Michael Atzor, PhD, Retired, formerly Bayer AG
- **Regulatory:** Viktor Mettler, Novartis Pharma AG
- **Student Advisor and Training:** Frank Scholl, Syntegon (formerly BOSCH GmbH)
- **Women in Pharma® Chair:** Zen-Zen Yen, Bayer AG
- **Young Professionals Chair:** Robin Schiemer, Student
- **Young Professionals Advisor:** Christian Wölbeling, Werum IT Solutions

ISPE BRIEFS

ISPE Expands Its Popular Webinar Series

To continue meeting the professional needs of ISPE members and with the global increase of virtual events due to COVID, ISPE has expanded its webinar offerings on topics important to ISPE members and industry sponsors.

Over the summer, ISPE introduced sponsored webinars, in which sponsors present on topics of their choice to help facilitate networking within the industry. Complimentary to ISPE members, this series has provided sessions on Operational Readiness, Implementation of Rapid Microbiological Detection Methods, and the Holistic Approach to Pharma 4.0™.

We also introduced our Extended Learning webinar series, which offers participants a deeper dive into industry-critical topics. These webinars allow more in-depth, actionable conversations and extended Q&A time. We've offered sessions on GAMP®5; FDA CSA, and the Future of Computer Systems Validation; Foundation of Proof—Exploring the Cryptography Behind Blockchain; The Importance of Data Integrity for Machine Learning: A Data Lifecycle Model; Annex 1 Revision 2020 and ISPE Commenting; and Process Validation Stages 1–3 (December 2020). This webinar series offers participants access to the sessions for up to one year postevent and will soon be available on demand in case you miss the presentation. To keep members up to date on COVID-19 issues, ISPE also offered several sessions on COVID-19-related topics, including panel discussions on Supply Chain Challenges and a session on the Risk-Based Approach to Mitigate SARS–COV-2 Challenge to the Virus Control Framework in Industrial GMP Manufacturing Facilities.

The ISPE Webinar Video Library is available at: https://ispe.org/webinars

Many more webinars are in development for 2021. To suggest a webinar topic, email ispeak@ispe.org

—Barbara Peck, ISPE Manager, Community and Industry Recognition

New ISPE Guide on Cleaning Validation Lifecycle Debuts

Regulatory agencies expect the development and validation of a compliant cleaning program. This critical activity ensures that the risks of contamination, product carryover, and cross-contamination are controlled, minimized, and monitored to safeguard patient safety and product quality. ISPE's newest guidance document, the *ISPE Guide: Cleaning Validation Lifecycle–Applications, Methods, and Controls,* is a reference for the cleaning life-cycle model and a practical guide to cleaning validation theories and concepts.

"The guide provides the requirements, principles, and practices for cleaning validation in a single volume and is the first of its kind in the industry," said Guide Team Co-lead Jose Caraballo, Head Audit Program Management Americas, Corporate Quality Audit and Inspections, Bayer US. "We decided to address the topic because the expectations for cleaning validation are changing. This guide was reviewed by regulators and practitioners in the field. It is a great resource for understanding and applying the principles for compliant cleaning programs, including how-to steps and examples."

Key areas addressed in the guide include:

- Application of risk management
- Adoption of a life-cycle approach for cleaning validation
- Cleaning methodologies
- Creation of cleaning validation acceptance criteria
- Determination of visual inspection limits
- Calculation and justification of residue limits
- Validation of testing and sampling methods
- Equipment issues and challenges
- Change management

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—Marcy Sanford, ISPE Editorial Assistant

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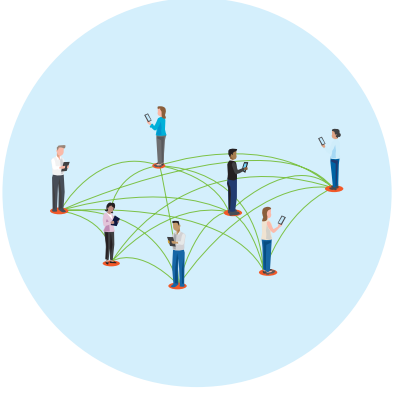

ISPE Implements First Virtual Hackathon

The move to a virtual 2020 ISPE Annual Meeting & Expo posed a unique challenge: how to hold a Student & Young Professional (YP) Hackathon online? In past Hackathons, student and YP teams met face to face for a weekend during the Annual Meeting to identify solutions to industry-relevant challenges and develop presentations to deliver to a group of judges.

The International Young Professionals Committee, led by LeAnna Pearson Marcum, took the Hackathon virtual in a pilot program from 27 July through 18 August that included US Chapters and a limited number of participants. Seven YP volunteers and Marcum, with support from ISPE staff, managed the three-week program, which culminated in the online judging of each team's presentation. Forty ISPE student and YP members were split into two teams, each with two subteams. Teams had one week prior to the launch of the Hackathon to meet virtually, select a virtual platform for the team to use, and schedule online meetings and discussions.

AveXis (now Novartis Gene Therapies) provided a challenging problem statement dealing with changes required in pharmaceutical manufacturing facilities because of COVID-19. To see the statement, visit: ispe.org/membership/young-professionals/hackathon-problem-statement

In the first two weeks of the Hackathon, each individual team determined their specific areas of focus and formulated solutions. During week three, teams developed and practiced their presentations for the judges. Throughout the program, dedicated industry professional coaches provided support to the students and YPs. Three AveXis professionals and two ISPE International Board of Directors members served as judges; they selected the winning team based on the most innovative and feasible solutions. Team A was selected as the winner. You can view the presentations at https://ispe.org/membership/young-professionals

The next virtual ISPE Student & YP Hackathon will be international and larger, and will incorporate lessons learned from the summer pilot.

—Debbie Kaufmann, ISPE Manager, Professional Communities

MEET THE ISPE STAFF

MELISSA DUPRIEST

In each issue of *Pharmaceutical Engineering®*, we introduce a member of the ISPE staff who provides ISPE members with key information and services. Meet Melissa DuPriest, ISPE's Assistant Controller in the Accounting Department.

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

I am responsible for the day-to-day financial operations of ISPE, such as the monthly financial reporting, overview/process improvement of accounts payable/accounts receivable, general ledger balance sheet reconciliation, and audit preparation and review. I ensure our company is adhering to GAAP standards and the financials are reported accurately.

What do you love about your job?

I love the people that make up this Society both internally and externally. I wholeheartedly enjoyed working at the 2019 ISPE Annual Meeting & Expo and getting to know our members and staff more. It truly enriched my opinion and understanding of my company. I also adore the complex puzzles that I come across in the accounting and process improvements from my daily tasks at ISPE.

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

I am an extrovert and love being outside. With the pandemic, I have taken up gardening and pool volleyball. I am studying to take the CPA exam, and I love playing sports, reading, listening to music, and driving. I also love spending time with my family: I have been married for 20 years and have three beautiful girls, ages 22, 19, and 16.

JUSTIFYING INVESTMENT in Manufacturing Execution Systems

By Dirk M. Sweigart, PMP, CISSP

Executives at manufacturing companies of all sizes need to make decisions about where to invest to maintain and grow their businesses. Investments in manufacturing execution system (MES) applications may reduce costs and increase revenues, but they also might compete with other investment priorities, such as marketing campaigns and capital equipment upgrades. This article offers guidance for life sciences companies considering investment in MES applications, including how to measure MES-related cash flow and reasonably evaluate an investment in MES versus other alternatives.

Manufacturers considering investment in an MES may wish to consult the *GAMP® Good Practice Guide: Manufacturing Execution Systems* [1], which provides an overview of issues to evaluate in a strategic assessment of MES options:

- The current status of the business pertaining to manufacturing system requirements
- The desired state of system requirements to be achieved, including a breakdown of high-level functionality required to advance the business while managing costs
- Analysis of desired functionality already in existing systems, and any needs for new systems to be added to the domain (automation, MES application, enterprise resource planning, quality control, data historian, etc.)

OPERATIONAL JUSTIFICATION

Output from the strategic assessment provides a roadmap and justification for MES application functionality. Sometimes, the need for MES applications is so overwhelming that this evaluation simply provides the scope of implementation. If it is not possible to operate a process without MES functions, the entire business case for manufacturing the product is based on having MES applications in place.

For existing production facilities, the operational justification for the MES is typically based on quality and patient safety needs, such as nonconformances, corrective and preventive actions (CAPAs), customer complaints, and inspection/audit observations, as well as business needs, such as expansion plans, anticipated process/product changes, and overall business agility to meet as-yet-unknown demands.

For new operations, using an approach such as failure modes and effects analysis (FMEA) can identify risks that can be mitigated by implementing MES applications, such as the following:

- Data collection risks: The data collection rate or volume is too high for reliable manual recording.
- Raw material risks: The number of materials, the use of similar materials, or criticality of material additions introduces the chance that incorrect materials could be added or materials could be added in the wrong order.
- Sample tracking risks: The number of samples or complexity of sample management introduces high potential for sample misplacement or mislabeling.
- Manual operations risks: The complexity of manual operations increases the likelihood of operator error.
- Compliance risks: Other required documentation cannot be accurately and consistently completed by a human without additional human review or observation due to the complexity or quantity of the documentation.

FINANCIAL JUSTIFICATION

Even when an MES can be justified solely on the basis of quality, identifying additional financial justifications strengthens the business case and can garner additional support from the investment decision makers. To financially justify a project, one must show that the company will profit by making this investment for current products or the investment will be necessary for future development.

A common metric used to evaluate or compare alternatives is return on investment (ROI). If there is only one alternative being considered, the evaluation is versus the current state, often referred to as the "base case." The base case is what would happen if the investment were not made. Two common methods of calculating ROI are internal rate of return (IRR) and net present value (NPV). These calculations are very similar, so we will focus on NPV.

In addition to IRR or NPV, investments are sometimes evaluated based on a payback period (how long it takes for the investment to pay for itself). Using a payback period can sometimes be

misleading because it only looks at how long it takes to "break even." Two options may have the same payback period, but one alternative may continue to provide benefits for a much longer time than the other. It is also possible that one solution would require much greater future investment (maintenance). Both of these are differentiating factors that are reflected in the NPV [2].

NPV Comparisons

To calculate NPV, look at all incremental costs and incremental benefits over the life of the system [2]. These are defined as cash flows—costs that must be spent to define, build, deploy, and maintain the MES (outflows), and real quantifiable benefits derived by having and using the MES (inflows). These are incremental because it is the difference between the proposed option and the base case, or between alternatives, that is important. For example, assume that the current system needs a server upgrade to continue functioning. In this situation, buying a new server for the MES is not an incremental cost because the new server is required regardless.

These costs and benefits (incremental cash inflows and outflows) occur over time. For example, the major cost of the MES occurs up front, whereas the cost savings occur over the following months and years. To make a fair comparison, costs or benefits that occur in later months or years are "discounted" to the present using a standard interest rate (often referred to as the "risk-free rate"). As an example, a quality improvement project that results in a rework cost reduction two years from now is not as valuable as having that reduction right now. The future reduction is discounted (to the present) so that it can be compared with all other costs and benefits, all discounted to the present (the NPV). This can be represented as:

$$NPV = \sum_{t=0}^{n} \frac{Rt}{(1+i)^t}$$

In this equation, *Rt* is the sum of all incremental cash flows (in or out) in a period, *t* is time (typically measured in months, but can be years or days), and *i* is the discount rate (the return that could be had in a risk-free investment, such as a certificate of deposit) for that period. The discount rate is often set by the company finance department.

The NPV calculation is available in Microsoft Excel as "=NPV (rate, list of values)."

As a simple example, let's say that in December (now), you are trying to decide whether to invest $50,000 in new MES applications. The entire investment can be made in January. Then, each month after that, the system reduces scrap by $5,000. We will look at one year. The finance department says they could invest that money at a risk-free annual rate of return of 5%. No other incremental cash flows have been identified.

The cash outflow in January will be $50,000. But that has to be discounted by the risk-free rate (0.42% per month). The NPV calculation using just the January cost is negative, as would be expected (Figure 1). On this basis, you would not do this project (negative NPV). Note that the $50,000 spent in January is equivalent to $49,790 spent now (that is, if you invested the $49,790 now at an annual rate of return of 5%, compounded monthly, you would have $50,000 in January).

In February, there is an expected positive inflow of $5,000 (reduced waste) and no outflows (Figure 2). However, on this basis, you would still not do this project because the NPV is negative (but less negative than in January).

> To calculate net present value (NPV), look at all incremental costs and incremental benefits over the life of the system.

Figure 1: NPV of MES investment at one month.

	Jan
Cash outflows	(50000.00)
Cash inflows	
Sum	-50000.00
Interest rate (0.05/12)	0.0042
NPV	($49,792.53)

Figure 2: NPV of MES investment at two months.

	Jan	Feb
Cash outflows	(50000.00)	
Cash inflows		5000.00
Sum	-50000.00	5000.00
Interest rate (0.05/12)	0.0042	
NPV (2 months)	($44,833.94)	

Figure 3: NPV of MES investment for year 1.

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Cash outflows	(50000.00)											
Cash inflows		5000.00	5000.00	5000.00	5000.00	5000.00	5000.00	5000.00	5000.00	5000.00	5000.00	5000.00
Sum	-50000.00	5000.00	5000.00	5000.00	5000.00	5000.00	5000.00	5000.00	5000.00	5000.00	5000.00	5000.00
Interest rate (0.05/12)	0.0042											
NPV (1 year)	$3,634.33											

For the first year, the NPV is $3,634 (Figure 3). This positive NPV indicates that the project would add value to the company. However, it may have a lower NPV than another project.

A proper NPV analysis should span multiple years and forecast both future investments needed and future benefits that would be gained. Additionally, the NPV for a specific investment should always be compared to the current state or another alternative (which would also have future costs or future benefits).

A proper NPV analysis should span multiple years and forecast both future investments needed and future benefits that would be gained.

Incremental Cash Flows

Incremental cash outflows are often relatively easy to collect, but one must be careful to examine each outflow to see if it is truly incremental. For example, the costs for a systems integrator are likely incremental because you would not have those costs if you did not do the project. However, assume you have an internal team that is currently supporting an application that will be retired and they will be implementing this new MES. The cost of that team is not a "new" (incremental) cost because it would be incurred if the current system stayed in place or if a new system were put in place. In contrast, if additional people were hired (or assigned to this project from elsewhere) for the duration of the project, the cost of the additional staff would be an incremental cost as long as they worked on the project.

If you are comparing this alternative to the current state, be careful to not only consider the current year for the current state. Existing systems (and processes) often require ongoing investment, such as support contracts, network capacity increases, hardware maintenance, and/or planned upgrades. Software maintenance is an example of an ongoing current-state cost. Training operators (such as new operators) on the existing process might be an example of ongoing non-software costs. If operators need to be routinely trained on something, no matter what system, then there is no incremental cost for the alternative relative to the base case.

Generally, hardware, software, and implementation costs can be relatively easy to quantify within a range. However, be careful when considering the time that people who are already employed would spend on the alternative: this is unlikely to truly be an incremental cost if they would be employed anyway.

The real skill needed for financial justification is to collect and quantify the benefits of the project to the company in terms of changes to future cash flows. Benefits can be classified in two categories: cost reductions and revenue increases. Some benefits may belong in both categories. For example, a 1% quality improvement could reduce the amount of waste for disposal (a cost reduction), increase the process throughput (less time needed to create a complete process order, also a cost reduction), and be a basis for a modest product price increase (revenue increase). It could also result in fewer product returns (another revenue increase or cost decrease). Each of these needs to be considered and estimated over time. Table 1 summarizes some common sources of cost reductions (reducing cash outflows).

Personnel reductions are often a sensitive topic, but they are a reality in this age of automation. Human resources costs need to be looked at closely and confirmed to be real. For example, suppose automating batch records frees up one hour a day for each of eight

Table 1: Examples of cost reductions associated with MES.

Category	Areas of Opportunity	Cost Estimate Methodology
Labor needs	MES will reduce human resources needs in several ways, such as: • Eliminating a second check (e.g., for weighing or dispensing) • Eliminating manual data entry, data transposition • Reducing management and storage of paper documentation and paper master batch records • Reducing time to review batch records (MES performs the checks) • Eliminating the need to rework nonconforming materials	Estimate cost savings based on current processes (value-stream mapping is one technique).
Materials conformance	Using an MES will reduce the number of nonconforming batches, thereby reducing material, labor, and disposal costs. Improving materials conformance also reduces product variability and improves the safety profile, avoiding recalls.	Review nonconformances, evaluate which ones would be eliminated if MES applications were in place, and estimate the associated costs. Some nonconformance examples are: • Using expired or quarantined materials • Missing data • Adding wrong materials, wrong amounts, or in the wrong order • Continuing to process material with excursions
Production capacity	Using an MES can increase production capacity by helping: • Eliminate nonconforming product • Improve cycle times • Improve yields If a unit operation is at or near full capacity, increasing throughput will directly affect revenue but also may require investment in additional capital or overtime shifts to expand capacity.	Evaluate cost savings and investments associated with MES-related increases in production capacity.
Waste disposal	Using an MES can reduce waste arising out of production of nonconforming materials.	Calculate the cost of disposing of excess waste from nonconformances or low yield.
Resource efficiencies	As the MES improves efficiency, increases yield, or reduces nonconforming materials, the per-unit labor required will also be reduced. An improvement in yield is both a cost reduction and a production improvement.	Estimate labor cost reductions to be realized by reducing staff, eliminating overtime, and/or role consolidation.

people (one labor-day). That may be the basis for a head count reduction. But if the head count is not actually reduced, the personnel costs of running the plant do not change (although there may be benefits realized by reallocating workers' time to other products or processes). Also, if one position is eliminated from the batch records staff but an additional (higher salaried) person is hired to support MES implementation, the difference between the salaries is actually a cash outflow.

Making less waste has many benefits that can be quantified (if the reduction can be truly attributed to the MES). These may include lowering waste disposal costs and the cost of the raw materials consumed. A less-wasteful system may also realize savings in machine time, human resources, and power consumption. These cash outflows decrease because a greater amount of saleable product is made in the same time.

If certain sources of waste can be eliminated altogether, some processes may no longer be needed at all. For example, manual sorting through boxes to repack "good" product versus "bad" product could be eliminated.

Executives typically divide these benefits into "hard" (quantifiable) and "soft" (difficult to quantify and hard to obtain) categories. Soft benefits are often considered to be not as good a basis for an investment as hard benefits. Whenever possible, hard benefits should be identified. It is possible that only the hard benefits will be used to evaluate this investment and that each one will be closely examined by the financial officers.

Table 2: Potential MES-related revenue improvements.

Improvement Type	Comments
Greater asset productivity	If the MES allows more saleable product to be made in the same time on the same equipment, the *margin* of that incremental product should be considered a cash inflow.
New sales or better support for sales growth	For a plant in a sold-out position, every additional unit that can be produced is a cash inflow of the margin of that unit.
Customer retention due to improved cost and quality	Getting new customers can be a lot harder than retaining current customers. However, if it can be shown that MES implementation retains a customer that would likely be lost given the current state, the retention can be considered an incremental cash inflow.
New product support	A flexible MES may reduce or eliminate costs that would be incurred if new products require changes to existing systems.
Faster decisions	Uncertainly about the disposition of a product can cause it to sit in a warehouse or delay shipment. Quicker resolution of such issues saves money and could lead to faster realization of revenue.
Better decisions	If the MES can provide data that ensure good product is not wasted and bad product is not manufactured or distributed, these data offer quantified examples of real revenue increases or cost savings. Also, the MES may support improvements in factory scheduling, maintenance work (particularly preventive maintenance), and staffing.
Better (and more accessible) data	Better data alone will not improve revenue and reduce costs. However, good, accessible data help companies respond to customer queries like "When will my order be done?" High-quality data are also useful to trace a quality problem to a raw material. Reducing the time needed to address these types of issues can mean fewer customer service personnel are required.
Reductions in working capital	Keeping material around when it is not immediately needed for production or sale is wasteful. These materials take up space and money. Eliminating them frees up working capital—money, space, or effort that would be spent dealing with these items can instead be used elsewhere. However, be careful when including these factors in cash-flow calculations: these are "one time" cash-flow changes.
Better compliance profile and inspection results	Fewer nonconformances and manual errors reduce the risk of regulatory scrutiny and subsequent regulatory actions. The monetary value of these improvements may be difficult to quantify; however, in certain cases, avoiding costs and increasing yield in this area could be large enough to justify MES on this basis alone.

When evaluating cash flows, be sure to consider all revenue improvements that can be identified. Table 2 identifies many potential types of revenue improvement that may be associated with MES implementation.

Ongoing Investments

In addition to the initial investment in purchasing, configuring, and deploying MES applications, ongoing costs associated with the MES need to be considered. From an IT perspective, MES operation will involve application and system support and maintenance, ongoing user training, periodic upgrades and enhancements, and user management.

Considering a Range of Outcomes

The future is uncertain, and projects often don't turn out as planned. Costs may be more than expected, or unforeseen glitches can arise. There may even be unforeseen benefits!

To compensate for this uncertainty, it is often wise to calculate three different NPVs: a best case, worst case, and expected case. For each cost and benefit, ask "What is the worst that could happen?"

and "What is the best that could happen?" This author has often found that what is presented as the expected case is actually the best case (if everything goes perfectly, this is what we can achieve).

If these three cases (worst, expected, best) all have a positive NPV, the project should be done. If only the best and expected cases are positive, you know what (risk) factors are key to making the project a success.

CASE EXAMPLE

A pharmaceutical packaging operation is in a sold-out position and running 24/7. Management has the following concerns with the current state:

- They are having trouble creating the documentation needed for compliance, which is currently done manually on paper worksheets. They have concerns that if they were audited, they would not pass.
- They are not meeting their production goals. They believe they should have a higher output, but they do not know what to do to improve it. With the 24/7 operation, they have struggled to identify the problems impacting production after hours.
- They are concerned about their future CAPA costs and believe they need to minimize those risks.

The company is considering whether to invest in a pilot MES application on one line to address these issues. The operations team is recommending systems that would greatly automate data collection, collect data on the process orders (including getting the causes of any lost production from the operators), and provide a real-time view of the progress of process orders through the packaging lines.

To make the business case for the MES, each of these items has to be realistically quantified in terms of their impacts on the company's cash flow. For example, what is the real potential for a compliance audit and what are the real consequences if the company does not pass it? The possibilities range from $0 (no audit or no issues) to the entire value of production for a time period (if production must be halted and orders are lost).

The projected costs for the MES are as follows:

- Hardware: $50,000 for a server and new workstations (in addition to existing hardware)

Figure 4: NPV for one year of MES investment.

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Total cash outflows	**-170000**	**-20000**	**-20000**	**-20000**	**-20000**	**-20000**	**-20000**	**-20000**	**-20000**	**-20000**	**-20000**	**-20000**
hardware	-50000											
software	-100000											
system integration	-20000	-20000	-20000	-20000	-20000	-20000	-20000	-20000	-20000	-20000	-20000	-20000
software maintenance												
Total cash inflows	**0**	**0**	**0**	**5000**	**5000**	**10000**	**10000**	**20000**	**35000**	**85000**	**40000**	**40000**
reduce personnel (3)				5000	5000	10000	10000	10000	15000	15000	15000	15000
1 less waste batch										50000		
1% improvement in yield (quality)								5000	10000	10000	10000	10000
1% improvement in yield (throughput)								5000	10000	10000	10000	10000
reduction in compliance processing costs											5000	5000
Net cash flows	-170000	-20000	-20000	-15000	-15000	-10000	-10000	0	15000	65000	20000	20000
Interest rate (0.05/12)	0.0042											
NPV (1 year)	($142,857.57)											

- Software: $100,000 for licenses, plus a 15% annual budget increase for maintenance
- Services: $240,000 to implement the software over one year ($20,000 per month)

Figure 4 shows a one-year NPV analysis. Note that the NPV is a large negative amount, as would typically be expected in the first year. For the purposes of this example, the benefits begin to be realized midyear, and the cash flow turns positive in September.

Figure 5 shows that a three-year analysis looks much better and has a positive NPV. Note that the payback period for this project occurs in the second quarter of year 2. The positive cash flow, however, could go on for years.

CONCLUSION

The decision to invest in MES applications should be driven by sound economics, based on real costs and benefits. The costs and benefits considered should be incremental, representing changes from what would happen anyway (the current state or base case) or, in the case of alternatives, real cash-flow differences between the options. Using NPV analysis over an appropriate time frame and considering the range of outcomes possible can help drive more

Figure 5: NPV for three years of MES investment.

	Year 1				Year 2				Year 3			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Total cash outflows	-210000	-60000	-60000	-60000	-15000	-10000	0	0	-15000	-10000	0	0
hardware	-50000											
software	-100000											
system integration	-60000	-60000	-60000	-60000		-10000				-10000		
software maintenance					-15000				-15000			
Total cash inflows	0	20000	65000	165000	120000	120000	170000	120000	120000	120000	170000	120000
reduce personnel (3)		20000	35000	45000	45000	45000	45000	45000	45000	45000	45000	45000
1 less waste batch				50000			50000				50000	
1% improvement in yield (quality)			15000	30000	30000	30000	30000	30000	30000	30000	30000	30000
1% improvement in yield (throughput)			15000	30000	30000	30000	30000	30000	30000	30000	30000	30000
reduction in compliance processing costs				10000	15000	15000	15000	15000	15000	15000	15000	15000
Net cash flows	-210000	-40000	5000	105000	105000	110000	170000	120000	105000	110000	170000	120000
Interest rate (0.05/12)	0.0042											
NPV (3 years)	$833,957.54											

rigorous, real, defendable, and profitable decisions. Creating best, expected, and worst cases can clarify the risks and should ensure that investments pay off if even the worst case has a positive NPV.

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About the author

Dirk M. Sweigart, PMP, CISSP, is the MES Solutions Manager at Applied Control Engineering, Inc. (ACE) in Newark, Delaware. He has over 30 years of experience as an IT and systems project manager, planning and leading control systems, manufacturing systems, and business systems projects and teams for DuPont, Koch Industries, ACE, and others. Dirk holds degrees in mechanical engineering and computer science from Penn State and has an MBA from the University of Delaware. He is a member of the MESA Cybersecurity Working Group and the ISPE GAMP® Special Interest Group for MES and a senior member of the International Society for Automation. A Certified Information Systems Security Professional (CISSP), he teaches industrial control systems and cybersecurity courses in the graduate program at Wilmington University. Dirk has been an ISPE member since 2017.

PASSIVE SEDIMENTATION CONTROL

in Containers Using Marangoni Forces

By Francisco J. Arias, PhD

When fluid-filled containers are stored for long periods of time with negligible motion, sedimentation and gravitational settling of particles can occur. This article discusses a passive sedimentation control mechanism that is driven by Marangoni stress, which is induced in enclosed geometries when their walls are lined with gas-filled hydrophobic microcavities.

The proposed concept has significant practical applications in the pharmaceutical industry, as it would allow medicines and active fluids to be stored for long periods of time using such containers and eliminate concerns related to sedimentation. Although additional research and development are required to arrive at a practical, optimized, commercial design, this preliminary work outlines the mathematical development and computational verification of the concept.

SEDIMENTATION AND MARANGONI FORCES

During gravitational settling of particles, a definitive vertical concentration gradient gradually develops. Undesired sedimentation occurs in unstable colloidal dispersions, which can then form loosely joined masses of fine particles of either aggregates or agglomerates (due to interparticle attractions) as the particles assemble. Although aggregation is a reversible process, agglomeration is not. Both should be avoided if possible.

If the walls of a container are lined with air-filled (or inert gas–filled) hydrophobic microcavities, a Marangoni force will appear because of the dependence of surface tension on concentration. This Marangoni force will propel the particles from the low-surface-tension region to the high-surface-tension region. The force will then act as a negative feedback and prevent sedimentation, agglomeration, and aggregation of particles by mildly, yet continuously, remixing the content.

The use of walls lined with air-filled hydrophobic microcavities and superhydrophobic surfaces is not new; however, its application has so far been limited to being a passive method for drag reduction in which the air-liquid interface, owing to the trapped air of the nanocavity, translates into the appearance of slip velocity in the superhydrophobic surface [1]. Active research in this topic encompasses science and technology to understand, mitigate, or prevent the phenomena [2–8]. This article provides a first assessment for a passive and self-sustained mechanism able to prevent gravitational settling, agglomeration, and cluster formation in enclosed geometries by using walls lined with air-filled hydrophobic microcavities. This concept has direct relevance to pharmaceutical engineering, as sedimentation and agglomeration issues play a very important role in the pharmaceutical industry.

SELF-SUSTAINED SEDIMENTATION CONTROL

The Marangoni effect is the mass transfer along an interface between two fluids due to a gradient of the surface tension. In the case of temperature dependence, this phenomenon is generally referred as thermocapillary convection [9, 10].

The explanation of this phenomena is straightforward: A liquid with a high surface tension pulls more strongly on the surrounding liquid than one with a low surface tension, and therefore the presence of a gradient in surface tension will naturally cause the liquid to flow away from low-surface-tension regions toward high-surface-tension regions. The surface tension gradient can be created by a thermal gradient, owing to its temperature dependence, or by a concentration gradient. The concentration dependence provides the possibility to use walls lined with air-filled (or inert gas–filled) hydrophobic microcavities as a self-controlled and completely passive method to prevent sedimentation, agglomeration, and cluster formation in enclosed geometries. As mentioned, during gravitational settling, a vertical concentration gradient starts to develop, with the higher concentration at the bottom (sedimentation). Thus, if container walls are lined with such microcavities, the concentration gradient can trigger a capillary motion that will act as a feedback, preventing or mitigating the sedimentation process. As the concentration gradient (sedimentation rate) increases, the capillary flow becomes stronger. (Figure 1 illustrates this idea.)

METHODS

First, consider a fully developed, two-dimensional flow between parallel plates that are separated by a distance, *b*, and a length, *h*, and lined with air-filled hydrophobic microcavities. When precipitation and gravitational settling start, a vertical concentration gradient appears and, as a result, a Marangoni stress is generated across the wall because of the free interfaces introduced by the microcavities (as described previously). The maximum velocity, v_{max}, attainable by this Marangoni flow—which might be used as a rough estimation of the capability for resuspension of particles—occurs at the wall, and can be estimated using the following equation [11]:

$$v_{\max} \approx \frac{b}{2\mu}\frac{d\sigma}{dz} \quad (1)$$

where *b* is the distance between plates, μ is the dynamic viscosity of the liquid, and dσ/*dz* is the surface tension gradient. In our case, because the surface tension gradient is driven by a concentration gradient, $\nabla_z c$, equation 1 can be rewritten as follows:

$$v_{\max} \approx \frac{b\sigma_c}{2\mu}\nabla_z c \quad (2)$$

where σ_c is the surface tension coefficient with concentration.

Finally, the feasibility for resuspension of sediment by the induced capillary flow may be preliminarily assessed by equating equation 2 with the terminal velocity of particles, which, for a low Reynolds number less than unity, is calculated as follows:

$$v_t = \frac{g(d_p^2)}{18\mu}(\rho_p - \rho) \quad (3)$$

where *g* is gravity, d_p is the diameter of the particle of solute, μ is the dynamic viscosity of the fluid, and ρ_p and ρ are the density of the particle and the density of the fluid, respectively. Equating equation 2 with equation 3, we obtain:

$$\nabla_z c = \frac{g d_p^2(\rho_p - \rho)}{9\sigma_c b} \quad (4)$$

which gives us the concentration gradient required to compensate the gravitational settling as a function of the diameter of the particle.

Looking at equation 4, one may think that the required concentration is reduced inasmuch that the distance between plates, *b*, increases. However, this is not the case because equation 2 for the capillary velocity cannot be used for any size of container. Further, in the derivation of equation 2 in the momentum equations, it was assumed that

$$\frac{v_z^2}{h} \ll \frac{\mu|v_z|}{\rho b^2}$$

and then the validity of the velocity flow by equation 2 is given by [11]:

$$b^3 \ll \frac{4\mu^2\rho h}{|\sigma_c|\nabla_z c} \quad (5)$$

To obtain some idea of the concentration gradient predicted by equation 4, let us assume some typical values for a NaCl solution with densities $\rho \approx 10^3$ kg/m³ and $\rho_p \approx 2.17 \times 10^3$ kg/m³; $\mu \approx 10^{-3}$ Pas; $\rho_c = 1.2 \times 10^{-3}$N/m(molarity) [12]; and a distance between plates *b* = 5 mm, compatible with the requirement given by equation 5.

Figure 1: Illustration of sedimentation control in enclosed geometries using air-filled hydrophobic microcavities.

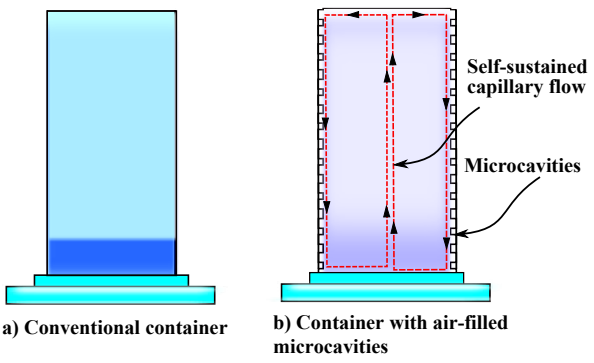


Figure 2: Gradient of concentration required for particle resuspension of solute from equation 4 for various diameters of solute particles.

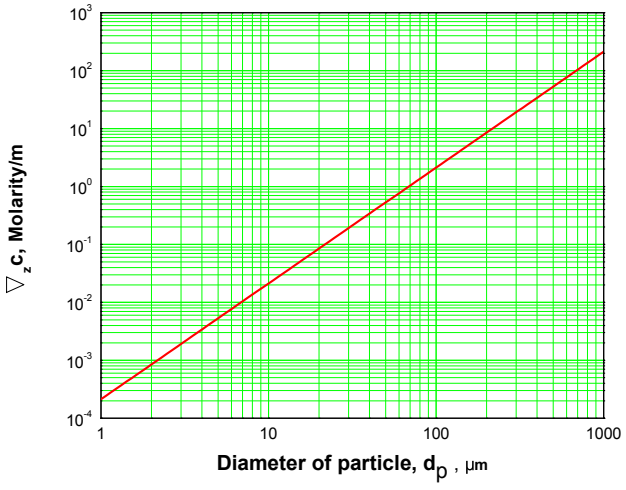


Figure 2 shows the resulting curve as a function of the particle diameter. It is seen that the required concentration gradient—even for solute particles with diameters ≥10 μm—is within the range of concentration one would expect in a sedimentation. However, as mentioned previously, the calculations must be given careful attention because the results are valid only when the distance between plates satisfies the relationship given in equation 5.

COMPUTATIONAL SIMULATION

To assess the capability for the proposed self-sustained control mechanism, hydrodynamic computational simulations in unsteady-state conditions were performed using Ansys Fluent computational fluid dynamics (CFD) software version 14. Figure 3

Figure 3: Geometry for numerical simulation. Schematic depicting the geometry and boundary conditions used in Ansys Fluent software.

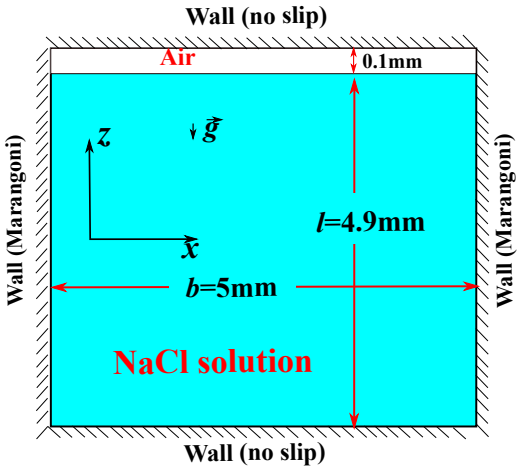


Figure 4: Final volume void fraction profile from gravitational settling of 1-µm-diameter particles and different initial concentrations, where z = 0 mm is the bottom of the container and z = 5 mm is the top.

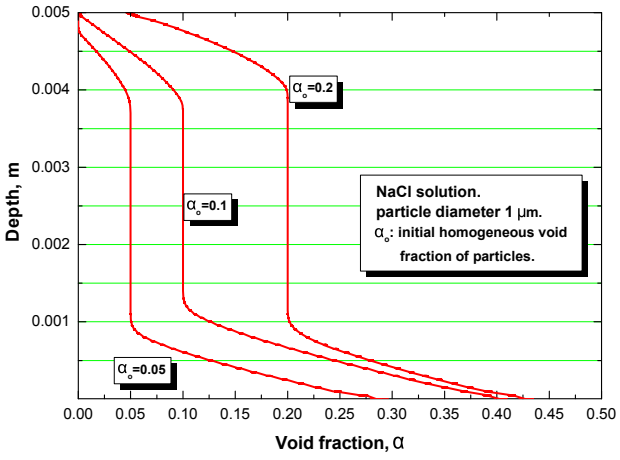


Figure 5: CFD concentration profile for gravitational settling of 1-µm-diameter particles without Marangoni stress.

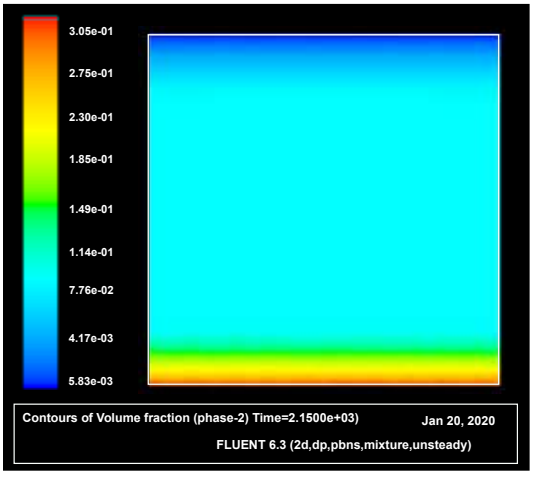
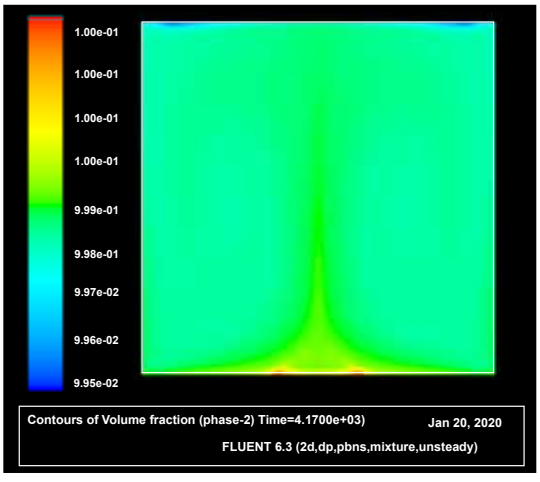


Figure 6: CFD concentration profile for gravitational settling of 1-µm-diameter particles with Marangoni stress.



shows schematically the problem to be considered. The NaCl solution was considered inside a rectangular box of sides l = 5 mm and b = 5 mm. The boundary conditions were as follows: The bottom and top of the box had a zero-slip condition, and the left and right sides had a Marangoni stress shear condition. However, because the Ansys Fluent CFD Marangoni stress option is only directly available for thermocapillary flow (i.e., considering thermal coefficient of surface tension), it was necessary to create a user-defined function to customize Fluent. The user-defined function read the local concentration gradient at the wall and then defined a "fictitious" thermal gradient associated at this place using the following expression:

$$\nabla_z T = \frac{\sigma_c}{\sigma_T} \nabla_z c \tag{6}$$

which allows reproduction of the Marangoni effect driven by local concentration gradients. To avoid any undesired collateral effect of using a fictitious thermal gradient, the fluid's thermal expansion coefficient was set to zero. Finally, to reproduce a free surface

at the top of the container, a gap of air with a thickness of 0.1 mm was introduced. The analysis was carried out with a simple algorithm and Presto for pressure discretization, and a second-order upwind scheme for momentum and energy. Relaxation factors were taken to be default values. Convergence criteria were set as 10^{-3} for continuity, z-momentum, and x-momentum, and as 10^{-6} for energy. Constant properties of water were considered, with $\rho = 10^3$ kg/mg^3 and $\mu = 10^{-3}$ Pas. For the thermal coefficient of surface tension, σ_T, and for the concentration coefficient of the surface tension for supersaturated solution of NaCl with particles near nanometric size, it was assumed that $\sigma = 100$ mN/m (mass fraction of NaCl).

CONCLUSION

From the simulations, it was found that the induced convective Marangoni flow could control the gravitational settlement of colloidal particles with diameters less than 1 µm or thereabouts. Figure 4 shows the final concentration profile after gravitational settling without Marangoni effect and considering several uniform initial concentrations. Likewise, Figures 5 and 6 show some sequences of the computational simulation for the concentration profile without and with Marangoni effect, respectively. Considering that particles before agglomeration and growth are expected to be around 1 µm or smaller, we may hypothesize that the walls of large containers can be lined with hydrophobic microcavities and the negative feedback from self-sustaining Marangoni forces can prevent sedimentation. As mentioned, with further research and development, this could offer a significant opportunity within the pharmaceutical industry for the long-term storage of medicinal products.

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Acknowledgments

This research was supported by the Spanish Ministry of Economy and Competitiveness under fellowship grant Ramon y Cajal: RYC-2013-13459.

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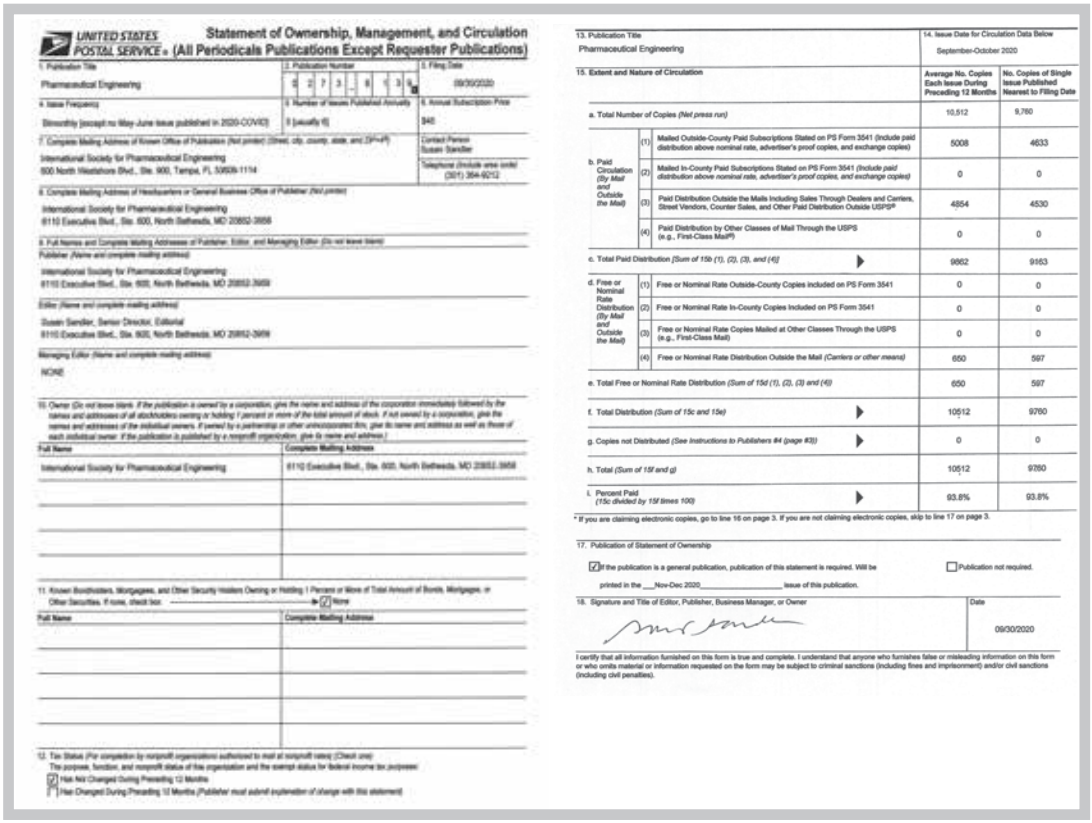

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1. Publication Title	2. Publication Number	3. Filing Date
Pharmaceutical Engineering	0 2 7 3 - 8 1 3 9	09/30/2020

4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price
Bimonthly (except no May-June issue published in 2020-COVID)	5 (usually 6)	$40

7. Complete Mailing Address of Known Office of Publication (Not printer) (Street, city, county, state, and ZIP+4®): International Society for Pharmaceutical Engineering, 600 North Westshore Blvd., Ste. 900, Tampa, FL 33609-1114 — Contact Person: Susan Sandler; Telephone (Include area code): (301) 364-9212

8. Complete Mailing Address of Headquarters or General Business Office of Publisher (Not printer): International Society for Pharmaceutical Engineering, 6110 Executive Blvd., Ste. 600, North Bethesda, MD 20852-3958

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor (Do not leave blank)

Publisher (Name and complete mailing address): International Society for Pharmaceutical Engineering, 6110 Executive Blvd., Ste. 600, North Bethesda, MD 20852-3958

Editor (Name and complete mailing address): Susan Sandler, Senior Director, Editorial, 6110 Executive Blvd., Ste. 600, North Bethesda, MD 20852-3958

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13. Publication Title	14. Issue Date for Circulation Data Below
Pharmaceutical Engineering	September-October 2020

15. Extent and Nature of Circulation			Average No. Copies Each Issue During Preceding 12 Months	No. Copies of Single Issue Published Nearest to Filing Date
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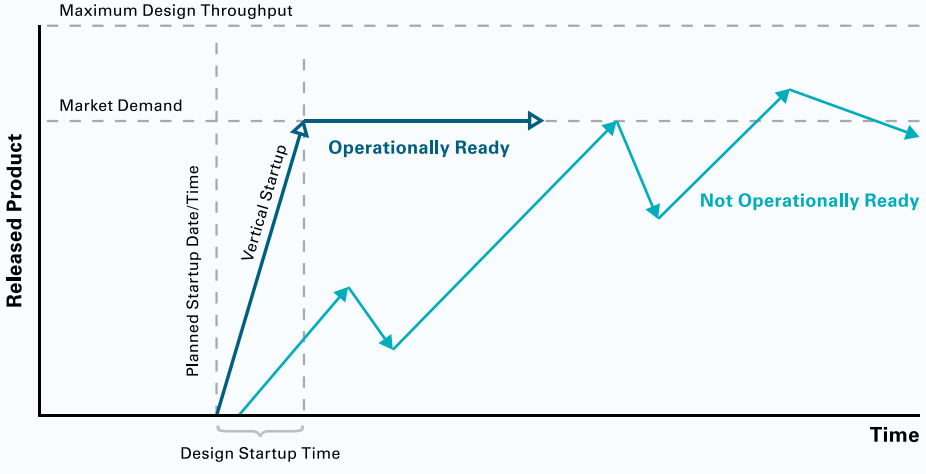

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