PHARMACEUTICAL ENGINEERING®

The Official Magazine of ISPE

July/August 2024 | Volume 44, Number 4

REPURPOSING A US CELL THERAPY FACILITY FOR FLEXIBILITY AND EU COMPLIANCE

Pharma Facilities, Composable Tools, and Validation 4.0

Gene Editing and Facility Retrofits for CRISPR and Beyond

ISPE®

ISPE.org/pharmaceutical-engineering

DELIVERING SOLUTIONS TO BETTER SERVE YOUR PATIENTS

ENGINEERING | PROCUREMENT | CONSTRUCTION
CQV SERVICES | SINGLE POINT ACCOUNTABLE

Leverage our subject matter experts to accelerate your product delivery platform schedules with quality solutions.

BIOTECHNOLOGY | PHARMACEUTICAL | VACCINES

For decades, Fluor has designed and built various types of biotech and bulk pharmaceutical facilities, employing batch, semi-continuous, and continuous operations. We offer the life sciences industry agility and robustness through expertise in process design while providing innovative professional and technical solutions.

NOW HIRING

Scan for information on open positions.

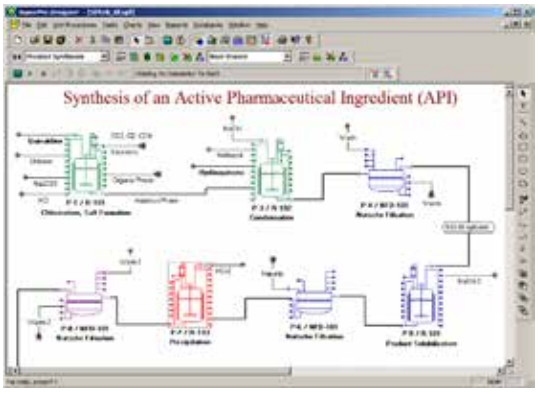
www.fluor.com

FLUOR®

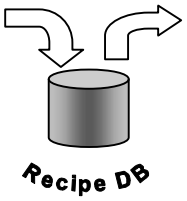
Intelligen Suite®

The Market-Leading Engineering Suite for Modeling, Evaluation, Scheduling, and Debottlenecking of Multi-Product Facilities

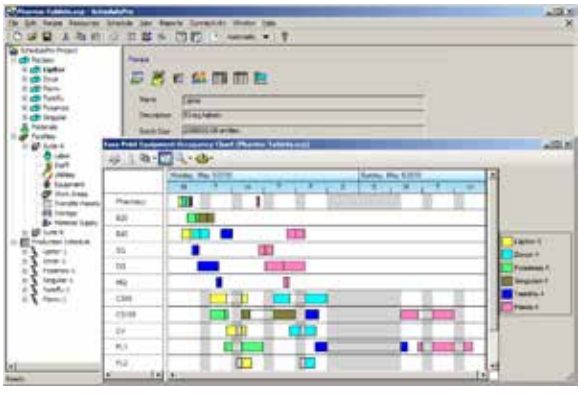
SuperPro®



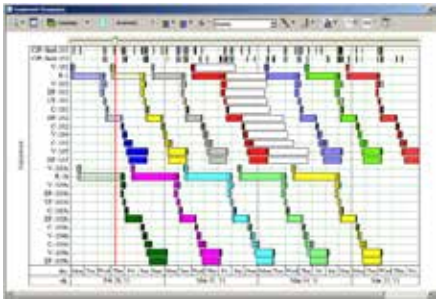
Use SuperPro Designer to model, evaluate, and optimize batch and continuous processes



SchedulePro®

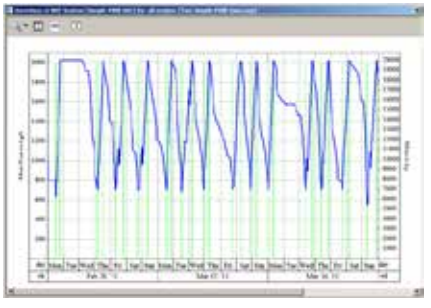


Migrate to SchedulePro to model, schedule, and debottleneck multi-product facilities



Easy production tracking, conflict resolution and rescheduling

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



Managing inventories for input, intermediate, and output materials

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

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

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

INTELLIGEN, INC. • 2326 Morse Avenue • Scotch Plains, NJ 07076 • USA
Tel: (908) 654-0088 • Fax: (908) 654-3866
Email: info@intelligen.com • Website: www.intelligen.com
Intelligen also has offices in Europe and representatives in countries around the world

PHARMACEUTICAL ENGINEERING®

JULY/AUGUST 2024

ON THE COVER The DNA and equipment images represent cell therapy manufacturing.

Reduce cost.

Increase speed.

Meet demand.

Streamline.

Eliminate waste.

Minimize risk.

Build sustainability.

One team. Start to finish.

Defining the gold standard in **EPCMV** integrated project delivery for 35 years. Enabling our clients to create and manufacture life-impacting products around the world.

ips

35 YEARS 1989 ips 2024

Engineering, Procurement, Construction Management, & Validation

37 AUTOMATION SUPPORTS ESG GOALS FOR PHARMA FACILITY CONVERSION

Implementing advanced automation technologies is a strategic move that can amplify the positive outcomes of environmental, social, and governance (ESG) initiatives. By leveraging ESG initiatives, pharmaceutical companies can enhance their competitive edge and contribute positively to global sustainability efforts.

DEPARTMENTS

PEOPLE + EVENTS

TECHNICAL

ISPE

PHARMACEUTICAL ENGINEERING

Volume 44, Number 4

ISSN 0273-8139
Pharmaceutical Engineering is published six times a year by ISPE and is online at ISPE.org/Pharmaceutical-Engineering

Editor-in-Chief: Nina Wang

Technical Copy Editor: Heather E. Saunders

Publications Coordinator: Marcy Sanford

Advertising and Sales
Laneisha Walker, Sales Operations Manager
lwalker@ispe.org

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

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

Stock Photography and Illustration
iStock

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

Printing
Sheridan NH

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

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

ISPE Operations
3001 North Rocky Point Drive East
Suite 200-242
Tampa, Florida 33607
Tel: +1 813-960-2105

US Postmaster
Send change of address to:
Pharmaceutical Engineering Magazine
3001 North Rocky Point Drive East
Suite 200-242
Tampa, Florida 33607 US

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

Canada Postmaster
Send change of address and undeliverable copies to:
Pharmaceutical Engineering Magazine
PO Box 122
Niagara Falls, ON L2E 6S8
Canada

Canada Post mail agreement #40012899

PLAN

We provide quality cGMP facility planning, design, process engineering, project delivery and staff optimization for the world's leading pharmaceutical manufacturing companies.

FACILITIES WITH FUTURE-FLEXIBILITY

Our design is dedicated to creating spaces that are safe, maximize production, and continue to thrive for years to come.

Scan Below to Maximize ROI with 3 Capital Planning Tips

HIPP®

HIPP
DESIGN +
CONSULTING

hipp-usa.com

By Scott W. Billman


Scott W. Billman

2024: A Year in Progress

As we get into the peak of the summer months and everyone is preparing for a well-deserved vacation, ISPE is in full swing. We just had a great Biotechnology Conference in Boston. Attendees heard about topics ranging from the use of digitization and artificial intelligence in manufacturing to quality systems maturity and the quality culture required to manufacture safe and efficacious therapies.

We engaged in discussions around the growing sustainability concerns in the industry and the current state of PFAS (per- and polyfluoroalkyl substances) in pharmaceutical filtration. Having the conference in Boston, a global hub of biotech companies and industry experts, always makes this an active and engaging forum for our membership to network and share their thoughts on where the biotechnology sector is heading.

We are also in the middle of the ISPE Board of Directors election process. The ballot has been set and sent to all members to vote on the upcoming open positions on the International Board. This process started in February with the collection of nominations from across the globe. The Nominating Committee, led by ISPE International Board Vice Chair Jeff Biskup, received dozens of nominations for industry professionals willing to volunteer their time and talents to help shape the future strategy of ISPE for the membership. With several current board seats up for election, I encourage you to participate in the election process by reading up on the candidates and voting for the 2024–2025 International Board of Directors.

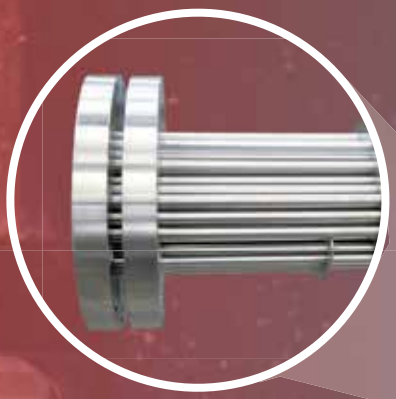
Heading into summer, the Regulatory Steering Committee published the results of our industry survey around enabling pharmaceutical innovation. This was the first phase of the effort around identifying barriers to interpretation and implementation of ICH guidelines with respect to progressing the introduction of new technology for development, manufacture, life cycle management, and distribution of pharmaceutical products and innovative medicines.

This is all in an effort to establish durable, globally harmonized regulatory process implementation and guidance to allow regulatory authorities to consistently assess and accept the new technologies. This was done through the input of our membership. Continue to look for ways to engage in this effort in the future so that we, as an industry, can continue to innovate and move new technologies forward.

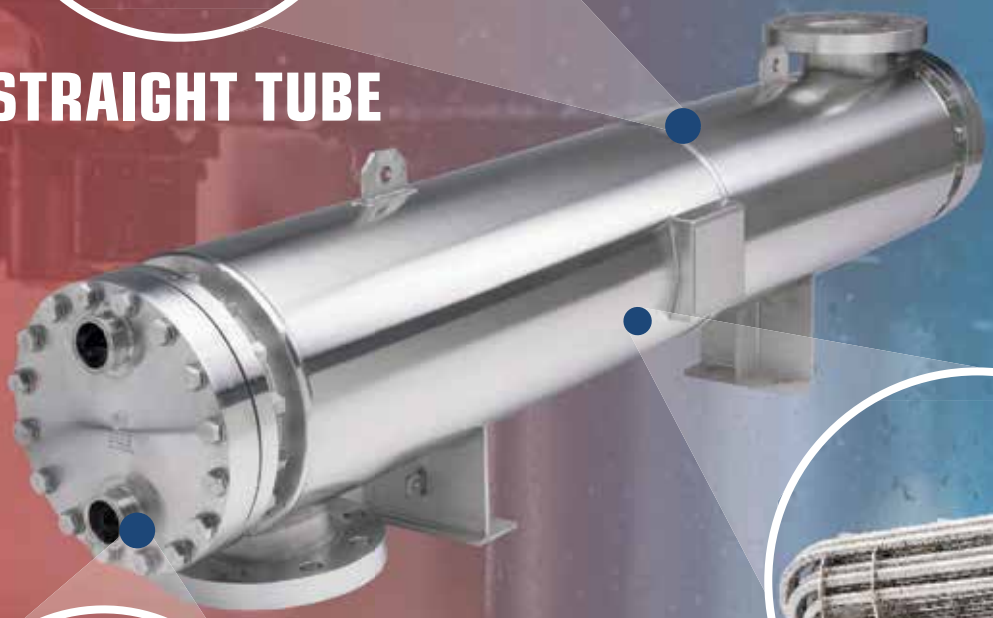
In this issue of *Pharmaceutical Engineering*®, you will find articles focused on facility retrofits and repurposing for new products and modalities. As companies continue to innovate to bring new products to patients, we will continue to need to adapt our current facilities and processes for future products. A facility retrofit can save time and costs over new facility builds. Time to market is so important for our patients that anything we can do as an industry to speed up the process and bring down the costs is a

ISPE®
PHARMACEUTICAL ENGINEERING®

Sanitary flow equipment



STRAIGHT TUBE



U TUBE

HEADERS DETAILS

HEAT EXCHANGERS

PERFORMANT ASEPTIC TAILOR MADE

Aerre Inox S.r.l.

via Gerola 4, 26010 Fiesco (CR) - Italia

info@aerreinox.it - (+39) 0374 370828 - www.aerreinox.it

The next big conference will be the 2024 ISPE Annual Meeting & Expo in Orlando, Florida, 13–16 October.

benefit for everyone. Look at the innovative thinking and project execution of these projects. Perhaps it will provide thoughts for your organization's plans. You will see that many of the Facility of the Year Award finalists developed innovative solutions through retrofit projects to meet their company's goals.

The next big conference will be the 2024 ISPE Annual Meeting & Expo in Orlando, Florida, 13–16 October. Remember to stick around for the annual golf tournament that benefits the ISPE Foundation on 16 October at noon. It's the perfect opportunity to boost your company's philanthropic contributions to the ISPE Foundation and its mission of fueling global health equity.

Through its Workforce Diversity Pillar programs, Women in Pharma®, and the ISPE Foundation Diversity Internship Program, the ISPE Foundation provides a pathway for the diverse and unique perspectives of all people to be heard within our industry. The ISPE Foundation's Technology without Borders program has achieved notable progress, particularly with the successful completion of its inaugural cycle in Brazil, with over 130 Portuguese-speaking individuals benefiting from resources and training in their native language.

A communication was sent out in May announcing ISPE President and CEO Thomas Hartman's retirement. Tom has served ISPE with passion, dedication, and strong leadership for the past four years. During his tenure, Tom fostered a culture of innovation and integrity, ISPE's membership flourished and grew to over 22,000, and ISPE's reputation as a thought leader in shaping the future of the pharmaceutical industry was enhanced. We are grateful for his commitment to the association, staff, and members. The Board of Directors has begun the search for a new CEO who will build upon the strong foundation established and lead us into a new era of growth and influence. Please join me in expressing our deepest gratitude to Tom and wishing him the best in his well-deserved retirement.

Scott W. Billman is Vice President of Global Engineering, Real Estate, and Facilities Services at Solventum and the 2023–2024 ISPE International Board Chair. He has been an ISPE member since 1996.

LISURE

Just Purification

Total DSP Solution

- Process Chromatography and Columns
- Membrane filtration /TFF/SPTFF/NF
- In-line dilution/conditioning process chromatography (ICPC)
- HPLC and Columns
- Tanks and vessels with CIP/SIP

Continuous Buffer Management System (CBMS)

Custom Engineering & S88 Batch Automation

Multi-Functional Pilot Scale POC Platform

Contact Information:

Tel:+86-512-62625790
E-mail: marketing@lisure-us.com /info@lisure-us.com
Website:www.Lisure-us.com

PURIFICATION MADE SIMPLE


Edyna Miguez

WOMEN IN PHARMA® AT THE 2024 ISPE ANNUAL MEETING & EXPO

Long gone are the days of early morning Women in Pharma breakfast meetings at ISPE international conferences—well, sort of. The long-awaited 2024 ISPE Annual Meeting & Expo is on the horizon and it's time to finalize your itinerary. Be sure to tie Women in Pharma activities into the mix.

If you aren't familiar with ISPE's Women in Pharma, it's a member-exclusive initiative committed to bridging gender, cultural, organizational, and geographic boundaries to maximize the impact women and other marginalized groups have on the pharmaceutical industry, and their respective communities.

Through in-person and virtual programming, Women in Pharma focuses on creating more inclusion by helping members of all cultural, gender, and geographic backgrounds hone and further develop their emotional quotient (EQ). We do this through global collaboration, relying on our members to drive conversations through webinars, panel discussions, networking events, and mentorship. Throughout the conference, we will host a series of events and activities that will allow you to expand your network and further develop your EQ in unconventional and exciting ways.

SUNDAY COMMITTEE MEETING

Join us for an open forum with Women in Pharma international leadership. ISPE Board members, Affiliate and Chapter leaders, and passionate members will gather to discuss Women in Pharma programming and strategic initiatives. These initiatives allow us to work collectively to drive the mission and vision of Women in Pharma. Come prepared with ideas and ready to share and collaborate, as this will serve as a brainstorming session that will guide the 2025 Women in Pharma programming.

SUNDAY WORKSHOP

This year, Women in Pharma will be hosting a Sunday workshop focused on leadership skill development and fine-tuning your personal and professional brand. Coordinated by ISPE Women in Pharma Steering Committee Members, this workshop will help you identify your leadership style, personal brand, and the different professional "love languages" to motivate and inspire your teams.

MONDAY NIGHT EVENT

Masked Connections: A Networking Soiree

Join us for an evening of art, history, and culture as Women in Pharma gathers once again in celebration of accelerated equality and inclusivity within our industry. Throughout the two-hour event, you'll immerse yourself in the ambiance of Italian culture, enjoying cocktails, Italian cuisine, and conversations while appreciating the rich history and cultural significance of the masquerade tradition dating back to 15th-century Venice.

Veiled by your mask, relish the freedom of anonymity as it fosters uninhibited exchanges and the forging of genuine connections. As the night unfolds, masks will be shed, unveiling identities and paving the way for the exchange of business cards and the cultivation of professional ties, fortified by the shared bond of ISPE's Women in Pharma.

Please note: All attendees must wear a Venetian-style mask throughout the duration of the event. We highly encourage masks to be elaborate and decorative, covering the eyes and nose area, but they should not obstruct vision or impede conversation.

TUESDAY MORNING

Women in Pharma Self-Defense Class

M.A.P.S! was founded by Bridget Collins: business owner, mom, ISPE member, and black belt in martial arts. The program name stands for mindset, awareness, preparation, and strike. The program offers empowering and educational seminars to teach women the basics of self-defense, helping them build a mindset and awareness around personal safety. This prepares them to avoid personal attacks and defend themselves when necessary.

Throughout this early morning session, you will enjoy a demonstration of martial arts techniques and practice maneuvers to release and defend the most common forms of attacks.

This event is open to all conference attendees. We recommend you wear comfortable workout clothes, as this will include a workout component for those who participate. A completed waiver will be required to attend the class; this will be available to fill out prior to starting the session.

Edyna Miguez is Membership Growth Manager at ISPE.

ELETTRACQUA

pure water technologies

SINCE 1966

PHARMACEUTICAL WATER SYSTEMS

DESIGN AND CONSTRUCTION OF PURIFIED WATER PACKAGES ♦ DOUBLE PASS REVERSE OSMOSIS ♦ R.O. + ELECTRODEIONIZATION HOT WATER SANITIZABLE ♦ ULTRAFILTRATION ♦ MULTIPLE - EFFECT DISTILLATION UNITS ♦ PURE STEAM GENERATORS ♦ STORAGE AND DISTRIBUTION LOOP ♦ COMPLETE TURNKEY PROJECTS ♦ VALIDATIONS IQ, OQ

www.elettracqua.com

By Monique L. Sprueill


Monique L. Sprueill

CELEBRATING STATE-OF-THE-ART PHARMACEUTICAL FACILITIES

Every year we celebrate the achievements of state-of-the-art pharmaceutical facility projects through the Facility of the Year Awards (FOYA). The buildings are beautiful, energy efficient, and sustainable; the equipment is new and innovative. This event showcases how cross-functional teams leverage the newest technology, skills, and talent to build facilities that supply life-saving remedies to patients.

Don't we all wish we could be on "that" project team? Of course we do! As an Emerging Leader, you have options. You are part of a collective group of people who use their "superpowers" to increase efficiencies, translate data, and improve processes.

Maybe you think it is time for a new challenge and you want to be a part of a team that is either building new structures or modifying existing ones. Perhaps you are trying to decide between a brownfield or greenfield project. What is the difference?

Brownfield projects use existing facilities and infrastructures. Modifications are done such that the facility is fit for purpose. Depending on the age of the structure, previous use, land condition, and community, the project could be relatively simple or very complex. Greenfield projects are built on sites that have not been previously used. The designer and clients can create something that meets status quo or defies the imagination.

I've worked on both types of projects, and each brings its own unique challenges. In the end, I contributed to ensure that the companies could increase capacity, extend reliability, and harness the benefits of new technology.

There are several opportunities to learn about FOYA projects at the 2024 ISPE Annual Meeting & Expo including the FOYA Banquet and Awards Celebration on Sunday 13 October.

You should also plan to arrive to the conference early and participate in the Hackathon. During the Hackathon, you work in cross-functional teams to resolve issues and complete a continuous improvement project or a project that requires a new approach.

Are you looking for ways to boost your career and expand your network? Join ISPE as an Emerging Leader. Build your network, get a mentor, and take your career to the next level.

Are you looking for ways to boost your career and expand your network? Join ISPE as an Emerging Leader. Build your network, get a mentor, and take your career to the next level.

Some key advantages of joining Emerging Leaders are:

- Professional development
- Access to Emerging Leader member-only resources
- Opportunities to establish and grow your network
- Exposure to thought leadership events
- Participation in Hackathons
- Career solutions to promote advancement

If you are not a member of ISPE, join today at www.ispe.org and:

- Gain access to Good Practice Guides and educational resources
- Join Communities of Practice and connect with other industry professionals
- Add content, ask questions, and post your ideas on Engage
- Write a blog or article
- Talk with your manager and colleagues about presenting your project at a conference or local program

Another way to network is to keep track of what is going on at your local Chapter or Affiliate. Find out which committees are in search of new members. Volunteer to gain more exposure. Actively participate in program planning to ensure that topics of interest will be offered.

Monique L. Sprueill, CQA, CMQ/OE, PMP, is a Quality Risk Management Leader and the 2023–2024 International Emerging Leaders Chair. She has been an ISPE member since 2002.

Visit us at ISPE BOSTON - BOOTH #E26

Vial Trays
Model No. 229108

Gel Cap Drying Trays
Model No. 642008
with Heavy-duty
Aluminum Universal Dolly

Deep Storage Stacking Box with Lid
Model No. 808208 and 808218 (Lid)

Slotted
Container with Lid
Model No. 808308

PHARMACEUTICAL TRAYS USED BY THE TOP PHARMA COMPANIES

Pharmaceutical processing & handling solutions that are easily integrated with automated machinery.

VIAL TRAYS

- Tapered front lip for easy loading
- Smooth, non-porous surface is easy to clean
- Vial gates available for various temp ranges

GEL CAP DRYING TRAYS

- Ventilated sides or ends for quicker drying
- Interlock stacking without warping or distortion
- Won't bend, dent or deflect under heavy loads
- Smooth surface is easily cleaned
- Easy integration with process equipment

DEEP STORAGE TRAYS

- Ideal for storing gel caps prior to packaging
- Stacking design ensures product protection and saves valuable work and storage areas
- Smooth surface is resistant to mild acids and alkaline solutions

STERILIZATION & BIOTECH TRAYS

- Great for handling, storing and shipping small parts
- Slotted and unslotted containers available
- Ideal for Gamma, Autoclave and ETO environments
- Optional lids and dollies available

Reinforced composites bring a new level of performance to pharmaceutical processing and handling. **The leading name in FRP is MFG.**

NSF. Made in the USA

MOLDED FIBER GLASS TRAY COMPANY
PH 800 458.6050 • www.mfgtray.com

MFG TRAY

REPURPOSING A US CELL THERAPY FACILITY for Flexibility and EU Compliance

By George Todorov and Aaron Weinstein

The explosive growth of advanced therapy medicinal products (ATMPs), particularly cellular therapeutics, has driven steady investment in facilities capable of manufacturing these therapeutics at scale [1, 2]. Meanwhile, the industry is collectively moving to adapt to European Union Annex 1 standards, which places a more stringent emphasis on contamination control [3].

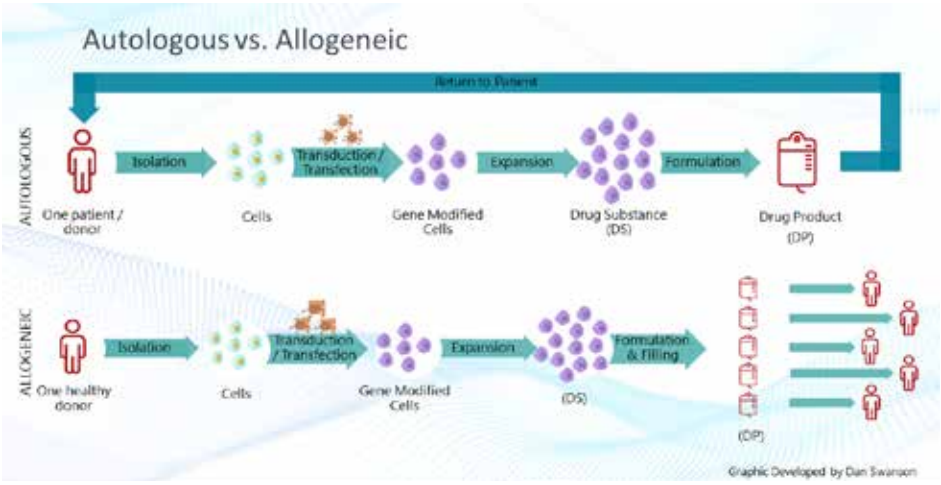
In this conceptual design case study, we discuss plans to convert an existing single-product cell therapy facility into a contract development and manufacturing organization (CDMO) facility. This facility would be capable of running multiple lines of batched-based therapies while maintaining GMP compliance with EudraLex Volume 4, Annex 1 and the guidelines on GMP for ATMPs [3, 4]. The new CDMO-focused portion of the facility will encompass 25,000 square feet of an existing 42,000-square-foot manufacturing area. It could be converted while the remaining space continues existing operations.

The transition of cell and gene therapies (C&GTs) from laboratory

Table 1: Risk review summary.

Potential Risk	Engineering Considerations
Handling of viral vectors in a multiproduct/multiclient facility could lead to cross contamination.	Design for dedicated, single-pass heating, ventilation, and air conditioning (HVAC) systems to ensure that the air in any given production suite is not recirculated back to other areas.
Use of pressure cascades in the production suites could lead to cross contamination in a multiproduct/multiclient facility.	Design airlocks with a bubble/sink configuration to protect the manufacturing environment and outside areas.
In a multiproduct/multiclient facility, final product, apheresis, equipment, etc. may be taken through a given area at the same time with the potential for contamination.	A strictly engineering solution cannot be implemented. This will require adequate procedures to ensure segregation of materials and personnel as needed.
The multiproduct/multiclient facility will have gases and water supplied to the suite with piping. Cleaning piping can be a challenge and could lead to contamination.	Design the piping to include easily cleanable covers and, when possible, recess the piping into the ceiling so that removable flex connections can be made.
Currently, the area transitions from controlled not classified (CNC) to Grade C. This increases the risk of regulatory observation and the potential for contamination.	Design the airlocks so that there is progression from CNC to Grade D, to Grade C, to Grade B.
Multiple batches may be stored in an incubator at the same time, increasing the risk of cross contamination.	• Engineering: Fully exhaust air from the incubators where this will happen. • Procedural alternative: Ensure segregation of batches within the incubator.
Manufacturing multiple batches in separate biosafety cabinets (BSCs) or isolators in the same room can lead to cross contamination.	• BSCs engineering: Fully exhaust air from any BSC in the room where multiple batches are being processed. • Procedural alternative: Ensure physical segregation of batches and dedicated operators within the room. • A BSC risk assessment must be conducted by the company to show why using multiple BSCs at the same time is acceptable, with or without BSC exhaust. • Isolators are the preferred engineering solution because they provide a high degree of assurance that the risk of cross contamination is reduced.

Figure 1: Autologous vs. allogeneic products.



to clinical use has been a revolution, decades in the making [5, 6]. ATMPs are poised to capture a significant portion of the biopharmaceutical industry, which motivated the subject company of this case study to expand its current business model to incorporate CDMO practices [1].

FACILITY CONVERSION DESIGN

The approaches to facility conversion design presented in this case study can serve as a model for repurposing existing manufacturing space for ATMP processes while adhering to the revised Annex 1 standards implemented as of 2023. Here, we provide an overview of the airflow and room classification modifications necessary to make this facility compliant with EU regulations for concurrently manufacturing multiple products. As part of the initial concept effort, risks were reviewed and addressed or identified and documented so that they could be further analyzed and addressed in later stages of the design (see Table 1).

ATMP OPPORTUNITIES AND CONSIDERATIONS

ATMPs encompass several cell- and tissue-based techniques, including in vivo and ex vivo gene and somatic cell therapies [6]. Cell therapies can be either autologous, which involves harvesting, manipulating, and administering modified cells back to the original donor patient, or allogeneic, which involves cell-based therapeutics derived from donated blood or tissues that are expanded at a much larger scale to enable treating multiple patients (see Figure 1) [7].

The transformative chimeric antigen receptor T cell (CAR T) therapy, for example, starts with a patient's own T cells, which are isolated from an autologous donation of blood or leukapheresis product (leukocytes or white blood cells isolated from blood). The donor blood or leukapheresis product is collected in a manufacturing facility in a closed IV bag known as a leukopak. Then, it is shipped to a manufacturing facility where the patient's T cells are modified to produce CARs. The CAR T therapeutics specifically target and destroy cancer cells, rendering tumors vulnerable to the patient's immune system [8, 9].

CAR T products fall into two different types: autologous products and allogeneic products. Understanding which products will be processed will heavily inform facility design. Autologous products focus on a single patient and/or donor, with all products being produced specifically for that patient. Allogeneic facilities have the potential to be much more efficient by generating larger batches for administration to a wider patient population.

In this facility, the company plans to focus on contract autologous CAR T processes, with the flexibility and capacity needed to scale-up CAR T and natural killer allogeneic processes.

Autologous therapeutic manufacturing presents a sizable challenge for GMP production at scale, which involves scaling out additional copies of the process, regardless of open or closed format [7]. In this mode of operation, increased batch turnover presents more opportunities for batch mix-up and cross contamination to occur. In addition, complex personnel flows, material flows, and higher batch throughput required to meet the demands of growing clinical and commercial programs increase the opportunity for microbiological contamination [10].

THE CHALLENGES OF COMPLIANCE WITH EUROPEAN REGULATIONS

Contamination control is a fundamental focus of the revised Annex 1 regulations. Although Annex 1 and the guidelines on GMP for ATMPs are specifically meant for therapeutics developed for European markets, they also represent a new gold standard for modern GMP across the industry. The US Food and Drug Administration (FDA) has not only taken notice, but has also helped contribute to defining Annex 1 standards. Annex 1 impacts a facility's design if even one product made on-site is intended for European markets.

Annex 1 requires manufacturers to develop a contamination control strategy to govern their manufacturing process, which

One of the driving factors in the new Annex 1 regulations is the contamination control strategy, including the prevention of cross contamination.

may require a comprehensive reexamination of processes at a given facility [3].

The simple solution is often new construction, which allows a fresh start with each new product line. However, the advent of ATMPs, benchtop processing equipment, and bioreactor-based manufacturing using single-use components has brought about new, beneficial economies to batch-based manufacturing [8]. These processes allow a single facility to produce a continuously changing array of new products without dramatically altering the manufacturing space. If the correct array of process utilities and adequate capacity are in place, manufacturers can leverage the same space and the same or similar benchtop bioreactors and equipment for different processes.

Mobile lab bench configurations and modular equipment enable equipment changes to support a range of client processes using different brands of equipment platforms. The question then becomes whether the facility, flows, engineering controls, and associated procedures can become robust enough to continuously change production while adhering to the current GMP.

In this case study, an existing cell therapy manufacturer leverages extra capacity, physical space, and in-house expertise in ATMP manufacturing for contract production as a CDMO. The company's intent was to take a facility nearing the end of its life cycle and modify it to provide new opportunities for growth and revenue streams.

OVERVIEW OF PROPOSED MODIFICATIONS

Built over a decade ago, the 180,000-square-foot facility remains a relatively robust, state-of-the-art ATMP manufacturing facility. The site was strategically built near a major transportation hub to expedite shipments of autologous cell products quickly and efficiently. The manufacturing floor consists of six Grade B production modules. Each currently houses multiple cell therapy processing workstations, including BSCs, incubators, centrifuges, and other technical equipment.

Upon completion of the project, most of the process (from donor material thaw to formulation and fill) will be contained within the individual production modules. The warehouse and product freezing/storage room will house controlled-rate freezers to cryopreserve intermediates and final products, as well as liquid nitrogen freezers to store incoming and outgoing materials. Liquid nitrogen freezers in the warehouse may also be used for long-term storage of master cell banks or working cell banks for allogeneic processes.

In the conversion, the owner intends to use four of the modules as a GMP manufacturing area that will initially produce cell therapy products for Phase I/II/III clinical trials. This will include the ability to support commercial manufacturing for select clients. The facility is currently designed primarily for autologous CAR T processes with built-in flexibility and capacity to accommodate allogeneic therapy manufacturing. The typical production processes within the Grade B modules are expected to take 7–14 days, depending on the nature and scale of the client's process. The remaining two modules will continue to manufacture the company's flagship ATMP.

One of the driving factors in the new Annex 1 regulations is the contamination control strategy, including the prevention of cross contamination. The new CDMO space will be a multiclient and multiproduct facility, which will require changes to how people and materials will move throughout the facility. Changes to room classifications and air pressure cascades will be implemented to comply with Annex 1 guidelines on containing potential contaminants.

The designed CDMO area of the facility contains the four identical Grade B production modules in addition to support spaces. These include areas for parts prep, product freezing and storage, labeling and inspection, and waste-out staging; a dispensary; chemistry, manufacturing, and control (CMC) stability rooms; quality control labs; a warehouse; and utility rooms.

The concept design for the production modules includes flexibility to meet future client processing needs with the capability to house equipment for open or closed processing. Meanwhile, the rooms are operated under Grade B or Grade C backgrounds, respectively (see Figure 2). Design features include portable benches and process gas utility panels placed in flexible locations to accommodate equipment changes. Process utilities are sized accordingly to support a range of cell culture vessels up to 200 liters (L).

To evaluate and determine the appropriate layout of the updated production modules, we performed a capacity analysis of various production module configurations. These included autologous open processing, autologous closed processing, and allogeneic closed processing at a concept design level. For both autologous and allogeneic closed process configurations, two equipment arrangement scenarios were considered. The tradeoffs of varying the number of closed process systems (such as Miltenyi Biotec CliniMACS Prodigy, benchtop bioreactor, and 200-L bioreactor systems) were weighed (see Table 2).

Three facility operational scenarios were also evaluated to study varying the number of autologous vs. allogeneic process modules and the impact on the facility production capacity. At a concept design level, we produced layouts of all configurations described in Table 1 and sized process utilities to support two modules with bench-scale reactor processes and two modules with 200-L bioreactors. A GMP equipment storage room has also been designed to accommodate turnover of the different module

Validate your MTP files **FOR FREE!**

Plug & Produce in Life Sciences with MTP

zenon MTP Suite for Equipment Producers (PEA) and End Users (POL):

- *Increase flexibility and reduce engineering and validation effort due to modular process automation*
- *Create or edit Module Type Package (MTP) files*
- *Validate your MTP files according to VDI/VDE/NAMUR 2658*
- *Manage your MTP library based on a central repository incl. versioning*
- *GMP-compliant HMI package for Process Equipment Assembly (PEA)*
- *Simplify the process orchestration of your equipment with a graphical editor (zenon POL)*
- *Integrate your existing skids using an MTP Gateway (independent from hardware and OS)*

go.copadata.com/mtp

Gold Microsoft Partner

GAMP 5

FDA 21 CFR Part 11 Compliant

zenon by COPA-DATA

Table 2: Production module configurations considered during concept design.

Configuration Description	BSC Quantity	Closed System Quantity	Bioreactor Quantity (Benchtop)	Bioreactor Quantity (200 L)	Module Quantity	Total Capability (Number of Concurrent Lots)
Operational Scenario 1						
Autologous - Open Process	6	-	-	-	1	6
Autologous - Closed Process Equipment Scenario 1	2 (inoculation/fill)	6	-	-	1	6
Autologous – Closed Process Equipment Scenario 2	2 (inoculation/fill)	-	6	-	2	12
Total CDMO capability (number of concurrent lots)						24
Operational Scenario 2						
Autologous - Closed Process Equipment Scenario 1	2 (inoculation/fill)	6	-	-	2	12
Autologous - Closed Process Equipment Scenario 2	2 (inoculation/fill)	-	6	-	1	6
Allogeneic - Closed Process Equipment Scenario 1	3 (inoculation/fill)	-	6	-	1	6
Total CDMO capability (number of concurrent lots)						24
Operational Scenario 3						
Autologous - Closed Process Equipment Scenario 1	2 (inoculation/fill)	6	-	-	2	12
Allogeneic - Closed Process Equipment Scenario 2	3 (inoculation/fill)	-	2	2	2	8
Total CDMO capability (number of concurrent lots)						20

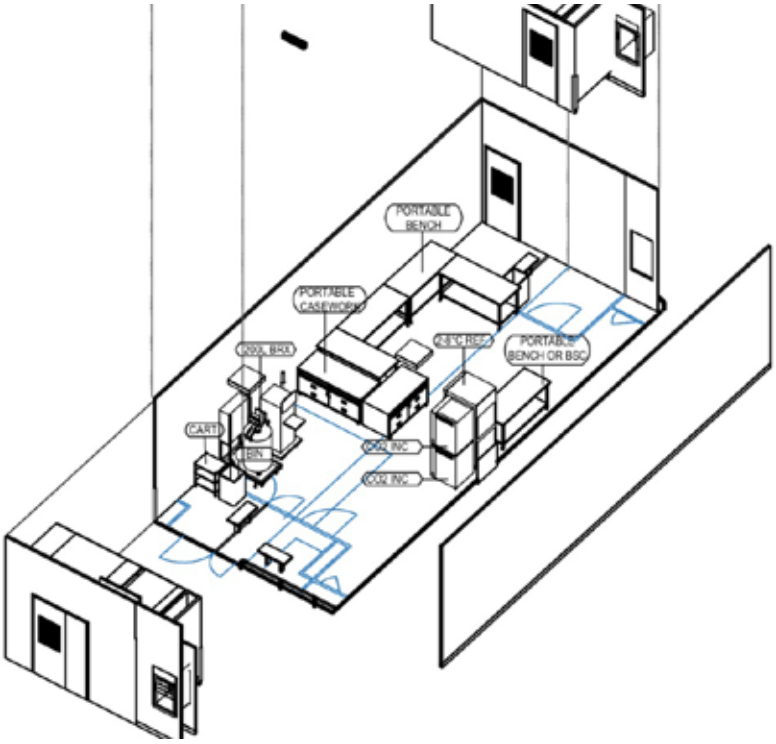
equipment configurations based on CDMO client need.

Considering that the four modules being repurposed for the CDMO function were fully staffed to produce the company's ATMP product, this conceptual study assumes a similar level of staffing and material storage requirements to the original operation.

Future design phases will leverage industrial modeling expertise to build detailed simulation models that will verify the following based on the final suite configuration and output required by the company: equipment quantities, staffing levels, scheduling, material movements, storage requirements, and total facility output.

Additional operational considerations such as multiple shifts, media prep, and cold room storage spaces shall also be considered and modeled during future design phases. Based on the number of 200-L processes chosen for the final facility layout, automated

Figure 2: Isometric view of a single production module designed to house various open and closed process equipment, ranging from benchtop systems to 200-L bioreactors.



The guidelines require technical and organizational measures to separate the activity, which concerns the flow of people and material through the processing suite.

filling and inspection equipment to support large-scale allogeneic processes must be carefully considered. Isolated filling lines can be operated in a Grade C or Grade D background, reducing the required Grade B footprint [3]. Semi- or fully automated inspection machines can be operated in CNC areas and offer the benefits of a lower inspection footprint and lower staffing levels.

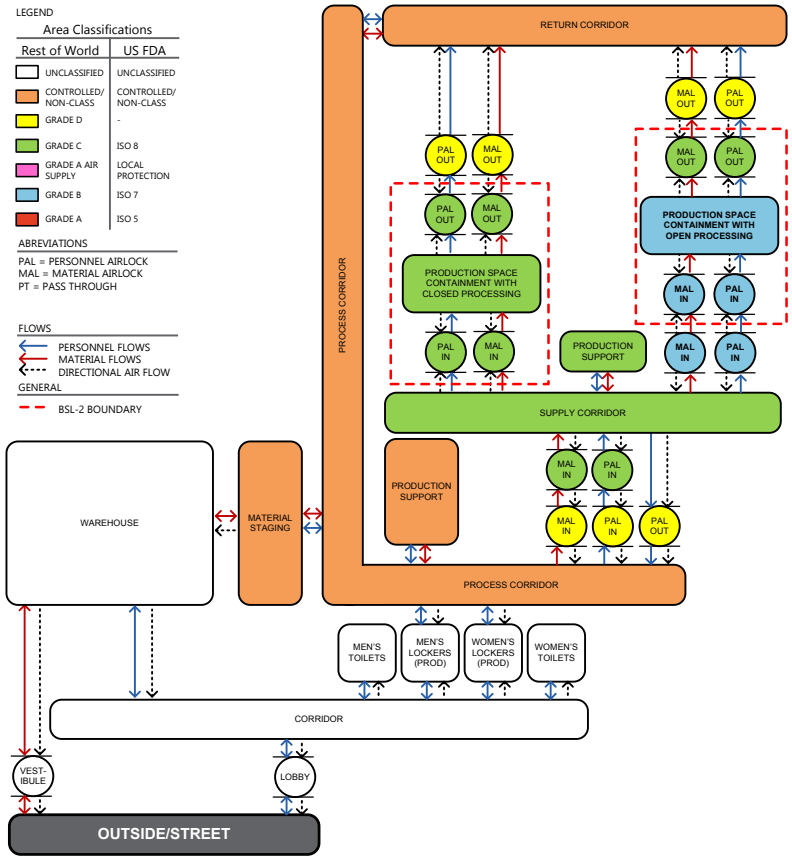
The construction phase will update supporting spaces for Annex 1 compliance. This includes directional airflows, ensuring airlock doors are interlocked, implementing active pass-throughs, and installing windows or cameras to allow visibility into production suites. The individual production modules will also be converted to comply with EU regulations for multiclient and multiproduct use as outlined in the guidelines on GMP for ATMPs. This includes the design of segregated areas for specific process steps, use of airlocks with pressure sinks and bubbles to confine potential airborne contaminants within a specified area, use of closed systems, and the use of single-use technology.

FACTORS FOR COMPLIANCE

On paper, the Annex 1 revisions and existing guidelines on GMP for ATMPs seem vague on requirements for a multiproduct ATMP facility. For that reason, it helps to keep the overall intent of the regulations in mind while interpreting them for specific circumstances—the prevention of mix-ups and cross contamination for the safety of the patients who will ultimately receive the therapeutic.

The guidelines require technical and organizational measures to separate the activity, which concerns the flow of people and material through the processing suite. One dramatic shift in the latest Annex 1 revisions clarified requirements for the transition between areas of different classifications. This allows only a single step up between classified spaces. For example, you could pass through an airlock between a Grade C and Grade B space, but not from Grade D to Grade B [3].

Figure 3: A zoning and transition diagram defining GMP area classifications, stepwise transitions, operational flows, and directional airflow.



This requires unidirectional people and material flows. This begins with a CNC space, an area that meets a company-defined criteria for entry into classified areas or where materials and personnel may traverse under controlled conditions outside of the classified environments. It then transitions through Grade D and Grade C spaces to enter the Grade B manufacturing modules (see Figure 3). People and materials move through a series of sink (negative air pressure) and/or bubble (positive air pressure) airlock transition spaces, where adjacent rooms of different grades have a pressure differential designed to better contain contaminants and viral vectors.

The Grade B modules will be used to manufacture biosafety level 2 (BSL-2) products, as the manufacturing processes use human cells and lentiviral vectors. Although there are no prescriptive regulations on directional airflow for BSL-2 processes, the Centers for Disease Control and Prevention (CDC) and National Institutes of Health (NIH) publication on biosafety in microbiological and biomedical laboratories recommends inward airflow and no air recirculation to spaces outside of the BSL-2 boundary when considering BSL-2 containment [11].

We considered this recommendation in the context of the updated multiproduct and multiclient facility and implemented a containment design featuring a bubble entry airlock and a sink exit airlock to prevent contaminants from entering or escaping, respectively.

The design establishes the rules that the layout should follow. To meet Annex 1 requirements for pass-throughs and stepwise transitions, existing material pass-through hatches between CNC/Grade C and Grade C/Grade B spaces must be converted to dynamic pass-throughs. This means the flow of objects through pass-throughs requires HEPA air filtration to allow the passage of material but not airborne contaminants. In addition, material airlocks from CNC to Grade C should be classified as Grade D, and pass-through hatches for materials entering Grade B production modules should be classified as Grade B to comply with Annex 1.

The guidelines on GMP for ATMPs also call for single-pass air for areas handling multiple viral vectors or for multiproduct suites. Conceivably, it is possible to recirculate HEPA-filtered air in suites devoted to a single product. Still, a contamination strategy would need to prove, with evidence, how the entire HVAC system would be decontaminated [4].

The design basis is to allow each module to continue operating independently from other air handling unit (AHU) systems, enabling the modules to be upgraded at different times. This would require

separate AHUs for each module. To meet multiproduct facility requirements for single-pass air listed in the guidelines on GMP for ATMPs, the current AHUs must be replaced with higher-capacity systems, which will also require additional modifications to utility supply lines and additional capacity to the current facility's chiller plant.

CONCLUSION

Upgrading an existing facility to meet the regulations outlined in Annex 1 and the guidelines on GMP for ATMPs involves complex decisions regarding HVAC and the flow of people and material. The facility's original layout allowed for cordoning off CNC spaces and room for the stepwise transition between classified spaces. Air handling and filtration will require significant capital costs to reconfigure the manufacturing space to accommodate the needs of a multiproduct CDMO.

Those costs, however, need to be weighed against the expense of developing new facilities from scratch. As ATMP technology matures, the demand for C&GT product manufacturing space will only increase. This brief example shows the significant considerations for converting a facility from a single ATMP product manufacturing to multiproduct manufacturing following a more stringent regulatory framework. It also demonstrates that the conversion is possible and that it may help bring these important products to the markets faster than a new greenfield facility.

References

1. *Cell Therapy Manufacturing Market by Type of Cell Manufactured, Source of Cell, Scale of Operation, Purpose of Manufacturing and Key Geographical Regions: Industry Trends and Global Forecasts 5th ed., 2022–2035.* Roost Analysis, July 2023.
2. Saez-Ibanez, A. R., S. Upadhaya, T. Partridge, M. Shah, D. Correa, and J. Campbell. "Landscape of Cancer Cell Therapies: Trends and Real-World Data." *Nature Reviews Drug Discovery*. 1 June 2022. www.nature.com/articles/d41573-022-00095-1
3. European Commission. "EudraLex, Volume 4: EU Guidelines for GMPs for Medicinal Products for Human and Veterinary Use. Annex 1: Manufacture of Sterile Medicinal Products." Published 2022. ec.europa.eu/health/sites/default/files/files/gmp/2017_12_pc_annex1_consultation_document.pdf
4. European Commission. "EudraLex, Volume 4: EU Guidelines for GMPs for Medicinal Products for Human and Veterinary Use. Part 4: EU Guidelines for Good Manufacturing Practice (GMP) Specific to Advanced Therapy Medicinal Products." November 2017. health.ec.europa.eu/document/download/ad33d9dd-03f0-4bef-af53-21308ce2187d_en
5. Crees, Z. D., and A. Ghobadi. "The History of Cellular Therapies," in *Gene and Cellular Immunotherapy for Cancer*. Cham, Bavaria, Germany: Humana Cham (20 December 2021):3–11. doi:10.1007/978-3-030-87849-8_1
6. El-Kadiry, A. E., M. Rafei, and R. Shammaa. "Cell Therapy: Types, Regulation, and Clinical Benefits." *Front Med (Lausanne).* 22 November 2021. doi:10.3389/fmed.2021.756029
7. Haddock, R., S. Lin-Gibson, N. Lumelsky, R. McFarland, K. Roy, K. Saha, et al. *Manufacturing Cell Therapies: The Paradigm Shift in Health Care of this Century*. Washington, DC: National Academy of Medicine, June 2017.
8. Levine, B. L., J. Miskin, K. Wonnacott, and C. Keir. "Global Manufacturing of CAR T Cell Therapy." *Molecular Therapy - Methods & Clinical Development*. 31 December 2016. doi:10.1016/j.omtm.2016.12.006
9. Sterner, R. C., and R. M. Sterner. "CAR-T Cell Therapy: Current Limitations and Potential Strategies." *Blood Cancer Journal* 11, no. 4 (2021). doi:10.1038/s41408-021-00459-7
10. Deveau, I. F. "FDA Inspectional Observations and Corrective Actions." US Food and Drug Administration. Accessed 15 April 2024. www.fda.gov/media/113601/download
11. Hatcher, B., P. J. Meechan, and J. Potts. *Biosafety in Microbiological and Biomedical Laboratories (BMBL),* 6th ed. (2020). Centers for Disease Control and Prevention Libraries. 28 September 2023. www.cdc.gov/labs/BMBL.html

About the authors

George Todorov is Senior Process Technologist at IPS. He has 11 years' experience with early- to late-stage process development programs, contributing to studies enabling investigational new drug applications, supporting external partnerships and consulting in the cell therapy and adeno-associated virus (AAV) gene therapy space. Prior to joining IPS, he led the strategic development of novel AAV manufacturing and analytical platforms through the evaluation of new technologies and continuous process improvement projects. George developed and implemented AAV process scale-up for transient expression systems in mammalian cells, leveraging design of experiments yield optimization studies. His hands-on and consulting experience includes designing and coordinating laboratory expansions and GMP facilities for various cell therapy and AAV process scale-up operations. George is a meticulous, inquisitive, and data-driven leader focused on empowering and developing teams and organizations. He has trained and managed technical staff in AAV process development and production spanning cell thaw to final formulation. He joined ISPE in 2021.

Aaron Weinstein is Senior Director of Validation Services at IPS. His principal responsibilities include project development and management, compliance consulting, business development, and departmental leadership. He has over 20 years of experience in commissioning and qualification (C&Q) and validation within the pharmaceutical and biotechnology industries. Aaron's experience includes planning and executing C&Q projects, preparing master plans, performing quality risk assessments and quality audits, and remediation. Aaron has a broad range of experience in the facilities, utilities, equipment, and automation related to CAR T manufacturing, biotech bulk manufacturing, bulk drug manufacturing, and specialized packaging. Aaron holds a BA in interdisciplinary studies (chemistry/biology) from Touro College. He is an active member of ISPE and a member of the Supply Chain, Operations and Packaging Excellence (SCOPE) Community of Practice Steering Committee. He joined ISPE in 2001.

PHARMA FACILITIES, COMPOSABLE TOOLS, AND VALIDATION 4.0

By Michelle Vuolo and Gilad Langer, PhD

The pharmaceutical industry stands at the precipice of a revolution as emerging digital technologies provide new opportunities to boost productivity through continuous process improvements. The Pharma 4.0™ framework, an adaptation of the broader Industry 4.0 movement, aims to transform how drugs are produced and delivered.

Fueled by a convergence of advanced digital technologies like Industrial Internet of Things (IIoT), big data analytics, artificial intelligence (AI) and machine learning (ML) [1], and cloud computing [2], this wave of digitalization promises to radically reshape and improve the landscape of pharmaceutical manufacturing.

As the industry drives to adopt Pharma 4.0™ and embrace digital transformation as a whole, brownfield facilities pose a unique set of challenges. These include the sheer complexity of integrating new technologies with existing systems to the cultural resistance to change that often comes with established working practices. Challenged by legacy systems and manual processes, brownfield facilities require a fundamentally different approach to adoption of the new digital reality that has transformation at its core.

The true challenge, beyond the buzzwords and lofty ideals, is real-world implementation for an existing site. Implementing Pharma 4.0™ necessitates a holistic approach that encompasses technological upgrades, organizational shifts, cultural transformations, and robust data governance strategies. By understanding the potential and practicalities of Pharma 4.0™ and adopting the associated practices, pharmaceutical manufacturers can make their operations smarter, safer, and more human-centric (see Figure 1).

FUNDAMENTAL CONCEPTS FOR DIGITAL TRANSFORMATION

Before we can break down how to successfully revamp facilities to meet the needs of today's digital age, it is crucial to discuss a couple of key concepts. One of the main differentiators with digital technologies is ease of use that makes it possible to democratize work that previously required specialists. This is achieved with "no-code", digital technologies that allow you to create solutions without a single line of code. Another concept called "composable" solutions provides unique and specific ways for frontline operators to interact digitally and enable them to be more productive.

A composable enterprise is defined by Gartner as an organization that delivers business outcomes and adapts to the pace of business change. It does this through the assembly and combination of digital content [3]. This digital content needs to provide the operator with a digital interactive solution where the physical and virtual worlds are interconnected. This is a critical principle in achieving productivity gains and is inherent to the new digital reality [3].

These novel concepts provide a transformative solution to the pharmaceutical industry and enable innovative solutions for digital content creation, including batch recording and GMP compliance. They allow the pharmaceutical industry to leapfrog from paper-driven processes (Pharma 2.0) directly into the new digital age (Pharma 4.0™). This is critical to revamping facilities and reaping the productivity gains of Pharma 4.0™.

COMPOSABILITY

To truly understand what composable is, we need to first understand what it is not. The opposite of a composable solution is a monolithic solution (see Figure 2). These types of solutions attempt to provide a process-centric approach to digitizing manufacturing processes. They are a known quantity and have been widely used in the industry for the last 25 years.

They are monolithic because they take a one-size-fits-all approach with finite functionality. They serve all types of processes and modalities, in all scenarios, with any machine, for all operators, and with one complex, configurable system.

Overall, monolithic systems have the following characteristics:

- Long time to value: They take months to years and high effort to implement and deploy.

Figure 1: A pharmaceutical manufacturing facility.

- Process-centric vs. human-centric: The operator serves the system vs. the more valuable alternative where the system serves the operator. This model inhibits productivity gains by not focusing on the operator.
- Complex customizations: They typically require customization to support the differing needs of each operation where they are implemented.
- Inherently complex and hard to maintain: They require a dedicated team with unique knowledge of the technology and the solution.
- Nearly impossible to extend: They do not extend nor scale well because they expect all operations to adhere to one standard data model.
- A strict top-down approach: They assume changes are minimal and are generally known.

These types of solutions are built to automate a process where humans have to play by a strict set of rules, ultimately robbing organizations of rapid time to value and exponential productivity increases.

On the contrary, composability is a framework through which solutions in the form of digital content, also called "apps," are built in a no-code environment by the people closest to the process. At a high level, composable solutions offer flexibility in the face of evolving standards and requirements because they can be continuously modified. The main concept here is to build content, one app at a time, in an iterative manner. During building, real-world process knowledge and operator feedback are continuously used to steer the design. These continuous improvement iterations result in realizing value quickly and improving content over time.

When it comes to the manufacturing space, a composable architecture [3] empowers operators to interact with digital solutions where the physical and virtual worlds meet [4], ultimately enabling them to drive new process efficiencies.

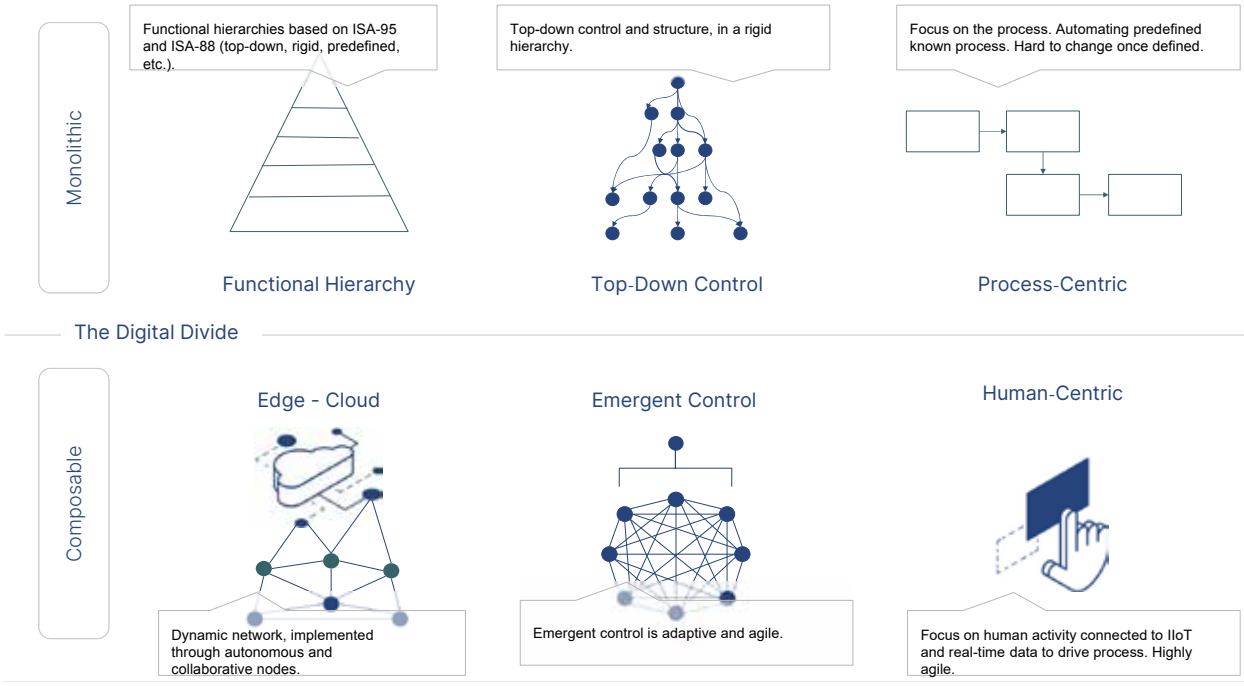
Composable solutions are purpose-built, highly configurable digital content that can and should be continuously changed and adapted to the latest operational needs. These solutions provide added value in their ability to easily integrate and collaborate with other systems.

This is at the core of the IIoT, where different autonomous devices and systems easily communicate and interact. The composable solution is built from composable elements, or apps, that are uniquely integrated with operators and equipment. Each one provides a specific and unique operational environment in which the operator is augmented with the right data, at the right time, from the right source. They instrument the activity and operational processes by capturing granular data in the context of the operation. This all requires a composable approach where apps have specific flows and connections to the local physical world.

These apps can do the following:

- Digitize processes and activities
- Connect to production equipment via edge devices and no-code-friendly integrations
- Use advanced sensors and vision technology to drive new efficiencies and higher quality
- Leverage AI and ML to augment decision-making and implement improved error-proofing

Figure 2: The digital divide between monolithic and composable solutions [5].



Modifying or enhancing an app is the same as changing master data because they represent the physical process and activities. The digital tool that supports the frontline operations is a data and process management tool that connects people, things (machines and devices), and systems used in a production or logistics process. Manufacturers can manage these app changes through a governed, version-controlled life cycle process to ensure compliance.

DEMOCRATIZATION

Democratization is defined as the process by which access to technology rapidly becomes more accessible to more people [6]. It means empowering individuals with access and agency that transcend technology in Pharma 4.0™ and it translates to unlocking the potential of citizen developers [7].

Citizen developers bridge the gap between domain expertise and technical development, bypassing lengthy IT cycles and accelerating problem-solving. This boosts productivity through targeted solutions and fosters ownership and engagement, leading to a more agile and responsive manufacturing environment. Democratization, through citizen developers, empowers individuals to become active participants in shaping their work, driving both productivity and innovation within the pharmaceutical industry.

Process and quality engineers are equipped with no-code tools to create solutions addressing specific pain points and serving frontline operators. Imagine a process engineer building an app to optimize equipment use based on their deep understanding of its nuances. These solutions can range from streamlined data collection procedures to automated quality control checks, directly impacting productivity and quality.

With modern digital technology, everyone can become builders of digital content. We already do this when using office tools such as Microsoft Word and Excel. As an example, we can easily program our smart door—a home IIoT device—to open automatically when we get within range so we don't have to take our key out. This is a big change compared to the high level of skills and expertise needed to build even simple automation tasks in traditional systems. No-code is a key enabler of democratization; it allows people with no programming or IT skills to build content that automates manufacturing processes in a simple and intuitive way.

The term "citizen development" might sound scary in a regulated environment or in larger companies that have separate organizations responsible for implementing technologies. Yet, it is a part of the cultural shifts that are a true success factor for a sustainable and engaged workforce in the digital age. Most of the new platform technologies provide accessible and transparent controls to manage content being created, distributed, and consumed.

THE PHARMA 4.0™ PARADIGM

Pharma 4.0™ is a framework for adapting digital strategies within the unique context of pharmaceutical manufacturing [5]. In practical terms, this framework introduces more connectivity, increased productivity, simplified compliance, and the ability to leverage production information to respond to problems as they emerge.

The term was trademarked by ISPE to align four key target

components (information systems, resources, organization and processes, and culture) and two enablers (digital maturity and data integrity by design) to this term. It also provides best practices for accelerating digital maturation across the pharmaceutical industry.

Pharma 4.0™ is more than just an approach to digital technologies: It's a shift in mindset. Manufacturers need to find new ways to identify problems and implement advanced technology to increase efficiency and effectiveness in meeting compliance requirements.

From connecting workers to introducing more human-centric workflows and driving shifts in company culture, humans are at the core of Pharma 4.0™. As such, companies must do more than automating processes.

To achieve this level of operation, the following should be considered:

- Eliminating paper-based processes and static, document-based evidence
- Eliminating data silos with better communication across the life cycle of drugs
- Improving data collection and sharing practices, allowing for less frequent interactions with and/or more visibility to regulatory bodies
- Shifting to a risk-based and integrated approach for validation
- Implementing a holistic control strategy tied to validation
- Increasing the focus on data for quality assurance and compliance

Pharma 4.0™ envisions a manufacturing paradigm that allows manufacturers to be agile, iterate quickly, connect resources and workers, and produce more quality products with better patient outcomes.

OPTIMIZING A DIGITAL TRANSFORMATION

It is evident with all the concepts introduced so far that digital transformation and adoption of Pharma 4.0™ are more than just a technology initiative. To truly embrace Pharma 4.0™ and realize its productivity gains requires having the right culture, processes, digital technologies, and resources in place across the organization.

The following steps can help deliver the ultimate balance between maximizing productivity, minimizing risk, and achieving compliance throughout your digital transformation journey.

Build a Digital-First Culture

Adopting a digital-first strategy is no longer optional for organizations in the pharmaceutical industry if they want to remain competitive. This means that pharmaceutical manufacturers must include digital as an integral part of their business strategy; they must define a data-driven business strategy. This is why building a digital-first culture is essential for long-term success.

Building this type of culture in today's manufacturing landscape requires the following:

- Innovation is encouraged: Workers feel empowered to identify problems and implement solutions with new digital technologies.
- Data is seen as a valuable asset: Real-time production insights power informed decision-making. Therefore, digital data in all forms, from every process, is necessary.
- Continuous improvement is adopted as a core principle: Iterative feedback loops enable workers to drive real business impact through continuously adapting digital content and instrumentation of all activities.

These cultural components of the strategy must be in place before the transformation begins. They are foundational to align the operational and quality organizations and provide a unifying direction with buy-in from all levels of the organization. This is achieved with a coherent strategy that puts culture first. The next step is to build out an agreed-upon change management program.

This program should highlight the benefits of the change by communicating the specific value of this new technology for different team members. It should define the implementation timeline and process, which includes creating and distributing a schedule with clear next steps. Finally, it should provide any necessary training by ensuring the workers involved are equipped with the guidelines, tools, and resources they need to adapt to this new way of working. They will need to understand how to do their jobs in a digital way. One of these skills is to understand where to find data in this new paradigm to enable action and decision-making.

Leverage a Composable Platform

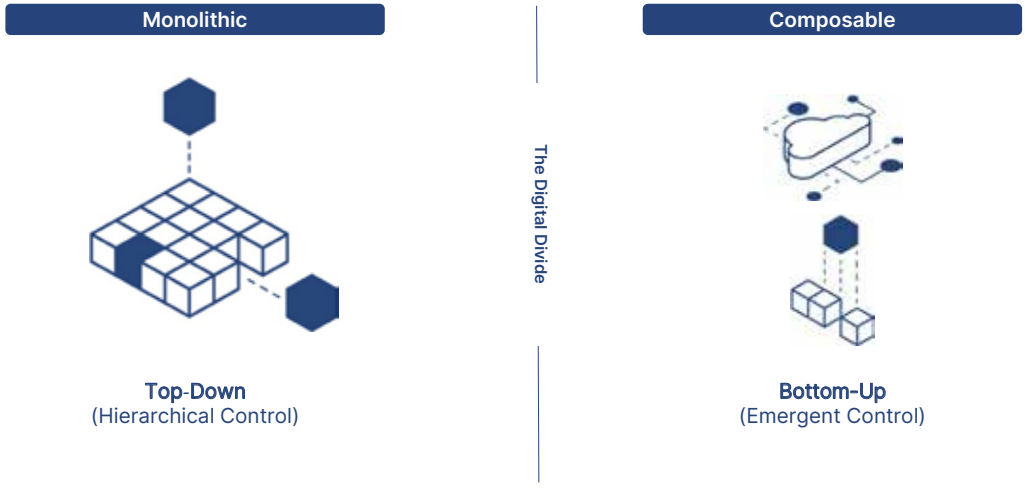
There's a common misconception that going from paper-based workflows to a Pharma 4.0™ facility requires overhauling your systems—and a massive effort in implementing complex, monolithic software systems. However, the digital technologies with democratization and composability allow for more flexible, adaptable systems that can be implemented from the bottom-up [8]. This approach simply means that the solution is built iteratively in small steps to solve one problem at a time. An added benefit is that it slowly can phase out existing systems while effectively digitizing all manual paper processes.

As previously defined, composable solutions enable a short time to initial value and a simple approach to real, continuous improvement. This is done in smaller increments if necessary. The resulting solution has a structure that allows modification and adjustment, big or small. This is advantageous because it reduces the risk; change can be implemented rapidly, and that enables operational agility.

When introducing new technologies into the facility, it is important to determine if they enable Pharma 4.0™ and are true digital technologies or if they are composable. If the technologies require customizations or point to solutions to fill in any functionality gaps, they are not suitable; they force processes to work around generic solutions. Oftentimes this leads to waiting to make changes or improvements and therefore stalling or even halting innovation.

Many composable systems tend to have no-code capabilities, which accelerate the solution development cycle and empower process experts to build solutions for specific use cases. This gives the power to those that understand the problems best. The composability provides a way for the process experts to start with one area of the facility and add use cases over time.

Figure 3: Monolithic (top-down) vs. composable (bottom-up) approach.



Consider tackling use cases for error-proofing work instructions that include compliant e-signatures or creating customizable dashboards to gain real-time operational visibility and enable better decision-making. In other words, prioritize GMP use cases that pose the highest risk or the area with the most opportunity to prove that compliance can be seamless.

Adopt a Bottom-Up Approach

Digital technologies are adopted most effectively in small steps, one app at a time. This bottom-up approach is critical and a core attribute of these technologies. Digital technologies differ in that processes do not have to be adapted to fit the solution. Rather, solutions are built that can adapt, which augments operators and facilitates processes.

Unlike monolithic systems that leverage top-down hierarchical structures to provide solutions that fit within certain constraints, composable architectures allows building solutions in a variety of ways. This drives rapid time to value and exponential productivity increases.

By adopting composable solutions that are built from the bottom-up in an iterative manner, you can digitize manufacturing operations in the most efficient way. This novel approach to designing and deploying solutions makes it easy to:

- Remove the difficulties associated with adhering to complicated standards and systems
- Free engineers to focus on building apps that fit the process and increase the rate of solution development
- Capture granular data about each discrete process and activity
- Easily adapt a solution with minimal impact to the overall system behavior
- Build apps starting with one use case and expand to cover the process, distributing complexity across apps so that they're easier to maintain
- Align with lean continuous improvement principles, without sacrificing sustainable, decentralized innovation
- Set the foundation for continuous validation by digitizing risk controls that can capture data from processes, which is highly aligned with continuous improvement

PROJECT MANAGEMENT BEST PRACTICES

An agile project management style leverages short, iterative development cycles to achieve continuous improvement. When integrating new technologies with existing infrastructures, this methodology will empower an organization to respond more quickly to changes through cross-functional collaboration, rapid iterations, and a flexible, bottom-up approach.

Complementing composability, an agile approach further aids in achieving value and iterating to improve quickly. This is done by engaging the frontline operators who work on the manufacturing floor every day. Incorporating insights from the workers who know the processes best helps more easily determine the type of solution that meets your organization's unique needs.

GOVERNED CITIZEN DEVELOPMENT

Democratization can happen organically as an output of no-code solutions and citizen development. It allows process engineers who have deep knowledge of the process to create digital solutions with quality in mind, or quality by design. This eliminates the need to translate the process and the supporting science to IT people to configure systems.

Recognizing that compliance is necessary, governance features are built into these modern operations platforms. The platform should implement a governance framework that includes granular access management, approval processes, and version control for the digital content. These capabilities are used to assure that the right data and audit trails are captured and the distribution and availability of the content are managed with ease. We recommend using this visibility into the digitized processes and managing the platform with data and governance.

The key component of governance is the enablement function that supports citizen developers and provides them with clear rules, best practices, and guidance. This can ensure quality solutions, which impacts business value and manufacturing productivity.

The enablement function requires a well-defined process and expertise to:

- Build and maintain a library of preapproved and prebuilt common content, templates, and technical solutions. This will guide reuse of common content. Doing so helps standardize key process requirements that ensure consistent quality.
- Create development and deployment best practices for content, including user interfaces (UI), functionality, data capture, and structures.
- Manage the ideation process so that a compliant content life cycle is started with a clear set of requirements. Here, it is critical to have a Validation 4.0 approach with defined user stories and process maps (see the following section for more information).
- Establish an effective review process to assess content for compliance, security, and functionality before deployment. This empowers the citizen developer while ensuring all applications meet regulatory standards.
- Create secure and isolated environments where citizen developers can build and test their applications without impacting live operations. This allows for experimentation and iteration while maintaining data integrity.

EMBRACE VALIDATION 4.0

We've provided the basic structure and points to consider when adopting a Pharma 4.0™ approach, focusing on the technological and organizational aspects required for success. Now we shift toward a focus on a critical operational change required to successfully deploy these approaches into the regulated space: validation.

The concepts around citizen development and composable solutions encourage engagement from the people who know their operations the best. However, these approaches to continuous improvement do not obviate the need for change management. Validation must be managed in a way that is risk-based and integrated with the changes to keep up with the iterative, continuous improvement cycles.

Whether the concern is the technology, processes, or people, we must always demonstrate control. Regulations are in place to assure this, and the root of the requirements is to demonstrate control around ensuring patient safety and product quality. This is especially true in terms of a brownfield implementation or overhauling an existing facility. We know that extensive change is required; workflows, processes, equipment, and systems are already in place.

The Validation 4.0 approach described in the *ISPE Baseline® Guide, Vol. 8, Pharma 4.0™* includes fundamental considerations for pharmaceutical quality systems, quality by design (QbD) [9], and quality risk management (QRM) [10].

To revamp an existing facility, the product and process knowledge from the existing QbD framework can be used to map out the relevant process(es) into process maps that clearly identify data flows. If a robust QbD framework is already in place, process and data maps may already exist. Whether they need to be created or already exist, their value is foundational in understanding the appropriate controls strategy. The data flows provide a contextualized basis to perform risk management and explicitly identify critical parameters.

Once your critical parameters are identified, you will determine appropriate risk controls. For the areas that challenge the desired level of product quality, there will be more robust controls. These will use, where possible, technical controls based on the features available in the composable platforms. This approach provides an effective mechanism to control the solutions' impact on quality. It might include mapping an entire process, defining a smaller unit operation, or homing in on a specific change to the process, facility, equipment, or system and then iterating in a QbD fashion. The iterations can either validate or invalidate that a defined control is successful in achieving the product quality indicators.

This approach to change implementation can yield validation as a de facto output. However, it does require product and process knowledge. It allows the right subject matter experts to be involved early and allows an agile approach so that companies are iterative on the continued increase of knowledge gained by this intentional approach to using QbD and QRM.

DIGITAL TRANSFORMATION IS NOT OPTIONAL

The age of Pharma 4.0™ is here, and those who do not transform their processes accordingly will be left behind. When starting your digital transformation journey, there are a few key concepts to keep in mind. Firstly, don't forget the operational, organizational, and cultural changes that need to come with adapting the Pharma 4.0™ approach. Investment in the people aspect of this change is one of the primary success factors, especially in the case of revamping existing facilities.

Secondly, be ready to embrace composability. Doing so will enable you to start small and continue to grow and improve your efforts over time. Ultimately, this approach leads to a quicker time to value and provides the agility that you need to succeed in today's fast-changing environment. Examples of manufacturers that have adopted this approach show how fast digitalization can be implemented with promising results. Implementation time is vastly reduced to 3–6 months from kick-off to first digital history

(electronic batch record) app validated and in production. In addition, the digital data that is a result is used for operational improvements and not merely compliant batch recording [11].

CONCLUSION

Although the concept of citizen development can sound scary, it is critical. Adopting this methodology will empower organizations to effectively leverage the knowledge of those who know the operations best: the engineers and frontline workers. People are the key to productivity in the digital age. By leveraging the latest technology to provide workforces with the data-driven context they need, when they need it, companies can streamline operations while maintaining compliance.

This augmented lean [12] approach is particularly critical considering the ongoing manufacturing labor shortage [13] and high workforce turnover rate [14]. To attract and retain skilled workers, organizations need to provide an environment in which employees feel empowered to improve their workplace. This will enable them to grow professionally and become more efficient. It will also help maintain compliance and the shipping of quality products in an agile operating environment.

References

1. US Food and Drug Administration. "Using Artificial Intelligence & Machine Learning in the Development of Drug & Biological Products." www.fda.gov/media/167973/download
2. Gartner. "Gartner Says Four Trends Are Shaping the Future of Cloud, Data Center and Edge Infrastructure." 16 May 2023. www.gartner.com/en/newsroom/press-releases/2023-05-16-gartner-says-4-trends-are-shaping-the-future-of-cloud-data-center-and-edge-infrastructure
3. Natis, Y., M. Pezzini, and A. Thomas. "How to Design Enterprise Applications That Are Composable by Default." Gartner. 26 April August 2021. www.gartner.com/en/documents/4000938
4. Kagermann, H., J. Helbig, A. Hellinger, and W. Wahlster. *Securing the Future of German Manufacturing Industry, Recommendations for Implementing the Strategic Initiative INDUSTRIE 4.0, Final Report of the Industrie 4.0 Working Group*. Forschungsunion. 8 April 2013.
5. International Society of Pharmaceutical Engineering. *Baseline Guide, Vol. 8, Pharma 4.0™, 1st ed*. North Bethesda, MD: International Society for Pharmaceutical Engineering, 2023.
6. Ferdinand, P. *The Internet, Democracy and Democratization, 1st ed*. London, England: Democratization, 2000.
7. "Citizen Developer." Gartner Glossary. www.gartner.com/en/information-technology/glossary/citizen-developer
8. Langer, G., and L. Alting. "An Architecture for Agile Shop Floor Control Systems." *The Journal of Manufacturing Systems* 19, no. 3 (2000):267–81. doi:10.1016/S0278-6125(01)80006-6
9. European Medicines Agency. "ICH Guideline Q8 (R2) on Pharmaceutical Development – Scientific Guideline." 22 June 2017. www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use-considerations-ich-guideline-q8-r2-pharmaceutical-development-step-5_en.pdf
10. European Medicines Agency. "ICH Guideline Q9 Quality Risk Management – Scientific Guideline." 26 July 2023. www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use-ich-guideline-q9-r1-quality-risk-management-step-5-revision-1_en.pdf
11. Tulip. "Outset Medical: A Digital Transformation Success Story, How to Build an Agile Frontline in Weeks, Not Years!" tulip.co/webinars/outset-medical-a-digital-transformation-success-story-how-to-build-an-agile-frontline-in-weeks-not-years/
12. Linder, N., and T. A. Undheim. *Augmented Lean*. Hoboken, New Jersey: Wiley, 2022.
13. Wellener, P., V. Reyes, H. Ashton, and C. Moutray. "Creating Pathways for Tomorrow's Workforce Today, Beyond Reskilling in Manufacturing." 4 May 2021. www2.deloitte.com/us/en/insights/industry/manufacturing/manufacturing-industry-diversity.html
14. US Bureau of Labor Statistics. "Economic News Release, Table 16. Annual Average Job Openings Rates by Industry and Region, Not Seasonally Adjusted." 6 March 2024. www.bls.gov/news.release/jolts.t16.htm

About the authors

Michelle Vuolo currently leads Quality at Tulip Interfaces, Inc., a platform developer that allows manufacturers of many industries to build digital content to manage their operations. Before joining Tulip, Michelle spent over 24 years in the biopharmaceutical and medical devices industries in quality control laboratories, engineering technical support, quality assurance management, and computerized systems compliance. Michelle has a strong understanding of the needs of the life sciences industry and is motivated to evolve stagnant ways of meeting compliance requirements, especially as it relates to the 4.0 world. She joined ISPE in 2008.

Gilead Langer, PhD, is an accomplished business leader with over 28 years of experience in digital transformation, manufacturing information technology, engineering services delivery, and technical operations. He has deep domain expertise in digital technologies and manufacturing business systems like IIoT, big data, AI, manufacturing execution systems (MES), quality management systems (QMS), distributed control systems (DCS), and supervisory control and data acquisition (SCADA). He has an accomplished track record of digital transformation to drive high levels of operational performance in the pharmaceutical, biotechnology, and medical device industries. He has also served as a trusted adviser and business consultant in the areas of technology directions, industry strategy, and software implementations. His focus and passion is Pharma 4.0 and digital technologies. He started his career in academia, researching concepts and architectures for agile manufacturing systems using novel concepts that were the archetype for Industry 4.0 and IIoT. He joined ISPE in 2010.

GENE EDITING AND FACILITY

Retrofits for CRISPR and Beyond

By Emily Heffernan,PE, and Stephen Judd, CEng, MICHemE, FIEI

With the approval of the first gene edited therapeutic in 2023, production of gene edited therapies is accelerating, introducing tough decisions for manufacturing development. Gene editing therapy production is complex, often involving multi-modality manufacturing operations in one facility to produce a single therapeutic. This article considers whether retrofitting an aging monoclonal antibody (mAb) facility for the manufacture of a gene editing therapy could be a solution.

BACKGROUND

Since the discovery of the CRISPR-Cas system's ability to edit genes in 2012, interest in gene editing as a therapeutic has accelerated. This is due to its potential to provide curative therapies for some of the most severe and often fatal genetic diseases. Gene editing is the process of adding, deleting, altering, or replacing DNA sequences at specific locations. In 2023, Vertex Pharmaceuticals and CRISPR Therapeutics obtained UK approval of the first gene edited product, an ex vivo gene edited stem cell therapy product for the treatment of sickle cell disease and transfusion-dependent beta thalassemia.

Figure 1 provides some data on the range of gene edited products in various phases of research and clinical trials as well as intended applications for prospective therapeutics.

Figure 1: Clinical trials data for gene edited products.

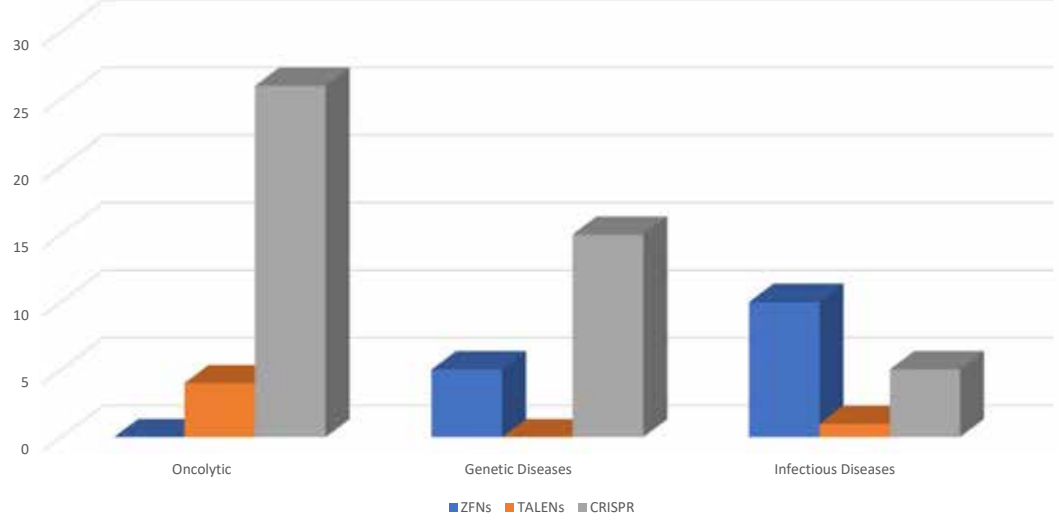


Figure 2: Gene editing components.

Table 1: Comparison of different gene editing technology.

Gene Editing Technology	Zinc Finger Nucleases (ZFNs)	Transcription-Like Effector Nucleases (TALENs)	Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR-Cas)	Base Editing
Discovery	1985	2011	2012	2016
Binding Technology	Protein-DNA	Protein-DNA	RNA-DNA	RNA-DNA
Endonuclease Technology	FokI Nuclease	FokI Nuclease	Cas9 Nuclease	Cas9 Nickase
Double Stranded Break Induced	Yes	Yes	Yes	No
Editing Capabilities	Knockin Knockout	Knockin Knockout	Knockin Knockout	Base Swapping
Companies Utilizing Technology	Sangamo	Cellectis	Caribou	Beam Therapeutics Verve Therapeutics

Gene Editing Therapy Manufacturing

Due to a complex manufacturing process, gene editing therapy often involves multi-modality manufacturing operations in one facility. With development of any new therapeutic, there is also uncertainty as to whether a therapy will make it through clinical trials to a commercialized product. Modern trends also focus on the most sustainable approaches to implementing new manufacturing capacity. Considering these factors, retrofitting old assets may be a better solution than building new facilities to develop the required manufacturing capacity for a new gene editing therapy.

Gene Editing Primer

At its core, gene editing technology is composed of two to three different components, each of which is functionally crucial to deliver a gene editing therapy to patients. The first component is the guide molecule, which is used to target a precise location within the patient's DNA where edits need to occur. The guide molecule can be either a protein or ribonucleic acid (RNA) sequence that is complementary to the corresponding DNA sequence of the patient. Figure 2 illustrates three different components that are used with gene editing technologies.

The second component is the DNA-cutting enzyme, or endonuclease. This molecule acts as the "molecular scissors" to cut the DNA at a precise location, allowing for edits to occur [1]. Once the DNA is cut, there are two predominant mechanisms for repair of the double-strand break: non-homologous end joining (NHEJ) and homology directed repair (HDR). NHEJ is used to make genes nonfunctional, also referred to as a gene knockout.

HDR provides new genetic material to correct a defective gene sequence and is referred to as a gene knockin. This mechanism requires a third component to be provided to the patient, a donor DNA template, for effective gene editing.

For each of these three components, there are several formats that can be used for manufacturing production and, in turn, delivery to patients. These include ribonucleoprotein (RNP) complex; viral delivery, commonly through use of a viral vector such as adeno-associated virus (AAV); and non-viral delivery, commonly through lipid nanoparticle (LNP) mediated delivery of guide RNA (gRNA) and messenger RNA (mRNA). These modality options will be discussed further in the upcoming sections.

GENE EDITING TECHNOLOGY

Although CRISPR is the most referenced gene editing technology, it is not the only option used in pre-clinical or clinical studies. Several different technologies are available for gene editing, each with its own bespoke design of the guide molecule and nuclease. Table 1 summarizes some of the more pertinent details of each type of technology.

Zinc Finger Nucleases (ZFNs)

ZFNs were the earliest gene editing technology with applications for human genome editing. With ZFNs, the guide molecule is composed of zinc finger proteins. Each zinc finger protein recognizes a three-nucleotide sequence. A typical ZFN will be composed of between three to six zinc fingers, resulting in complementary recognition of DNA in the range of 9 to 18 nucleotides total. The zinc fingers are fused to a Fok1 endonuclease. The Fok1 endonuclease must dimerize to cut DNA, which requires a pair of ZFNs to be used for editing [2]. This has benefits in improved specificity but also increases the cost and complexity of manufacturing. Clinical trials are underway using ZFNs for chronic diseases, including HIV-1 [3].

Transcription-Like Effector Nucleases (TALENs)

TALENs are similar to ZFNs. TALENs are specific DNA binding proteins that, like ZFNs, are fused to the Fok1 endonuclease. Unlike ZFNs, however, TALENs bind to single nucleotides rather than triplets, resulting in lower costs and simpler engineering. TALENs have shown preliminary success in clinical trials for oncolytic applications, with the TALENs used to knock out genes in allogeneic T cell therapies that could lead to graft-versus-host disease in patients [4].

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR-Cas)

The discovery of CRISPR technology, originally a bacterial defense system, in 2012 has accelerated the interest in and led to exponential growth of the gene editing industry. The primary difference between CRISPR and prior technologies, such as TALENs and ZFNs, is that CRISPR relies on RNA–DNA interactions rather than protein–DNA interactions. This leads to a simpler-to-engineer, more cost-effective, and highly precise gene editing tool. Overwhelmingly, therapies in the clinic utilize single nucleotide base variants (see Figure 1) [5]. CRISPR has applications in the development of off-the-shelf T cell therapies and monogenic disorders, such as sickle cell disease.

Base Editing and Future Technologies

The previously discussed technologies all edit genes by inducing a double-stranded break in the patient's DNA. Double-stranded breaks are associated with a higher risk of off-target edits, including random additions or deletions of DNA. In turn, newer technologies, including base editing, have been developed to address these safety issues.

Base editing also uses the CRISPR guide system to target a precise location for edits. However, instead of using a Cas nuclease, which induces a double-stranded break, a Cas nickase is used, which induces only a single-stranded break. Unlike the technologies previously discussed, base editing cannot perform multiple nucleotide knockins or knockouts. However, it can correct single nucleotide base variants [6]. Although this may seem limiting, approximately 60% of all human genetic diseases are linked to a single-point mutation, making it an effective weapon in the overall arsenal of gene editing technologies [7].

Newer technologies continue to be developed that also avoid double-stranded DNA breaks but can edit longer stretches of DNA. They include prime editing and programmable addition via site-specific targeting elements.

GENE EDITING PROCESS DISCUSSION

The manufacture and delivery of a gene editing therapeutic can be accomplished via many different approaches. In practice, there are primarily three methodologies used to deliver gene editing therapies: ribonucleoprotein complex (RNP), non-viral delivery, and viral delivery.

RNPs deliver the guide RNA and nuclease protein in a fully assembled, ready-to-edit format. They overcome a significant limitation of viral and non-viral delivery in that there is no delay between administration and onset of gene editing. RNPs are limited in other ways, however. The most critical limitation is that they must be delivered via electroporation. This limits their use to only ex vivo therapeutics. This option will not be considered further here because there are significant differences to the more traditional biopharmaceutical processes.

The selection of a delivery platform, which is typically made very early in the drug development process, leads to very different facility requirements for clinical and commercial manufacturing. This section discusses the non-viral and viral delivery approaches and looks in depth at the specific manufacturing requirements associated with each. The information outlined in this section will then be compared to a mAb manufacturing process. This will help determine which approach would be most suitable for the conversion of a mAb facility.

Non-Viral Delivery

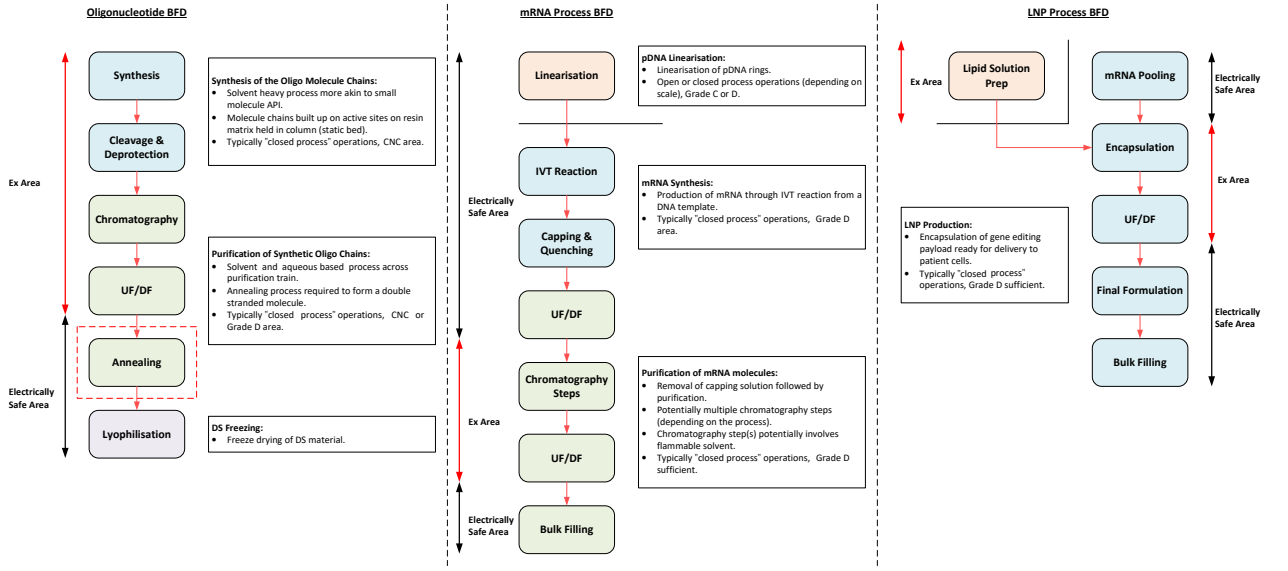
Non-viral delivery is typically accomplished using two modalities: oligonucleotide synthesis and mRNA synthesis. Oligonucleotide synthesis is used to manufacture the short gRNA molecule and in vitro transcription (IVT) is used to synthesize the long mRNA molecule, which encodes for the endonuclease protein.

Both mRNA and guide RNA may be combined within the same LNP complex for patient delivery. Although mRNA, oligonucleotides (oligos), and LNP are safe and effective options, there are limitations with their use for gene editing. For one, the mRNA molecule must be translated to protein within the patient prior to gene editing. This results in a delay in editing that could affect efficacy as the gRNA molecule may begin to degrade.

This section will focus on oligo, mRNA, and LNP manufacturing processes (see Figure 3 for a block flow diagram [BFD] representation of each of these processes) and segregation requirements associated with the different manufacturing operations.

The mRNA manufacturing process will require a DNA template for the IVT reaction, which can be purchased or manufactured in-house through an *E. coli* fermentation process. Purchasing the DNA template material will remove a distinct manufacturing process from the

Figure 3: Process BFDs: oligo, mRNA, and LNP processes.



in-house requirements but can add cost and business continuity risks, as market supply chains for this ingredient are currently very stretched.

Oligonucleotide synthesis process

The oligonucleotide synthesis process involves the building of the oligo molecule chains on a solid matrix, which is packed into a column similar to that of a chromatography column. Each molecule chain is built up through a series of coupling reactions. In these, each of the amidites (the building blocks used in chemical synthesis of oligos), solvents, and reagents are transferred to the column and flushed through the static bed via the synthesizer skid. Once synthesis of the RNA molecule chain is complete, the cleavage and deprotection steps are carried out. The bed is immersed in an ammonia-based solution and heating is applied to remove the protecting groups and cleave the oligo molecule chains from the resin bed.

The product, now in solution, is collected in a pool tank and ready for purification. The synthesis manufacturing process needs to be carried out in a fully closed manner due to the hazardous nature of the solvents involved. There is also a negligible risk of contamination of the chemical-based process, so these operations are typically carried out in a controlled-non-classified (CNC) area.

The downstream process steps typically involve chromatography (ion exchange or reverse phase) and ultrafiltration/diafiltration (UF/DF) (the order of operation may change depending on the process). The chromatography step purifies the product, and the eluate is collected in fractions. The composition of each fraction is then tested, and the appropriate fractions pooled ready for transfer to the next process step.

The UF/DF step then concentrates the product to the appropriate drug substance (DS) concentration and the carrier solvent is removed and replaced with the formulation buffer solution. The purification process is typically carried out in a ballroom manufacturing suite, with all process steps being completed in a closed manner. Flammable solvents will potentially be required for the initial part of the purification process with the final formulation, following the UF/DF step typically being an aqueous solution. The purification suite is commonly a Grade D area.

mRNA manufacturing process

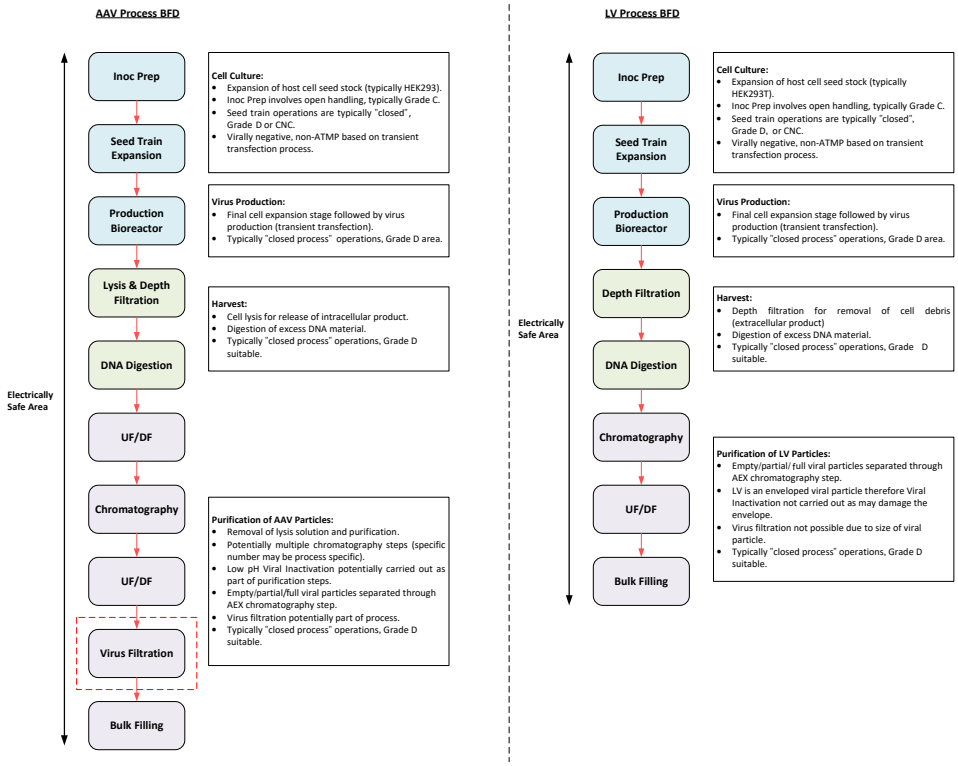
The mRNA manufacturing process would again be split into synthesis and purification stages but is a more aqueous-based process with some flammable solvent usage. If the DNA template for the mRNA synthesis is purchased, this will typically need to be linearized prior to the IVT process. The IVT process is typically carried out in a single-use mixer (SUM) or a single-use bioreactor (SUB). It is terminated through quenching and capping steps following transfer to a larger SUM downstream of the IVT reactor.

The crude mRNA product then undergoes a series of chromatography and UF/DF steps to remove impurities and produce the final DS formulation. There are a number of variations associated with the mRNA purification train, which include the use of flammable solvents for certain chromatography steps. Processes for mRNA purification may not involve flammable solvents, but certain chromatography steps may involve the use of concentrated ethyl alcohol (EtOH) or 70% acetonitrile (ACN). Single-use equipment is commonly used for the process steps associated with aqueous solutions.

Stainless steel (SS) equipment is required for any steps that use flammable solvents due to the electrically nonconductive nature of single-use plastics. The chromatography steps that involve the use of flammable solvents can potentially be installed in a defined hazardous area within a larger ballroom suite.

The synthesis and purification operations can either be carried out in separate manufacturing suites or a common ballroom suite based on closed-process operations. The linearization process prior to the IVT step should potentially be in a dedicated manufacturing

Figure 4: Process BFDs: AAV and LV viral vector processes.



suite for flexibility of operation. This should operate on a campaign basis and the linear templates should be frozen, staged, and ready for use.

LNP process

The oligo and mRNA components then need to be encapsulated in LNPs. The lipid solution is made up by adding the lipid components to a volume of concentrated EtOH and dissolving at a temperature of 30°C–40°C. The encapsulated product is then produced by feeding the lipid solution and the DS material in parallel feed streams into the encapsulation system (microfluidic platform [8] or impingement jet mixer [9]). The process outlet is then diluted with an aqueous buffer solution on exiting the encapsulation system and fed directly to a UF/DF system for removal of the EtOH.

This operation is time sensitive due to product stability considerations. Any final formulation adjustments will then be made, and the product will be filtered into bags and frozen ready for transfer to the fill/finish area or facility. The lipid solution prep would typically be carried out in a dedicated area adjacent to the main process suite. The main process suite should then be a ballroom with the encapsulation system (and potentially the downstream UF/DF system) being installed in a defined hazardous area within the larger ballroom suite.

The non-viral synthetic approach would require three defined manufacturing areas for flexibility of operation. A dedicated oligo manufacturing area, mRNA manufacturing area, and LNP processing area will allow parallel manufacturing of each of these processes. The main support functions associated with these operations (solvent storage and distribution, buffer prep, and process utilities), can potentially be shared, as long as risk mitigation against cross contamination is ensured through the design. The appropriate risk mitigation and quality risk management (QRM) strategies should be assessed through facilitated risk assessments.

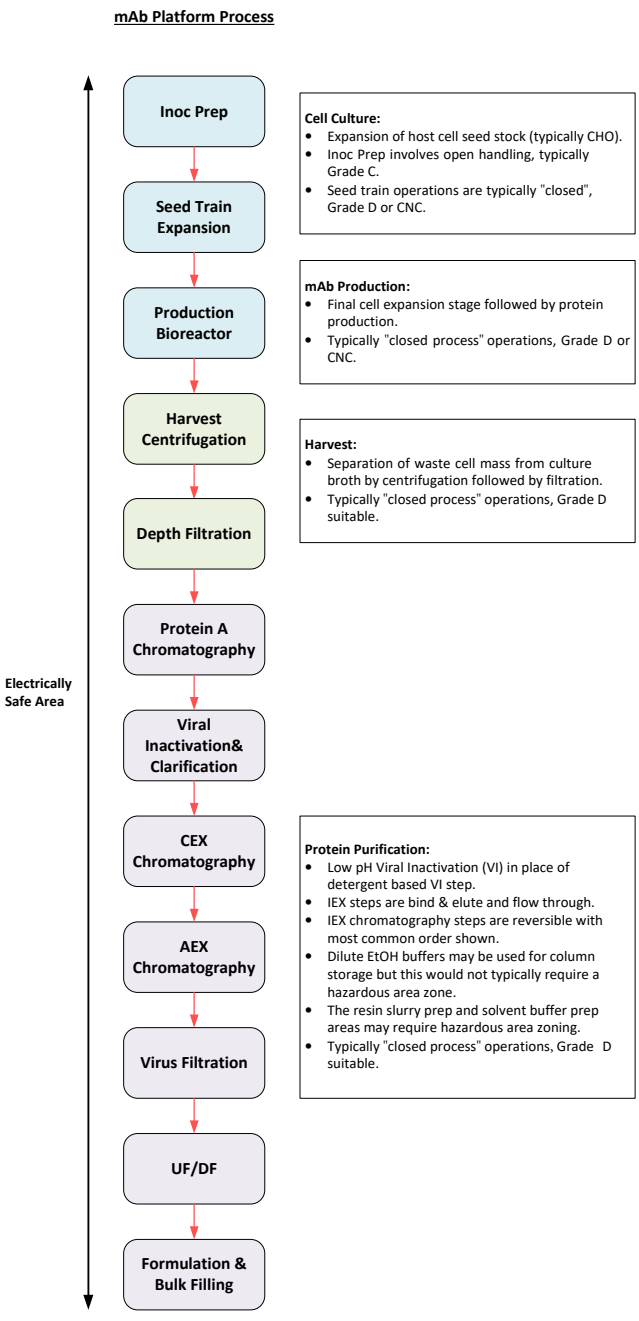
Viral Delivery

Viral delivery may be done through a viral vector (VV), such as AAV or lentivirus (LV). VVs are commonly used in gene therapy or cell therapy applications and have applications for both in vivo and ex vivo gene editing. Similar to gene therapy, a VV is manufactured to code for a gene of interest. In this case, the gene of interest delivers the instructions to the patient to manufacture both the gRNA and the endonuclease protein. Although the use of VVs has had success in commercial cell and gene therapies (C&GTs), cost, safety, manufacturing scalability, and the ability to redose patients are valid concerns.

This section will focus on VV manufacturing processes. With respect to gene editing, AAV is typically associated with in vivo processes, and LV is mainly associated with ex vivo processes, with some in vivo candidates in development. Figure 4 shows a BFD representation of these types of processes. Different types of VV processes have different typical capacities and variances in the specific process trains, but the core process stages are similar.

The process starts with inoculum prep activities, which encompass a number of cell expansion steps carried out in flasks

Figure 5: Process BFD: mAb platform process.



installed in a shaker incubator. Preparation of each flask involves open operations that are carried out in a Type 2 biosafety cabinet (BSC), typically installed in a Grade C environment. This is followed by the seed train operations, which are carried out in a combination of wave bioreactors and stirred tank (STR) bioreactors. Single-use technology (SUT) is typically utilized for these steps in VV processes because SUT is flexible and is a risk mitigation measure against cross contamination.

The upstream process (USP) then culminates with the production bioreactor step when the transfection process is carried out and the viral particles are produced. SUT facilitates fully closed operation and allows the manufacturing area to be Grade D or potentially CNC. The transfection solution preparation needs to be carried out near the SUB and will potentially involve an element of open processing. If this operation is carried out in a Type 2 BSC, then this would drive a Grade D environment as opposed to CNC.

The specific clarification steps vary between AAV and LV. AAV is typically an intracellular process, requiring a cell lysis step, whereas LV is typically an extracellular process. The process steps for these two types of processes are carried out in similar equipment. The downstream processing (DSP) steps then encompass a series of chromatography, filtration, and UF/DF steps prior to filling the bulk DS into bags.

Another potential difference between the AAV and LV processes is that an AAV process may include a virus filtration step for mitigation against adventitious agent contamination. This step is not possible for an LV process due to the diameter of the viral particle compared to the nominal pore size of a virus filter. The clarification and DSP operations typically utilize SUT. Therefore, physical segregation between the pre- and post-viral areas for an AAV process is not specifically required based on closed processing. If the facility is designed for flexible and multi-modal operation, having the full DSP operations in a single ballroom suite is a reasonable approach for consistency between the manufacturing processes.

If the therapy is an in vivo process, then the bulk DS is frozen and staged ready for transfer to the fill/ finish area or facility. VV processes involve small-scale, single isolator filling operations, which are commonly carried out in a separate area of the same facility as the DS manufacturing operations. If the therapy is associated with an ex vivo process, then the drug product (DP) is produced through a small-scale cell therapy manufacturing process prior to a manual or semi-automated filling process. The cell therapy process may be carried out in a separate area of the same site as the DS manufacturing operations, or the frozen DS may be shipped to a different site.

GENE EDITING RETROFITS: FROM MAB TO CRISPR

As discussed in the prior section, facilities for the manufacture of gene editing therapeutics can take on many formats and modalities depending on the technology used. This section will compare the manufacturing processes associated with the non-viral and viral gene editing delivery mechanisms, with that of a typical mAb manufacturing process. This will help determine which of these approaches would be most suitable for retrofitting a facility previously utilized for manufacturing of mAb products.

Manufacturing of mAb products is now quite a mature industry sector and a platform manufacturing approach is very common across the industry. Figure 5 shows a BFD representation of a typical platform approach.

Manufacturing VV products has a high level of synergy with the mAb manufacturing process. Additionally, there is commonality in the support functions between these modalities with both requiring media for USP operations, buffer for DSP operations, and similar process utilities. Manufacturing a gene editing therapy that uses an in vivo delivery platform would therefore be a good fit for a facility conversion. Ex vivo administration of gene editing therapeutics requires a cell therapy manufacturing component. This involves an additional distinct manufacturing process that is significantly different to a mAb process.

The non-viral synthetic approach discussed in the previous section would be more challenging to retrofit due to the differences in design requirements for the manufacturing areas. The manufacture of oligos potentially requires extended ceiling areas to facilitate installation of head tanks and uses large volumes of flammable solvents. Buildings associated with the storage and use of flammable solvents need to align with the requirements of the International Building Code Group H buildings. This is not necessarily required for a mAb manufacturing facility, so conversion to this type of facility may have implications for the general building design that could be very costly.

The manufacturing suites are also electrically classified with all fixtures and fittings within the suite required to be spark-proof and intrinsically safe for operation around flammables. In the US, the National Fire Protection Association 70 [10] or the National Electrical Code define these requirements, whereas in the EU, ATEX directives [11] and the International Electrotechnical Commission standards [12] must be followed.

Although many formats could be accommodated given sufficient time and funding, the modality that can most readily be retrofitted into a mAb facility, for moderate capital and time investment, is VV manufacturing. The facility could then be used to produce gene editing therapies for an in vivo viral delivery platform and support ex vivo cell therapies produced elsewhere.

VV AND MAB SYNERGIES AND DIFFERENCES

Having identified the viral delivery approach as the most suitable when looking at the conversion of a mAb facility, this section will now investigate the commonalities and key differences between mAb and VV manufacturing operations. Every facility has its own nuances and therefore every facility conversion will be different; this section will focus on the main considerations when comparing the different operations.

Equipment and Scale

Often, mAb and VV facilities have many similarities in terms of equipment, facility design, and approach. Converting from one process to the other is feasible with a few considerations in mind. Both are divided into USP, harvest, and DSP operations. Facility size and capacity can vary greatly, with the throughput determined by the quantity and size of production bioreactors. For mAb, this can range from 2,000-liters (L) SUBs to multiple 20,000-L stainless steel bioreactors. The production SUBs associated with VV facilities typically range from 200 L to 500 L, with the largest currently in operation being 2,000 L.

VV facilities heavily favor single-use equipment for flexibility to accommodate shifting throughput targets and risk mitigation against cross contamination, which is paramount when working with vectors. Converting an existing asset will potentially involve an older facility, which may comprise more SS equipment with some degree of a hybrid approach for certain operations.

The process support and process utility systems associated with the original asset will be similar to those required for the new manufacturing operations and therefore may be able to serve the new facility with some modification.

Facility Design

With mAb facilities, the industry has both facilities with distinct USP and DSP suites, as well as a more progressive ballroom approach, where all unit operations occur within the same room. Manufacturing of different products in parallel in the same area is permitted for mAbs from a regulatory standpoint, provided a suitable QRM strategy is in place. For conversion of older assets, the facility design will potentially have a more conservative approach with a greater degree of physical segregation. For example, the DSP train may be split into three separate suites: viral inactivation, pre-virus filtration, and post-virus filtration.

Segregation points in the older asset could be beneficial for multi-product manufacturing of VV products. The difference in scale between the mAb and VV DSP operations could potentially allow these suites to be used for separate DSP trains which would facilitate parallel manufacturing of different advanced therapy medicinal products (ATMPs).

VV facilities tend to have segregation of the USP and DSP operations or segregation at the V- / V+ boundary (between the N-1 and N stage SUBs). Segregation at the V- / V+ boundary provides flexibility of operation because this is the point where the product is considered an ATMP (based on a transient transfection approach)—and the point where parallel manufacturing of different products in the same area, without adequate containment measures, is not permitted [13]. Additionally, VV facilities often incorporate the DP manufacturing in the same facility as the DS manufacturing. In contrast, the DS and DP operations associated with a mAb process are commonly carried out at different sites .

Biosafety Level

Most mAb facilities are either good large-scale practice or biosafety level 1 (BSL-1), whereas most facilities for VV manufacturing are either biosafety level 2 (BSL-2) or biosafety level 2 enhanced (BSL-2+). The manufacture of BSL-2 therapeutics has specific requirements for the handling of both product and waste materials to ensure safety of personnel and environment. Retrofits that may be required include the addition of the following:

- A liquid biowaste inactivation skid to serve all DSP operations
- A deactivation autoclave for solid waste (mainly single-use consumables)

- Airlocks with appropriate pressurization schemes for containment of any aerosolized VV particulates
- Handwashing sinks
- Room sterilization using vaporized hydrogen peroxide (VHP), depending on the production requirements and risk tolerance between campaign changeovers

cGMP Flows

The movement of personnel, materials, and waste through a facility is one of the key attributes that is difficult to retrofit later. Most mAb facilities employ a bidirectional approach to movement of personnel and materials, as the products and processes have low biosafety consequences. Most processes are functionally closed, which reduces the risk of contamination.

In contrast, the V+ areas of VV facilities tend to employ unidirectional flows of personnel and materials. This approach facilitates isolation of each applicable manufacturing suite from the surrounding area by having a pressure regime where the entrance airlock is a pressure bubble and the exit airlock is a pressure sink. This is especially critical for multi-product VV facilities because cross contamination between products is a key concern.

This is the typical approach, but not a stipulated regulatory requirement. The EU regulatory guidance that relates to manufacture of mAb products is the EudraLex, Volume 4, Annex 2 [14]. This indicates that the layout of the different manufacturing areas needs to appropriately mitigate against the risk of cross contamination between process stages or products using QRM principles [14]. The EU regulatory guidance that relates to manufacture of VV products is the EudraLex, Volume 4, Part IV. This indicates that the manufacturer should take a risk-based approach to ensure the quality of the ATMP products that they produce [13].

Manufacture of mAb products is a mature industry with established QRM principles. The industry has evolved over time, enabling more robust knowledge-based outcomes to risk management. VV manufacturing is still a relatively new commercial landscape, with knowledge and processes rapidly evolving. Consequently, this is reflected in the implementation of QRM processes and the acknowledgement by regulatory authorities that "a certain level of flexibility" [13] is appropriate based on the outcome of the QRM process.

CONCLUSION

With the approval of the first gene edited therapeutic in 2023, the field of gene editing shows promise. Additional commercially approved products are likely in the future. Gene editing therapies have the potential to provide long lasting, if not permanent, cures for several devastating genetic diseases and applications in oncolytic therapies.

With a greater focus now being placed on sustainability when it comes to development of new facilities, there is likely to be a greater emphasis on repurposing of redundant or low-occupancy assets instead of building new facilities. The most applicable approach for conversion of a mAb facility into a gene editing manufacturing facility is the viral delivery mechanism for an in vivo therapy (or VV component of an ex vivo therapy). Conversion of an existing asset also has the potential to increase speed to market compared to building a new facility, provided that the modifications are not too extensive.

References

1. Lee, K., V. A. Mackley, A. Rao, A. T. Chong, M. A. Dewitt, J. E. Corn, et al. "Synthetically Modified Guide RNA and Donor DNA Are a Versatile Platform for CRISPR-Cas9 Engineering." *eLife* (2017). doi:10.7554/eLife.25312
2. Wei, J., and Y. Li. "CRISPR-Based Gene Editing Technology and Its Application in Microbial Engineering." *Engineering Microbiology* 3, no. 4 (2023). doi:10.1016/j.engmic.2023.100101
3. Reardon, S. "Gene-Editing Method Tackles HIV in First Clinical Test." *Nature* (2014). doi:10.1038/nature.2014.14813
4. Becker, S., and J. Boch. "TALE and TALEN Genome Editing Technologies." *Gene and Genome Editing* 2 (2021). doi:10.1016/j.ggedit.2021.100007
5. Kozovska, Z., S. Rajcaniova, P. Munteanu, S. Dzacovska, and L. Demkova. "CRISPR: History and Perspectives to the Future." *Biomedicine & Pharmacotherapy* 141 (2021). doi.org/10.1016/j.biopha.2021.111917
6. Porto, E. M., and A. C. Komor. "In the Business of Base Editors: Evolution from Bench to Bedside." *PLOS Biology* 21, no. 4 (2023). doi:10.1371/journal.pbio.3002071
7. Based Editing. "Understanding the Human Genome." Accessed 29 January 2024. beamtx.com/science/base-editing/
8. NanoAssemblr Platform. "A Disruptive Technology Enabling Transformative Medicine." Accessed 26 February 2024. www.precisionnanosystems.com/platform-technologies/product-comparison
9. Knauer. "Impingement Jets Mixing Skids for High-Flow Production of Nanoparticles (LNP, Microemulsions, etc.)." Accessed 26 February 2024. www.knauer.net/en/Systems-Solutions/LNP_lipid_nanoparticles/impingement-jets-mixing-skids-for-high-flow-production-of-nanoparticles
10. The National Fire Protection Association. *NPFA 70, 2023 National Electrical Code*. 8 December 2021. www.nfpa.org/codes-and-standards/nfpa-70-standard-development/70
11. European Committee for Standardization. "ATEX Directive 2014/34/EU." 26 February 2014. https://single-market-economy.ec.europa.eu/sectors/mechanical-engineering/equipment-potentially-explosive-atmospheres-atex_en
12. International Electrotechnical Commission System for Certification to Standards Relating to Equipment for Use in Explosive Atmospheres (IECEx System). Accessed 08 May 2024. www.iecex.com/publications/standards/
13. European Commission. "EudraLex Volume 4: Good Manufacturing Practice. Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products." 22 November 2017. health.ec.europa.eu/document/download/ad33d9dd-03f0-4bef-af53-21308ce2187d_en?filename=2017_11_22_guidelines_gmp_for_atmps.pdf
14. European Commission. "EudraLex Volume 4: EU Guidelines for GMPs for Medicinal Products for Human and Veterinary Use. Annex 2: Manufacture of Biological Active Substances and Medicinal Products for Human Use." 13 November 2007. health.ec.europa.eu/document/download/380fdf24-8a1e-4f65-809b-e08d990d5f9e_en?filename=2018_annex2_en.pdf

About the authors

Emily Heffernan, PE, is US Director of New Process Technologies at Arcadis and a process subject matter expert, specializing in biological process and facility design. She has over 20 years of experience and her expertise spans across multiple therapeutic areas, including monoclonal antibodies, vaccines, C&GTs, and RNA therapeutics. In her current role, Emily works with biotechnology companies to bring new and emerging life science technologies to market. She often works on projects that require creative solutions to scale up from pre-clinical development to commercial production. Emily is an accomplished speaker and author, and she frequently presents at industry-leading events across the US and Europe, including at conferences for ISPE, PDA, and INTERPHEX. She holds degrees in both engineering and science, bringing a unique perspective to the table. She joined ISPE in 2021.

Stephen Judd, CEng, MICHemE, FIEI is a Chartered Chemical Engineer and Fellow of Engineers, Ireland. He is an experienced Technical Manager and Principal Process Engineer with 18 years of experience in process engineering and facility design. He has an excellent mix of office and field design experience across a wide range of international clients with significant experience in process technology selection and facility design. He has experience across the full project life cycle from feasibility study to commissioning and qualification and currently focuses on the early project phases developing the facility design and manufacturing philosophies. Stephen has authored or co-authored a number of technical papers, including a paper on multi-modal facility design published in *Pharmaceutical Engineering*® (winner of the 2022 Roger F. Sherwood Article of the Year Award). He joined ISPE in 2016.

AUTOMATION SUPPORTS ESG GOALS for Pharma Facility Conversion

By John Glenski, CPM, Will Knapp, and Marianna Moores, WELL AP, LEED AP, ActiveScore AP

Implementing advanced automation technologies is a strategic move that can amplify the positive outcomes of environmental, social, and governance (ESG) initiatives. By leveraging ESG initiatives, pharmaceutical companies can enhance their competitive edge and contribute positively to global sustainability efforts.

As pharmaceutical manufacturers transform their facilities to meet new operational demands and comply with evolving regulatory standards, a compelling opportunity emerges. The integration of cutting-edge digitalization technologies during facility conversions can serve as a catalyst for profound ESG advancement. It offers enhanced energy efficiency, waste reduction, and improved social governance. This approach can increase a manufacturer's efficiency and sustainability commitments at a time when operations and ESG stewardship are increasingly linked.

ESG IN PHARMA FACILITY OPERATIONS

There is often a disconnect between the ESG goals set at the organizational level and determining how these goals will impact the operations or decision-making processes within a facility. Corporate sustainability policies in the pharmaceutical industry are driven by the evolving global regulatory landscape [1] as well as internal and external stakeholders [2]. Although this provides a strong path for goal setting, alignment of these goals with day-to-day operations often leaves gaps.

At the facility level, the material key performance indicators (KPIs) mainly align with the "E" of ESG; the primary focus is the environmental impact of the facility, with less focus on the social and governance drivers of the company. The question is how to identify and leverage the opportunities on-site to make progress toward corporate ESG goals in carbon, energy, water, waste, and beyond?

Facility operations and ESG strategies have a shared goal of reducing operational risk and operational cost, which can both be achieved without negatively impacting facility operations. For

Figure 1: Results of Deloitte survey [2].

ESTABLISHED A CROSS-FUNCTIONAL ESG COUNCIL OR WORKING GROUP	LIFE SCIENCES AND HEALTH CARE n=100
Yes, this is already established	59%
Yes, we are in the process of establishing one	39%
No, but we are making plans to	1%
No, and we have no plans to	1%
Do not currently have (net)	41%

Source: Deloitte

Figure 2: Drivers of sustainable pharmaceutical trends.

example, heating, ventilation, and air conditioning (HVAC) currently account for approximately 65% of plant energy expenditures [3]. Increasing HVAC efficiency can decrease operational cost and risk while also improving operational efficiency.

ESG goals are guided by data—at a minimum requiring utility data collection. The more granular and/or real time the data collection is, the more actionable the data becomes. As granularity increases, monthly or annual reporting moves to real-time identification of energy load as well as any anomalies or deficiencies in usage. This empowers the facilities team to better manage plant equipment throughout its life cycle.

Automation in data collection and equipment monitoring enables trend tracking in real time and, through this, the ability to adapt to environmental changes. This can be facilitated with the use of a digital twin, which acts as a performance twin that mirrors plant equipment operations. Digital twins can also provide feedback on performance that can be used to inform planning at the facility and portfolio levels, including operations budgeting, capital spend, etc.

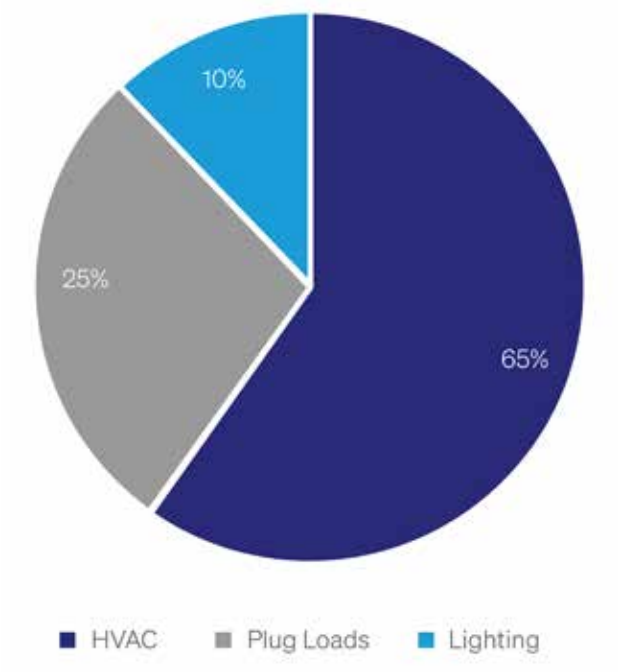
ENERGY CONSUMPTION IN PHARMACEUTICAL FACILITIES

Having a clear understanding of a facility's energy consumption is a critical first step in becoming more efficient and sustainable. Companies without an understanding of their energy consumption rates will struggle to define their financial and sustainability targets.

The pharmaceutical industry consumes approximately US $1 billion (about $3 per person in the US) worth of energy each year [4]. Recent estimates have shown that approximately 65% of the energy consumed in pharmaceutical facilities is used by environmental control systems such as HVAC systems, chillers, and cooling systems. Additionally, another 25% comes from plug loads and processes (tunnels, washers, incubators, or sterilizers), with 10% of energy being consumed with lighting the facilities [5].

Historically, broad designs and systems are no longer viable

Figure 3: Pharmaceutical facility energy use [5].



options for facility designs, as they are key factors that increase pharmaceutical facility energy consumption. A low-energy-use facility instead requires improved facility, system, process, and equipment designs, and initiatives such as eliminating steam use, open loop systems, and heat loss.

Understanding new technology and equipment options for the initiatives is also required to develop a facility ESG conversion plan. To understand facility energy consumption and efficiency, the facility owner will need to assess the facility's current

Implementing digitalization through Pharma 4.0™ will decrease energy consumption and waste by creating a facility that is automated, predictable, and operates in an efficient and sustainable manner.

digitalization level and develop a digital plant-maturity model. New technologies include:

- Improved utility metering and reporting
- Facility digitalization and monitoring systems for peak performance
- Predictive maintenance systems to monitor and improve equipment and systems

Pharma 4.0™ refers to the adoption of the Industry 4.0 framework within the pharmaceutical manufacturing sector. It emphasizes the integration of advanced technologies such as the Industrial Internet of Things (IIoT), artificial intelligence (AI), big data analytics, and cloud computing into pharmaceutical production processes. Implementing digitalization through Pharma 4.0™ will decrease energy consumption and waste by creating a facility that is automated, predictable, and operates in an efficient and sustainable manner.

FRAMING ROI IN AUTOMATION AND DIGITALIZATION

Automation in pharmaceutical manufacturing facilities is a rapidly evolving field, subject to nondisclosure agreements on facility designs. It also presents a challenge to pinpointing return on investment (ROI) with traditional, lagging metrics. This section delves into the pivotal indicators that define the current ROI landscape and offers suggestions for evaluating success in automation and digitalization strategies.

Efficiency and Innovation

Automation technologies such as robotics, smart workflows, advanced analytics, data visualization, natural language processing, and cognitive agents are driving efficiency and fostering innovation [6]. The major pharma manufacturers are already deeply invested in digitalization, leveraging machine learning (ML) to accelerate time frames for compound discovery, precision medicine, and optimization [7]. Other innovations in pharma digitalization include measuring energy usage and leveraging data to offset peak power usage [8].

Applications

Research estimates that with every 2.2 pounds (lbs.) of drug manufactured, a staggering 220.46 lbs. of waste is produced [4]. Automation has been applied to quality control, process optimization, and data analysis [9]. This increases the speed and accuracy of processes such as filling, packaging, and inspection [10]. Industries outside of pharma are leveraging sensors and IIoT-enabled software to precisely monitor elements like compressed airflow. This allows manufacturers to identify leaks, optimize process, and improve efficiency. Examples include Colgate-Palmolive reducing energy use in several packaging lines by 15% [11].

Reduced Administrative Expenses

General and administrative (G&A) expenses in the biopharma industry equal about 7% of total revenue, 1.5%–2% higher than in comparable sectors. Automation can break the linear relationship between workload growth and cost. The potential impact is significant. McKinsey reports that best-practice pharma companies, which have fully automated tasks, report G&A spending as low as 3.5% of revenue [6].

Risk Management

Pharma 4.0™ initiatives support augmented manufacturing, personalized medicine, additive manufacturing, localized 3D printing of treatments, and even a future where humans are no longer intimately involved with production. This can substantially improve the challenges with aseptic manufacturing [12]. Leveraging IIoT reduces risks through data-driven preventative maintenance, controls the drug manufacturing environment, and facilitates supply chain monitoring [13].

Regulatory Compliance

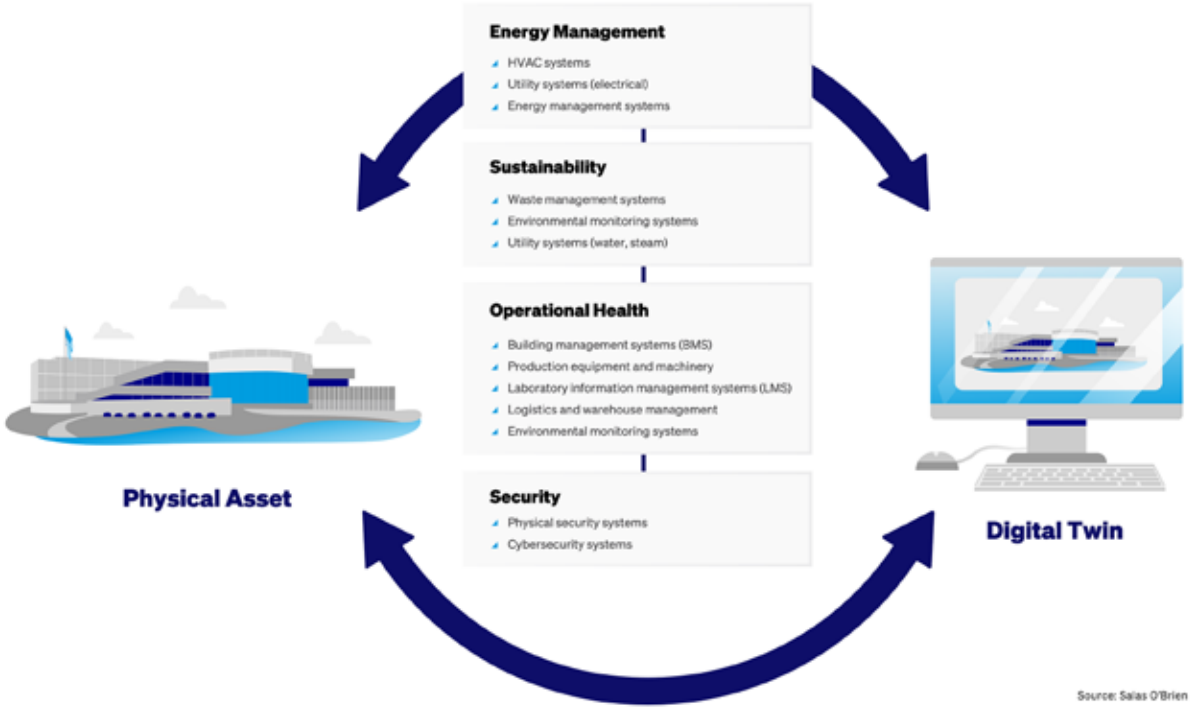
Deploying automation can help pharmaceutical companies follow stringent regulatory and compliance standards, in addition to reducing operational costs [10]. The recent Securities Exchange Commission's ruling on Climate Disclosure [1] signals an increasing focus on climate risk as financial risk, heightening the need for ESG reporting as regulatory compliance.

AUTOMATION'S ENERGY OPTIMIZATION

Automation's role in energy optimization intersects with areas such as modeling usage, improving efficiency, reducing waste, and enhancing overall energy management. For instance, monitoring fuel and steam usage to detect anomalies offers the potential for multiple system improvements. This can collectively yield savings of up to 10%–15%. The project payback period for implementing monitoring systems is generally under two years [14].

Digitalization connects facility utilities through smart facility plans. This connectivity enables key personnel to make faster decisions in real time and while maintaining control over energy

Figure 4: Digital twins in pharmaceutical manufacturing.



consumption and optimization. Graphic interfaces and process monitoring transmit data to relevant staff for benchmarking and identifying system issues and malfunctions. This flow of information can lead to efficient, controlled, and stable energy usage and optimization.

Leveraging Digital Twins: Energy Optimization

Digital twins are virtual replicas of physical entities or systems, created to simulate real-world objects, processes, or systems. These digital models are used for analysis, to predict the performance and issues of their physical counterparts, and to optimize operations or processes before applying changes in the real world. They integrate IIoT, AI, ML, and software analytics with spatial network graphs to create living digital simulation models that update and change as their physical counterparts change.

Although digital twins have been around since the 1970s, they have recently taken on a heightened importance for many life science manufacturers, from simulation and what-if analysis to life cycle management and energy optimization. They can provide a basis to clearly showcase what the facility will look like after conversion before any physical modifications take place.

A digital twin is a digital representation of a physical system and can take on many forms (asset twin, performance twin, and simulation twin). Many manufacturers have used a performance or simulation twin to model their factory and help drive energy reduction through optimization of operations. This can include real-time modifications to equipment settings or production schedules to maximize production during low-cost energy periods.

However, there is a greater potential in harnessing the power of digital twin technology with energy optimization through active modeling and settings: One can expand the power of a digital twin by modeling both the building and energy sources, using data inputs to recommend the most efficient energy sources for specific time frames.

Picture this: Based on energy profiles, a ground pump is set as the primary heat source for the next four days, strategically aligned with favorable weather conditions rather than relying on steam. This sophisticated strategy leads to substantial cost savings and makes significant contributions to carbon reduction efforts. The foresight provided by this approach allows for a more informed ESG conversion plan, seamlessly integrating sustainability into the facility's design during conception and then extending to operations. This approach focuses on more than just energy flow visualization and IIoT sensor integration; it actively shapes energy consumption patterns for maximum efficiency and environmental impact mitigation.

Digital Twins for AI and ML

As described previously, a digital twin foundation coupled with IIoT sensors lays the groundwork for harnessing the power of AI

The synergy in a facility that uses digital twins, IIoT sensors, and AI can facilitate precise energy optimization.

and ML. The integration of IIoT sensors with digital twins enables the continuous collection of real-time data from various assets and processes within a manufacturing facility. This information becomes a valuable resource for AI and ML algorithms, which then analyze patterns, detect anomalies, and predict potential equipment failures.

In addition to energy optimization, AI algorithms can forecast when equipment is likely to experience issues, allowing for proactive, predictive maintenance interventions. This reduces unplanned downtime and extends the lifespan of equipment, furthering energy optimization.

The synergy in a facility that uses digital twins, IIoT sensors, and AI can facilitate precise energy optimization. This approach reduces overall energy and enhances the reliability and efficiency of manufacturing processes.

Cybersecurity for Operational Technology

As pharmaceutical manufacturers navigate the integration of advanced digitalization strategies, it is imperative to develop a comprehensive cybersecurity framework. This framework should encompass regular security audits and vulnerability assessments to preemptively identify and mitigate potential threats. Additionally, the adoption of a zero-trust architecture is crucial, ensuring that access controls are strictly enforced. Network segmentation further fortifies this approach, allowing for controlled access and minimizing the risk of lateral movement within the network.

Integral to this cybersecurity matrix are robust firewalls and sophisticated endpoint security measures, forming a multilayered defense that safeguards critical infrastructure against evolving cyberthreats. This strategic approach to cybersecurity is not just a safeguard but a fundamental pillar supporting the integrity and resilience of pharmaceutical operations as digital automation is increasingly integrated.

Facility Conversion Roadmap

Facility conversion necessitates a structured and thoughtful approach. This will allow seamless integration of new automation technologies and digital capabilities to achieve the desired energy savings goals. The process includes the following six steps.

1. Map and audit to assess the current state of the facility's digital maturity model.
2. Define the facility's digital maturity model vision and goals.
3. Implement and connect the facility's digital maturity model action plan and roadmap.
4. Monitor digital data systematically to uncover insights and identify any irregularities.
5. Share relevant data and insights with key stakeholders.
6. Leverage the collected data to make informed decisions and enhancements; turn information into outcomes.

LEVERAGING ESG INITIATIVES

ESG reporting and goal achievement are increasingly prioritized, whether it be through ties to executive compensation or a consideration during budget allocation. Facilities must use new tools to communicate the need for capital project spending. Greenlighting funding for a facility improvement is no longer based solely on cost and ROI. The change in environmental impact must be documented and communicated in line with corporate ESG goals. The more granular the on-site data collection, the more accurate these projections can be. In the case of digital twins, the current and proposed project can be modeled to provide this data with the upmost accuracy.

By leveraging digital twin technology for precise data collection and project modeling, companies can make compelling cases for their digitalization initiatives by showcasing the expected ESG benefits in a language that resonates with stakeholders. This approach not only facilitates the approval and funding of vital facility improvements, but also positions the company as a leader in sustainable innovation, enhancing its reputation with investors, customers, and the public.

CONCLUSION

Through smart factory initiatives, pharmaceutical facilities can optimize energy consumption across processes, from research and development to manufacturing and packaging. This aligns with ESG goals by significantly lowering carbon footprints and propels facilities toward achieving greater economic sustainability. There are many benefits of integrating environmental considerations and automation into operational strategy, including efficiency, regulatory compliance, risk mitigation, and reduction of waste and administrative expenditures.

Leveraging ESG initiatives to fund digitalization projects is a proactive financial vehicle to support sustainability goals. By doing so, pharmaceutical companies enhance their competitive edge and contribute positively to global sustainability efforts. This approach fosters a culture of responsibility and innovation, encouraging stakeholders at all levels to commit to environmentally and socially responsible practices.

References

1. U.S. Securities and Exchange Commission. "SEC Adopts Rules to Enhance and Standardize Climate-Related Disclosures for Investors." 6 March 2024. Press Release. www.sec.gov/news/press-release/2024-31

2. Deloitte. *Sustainability Action Report: Survey Findings on ESG Disclosure and Preparedness.* December 2022. www2.deloitte.com/content/dam/Deloitte/us/Documents/audit/us-survey-findings-on-esg-disclosure-and-preparedness.pdf
3. Salas O'Brien. "Advancing Sustainable Delivery in Pharmaceutical Manufacturing." 19 July 2023. salasobrien.com/news/pharma-manufacturing-sustainability/
4. Pharma News Intelligence. "7 Ways to Increase Pharmaceutical Sustainability." 5 September 2023. pharmanewsintel.com/features/7-ways-to-increase-pharmaceutical-sustainability
5. Centrica Business Solutions. "Pharma Companies Cutting Energy Consumption to Gain a Competitive Advantage." Accessed 26 March 2024. www.centricabusinesssolutions.com/us/blogpost/pharma-companies-cutting-energy-consumption-gain-competitive-advantage
6. Bremme, L., L. Darino, B. Parry, and K. Teo. "Automation and the Future of Work in the US Biopharma Industry." McKinsey & Company. 13 August 2020. www.mckinsey.com/industries/life-sciences/our-insights/automation-and-the-future-of-work-in-the-us-biopharma-industry
7. Schneider, G. "Automating Drug Discovery." *Nature Reviews Drug Discovery* 17 (2018):97–113. doi:10.1038/nrd.2017.232
8. Bui, D., and J. McCollum. "Securing Off-Grid Power: The Role of Microgrids in Resilient Hospitals." Salas O'Brien. 9 January 2024. salasobrien.com/news/hospital-microgrid/
9. Praxie. "Transforming the Industry: The Advantages of Automation in Pharmaceutical Manufacturing." Accessed 26 March 2024. praxie.com/automation-in-pharmaceutical-manufacturing/
10. Pharmaceutical Technology. "Process Automation and Equipment." Accessed 26 March 2024. www.pharmaceutical-technology.com/buyers-guide/process-automation-equipment/
11. Emerson. "How Automation Can Help Your Organization Achieve its ESG Goals." Harvard Business Review. 31 October 2022. hbr.org/sponsored/2022/10/how-automation-can-help-your-organization-achieve-its-esg-goals
12. Aeologic. "Process Automation Solutions in Pharmaceutical Manufacturing." 10 October 2022. www.aeologic.com/blog/process-automation-solutions-in-pharmaceutical-manufacturing/
13. Pharma IQ. Shugalo, I. "The Role of IoT in Pharma Manufacturing and Distribution." 26 February 2019. www.pharma-iq.com/manufacturing/articles/the-role-of-iot-in-pharma-manufacturing-and-distribution
14. Newenham, P. "6 Steps to Energy Optimisation in Pharmaceutical Manufacturing." Cool Planet. 24 November 2022. www.coolplanet.io/blog/articles/energy-optimisation-pharmaceutical-manufacturing

About the authors

John Glenski, CPM, is a Principal for Automation & Digital Solutions at Salas O'Brien. He is a leader in digital transformation in the industrial sector with a demonstrated history of providing data-driven outcomes for the world's largest manufacturers. John works collaboratively with internal and external partners to deliver innovative solutions for smart manufacturing (automation, material handling, and data/information solutions) with a focus on sustainable applications.

Will Knapp is Director of Pharmaceutical Projects at Salas O'Brien. He is a leader in pharmaceutical manufacturing with over 20 years of experience and expertise in biopharmaceuticals, aseptic processing, oral solid dosage (OSD), medical devices, validation, and compliance. His innovative approach and commitment to excellence have significantly contributed to advancements in product quality and manufacturing efficiency. He joined ISPE in 2020.

Marianna Moores, WELL AP, LEED AP, ActiveScore AP, is an Associate Vice President at Salas O'Brien and a leader in the field of ESG consulting. With her unwavering commitment to sustainability and profitability, she revolutionizes the way businesses approach their operations. By leveraging data-driven insights and scientific methodologies, Marianna empowers clients to harmonize their environmental and social responsibilities with their financial success.

Investing in **People.** Building the **Future.**

Please consider making a charitable donation to the ISPE Foundation.

Your donation is needed to help fund key Foundation programs that positively impact patient populations across the globe both now and in the future.

WAYS TO DONATE

- Online at ISPEFoundation.org/donate
- Scan the QR code

ISPE® FOUNDATION

Why You Should Attend the Annual Meeting & Expo

By David Churchward

The 2024 ISPE Annual Meeting & Expo will be held 13–16 October in Orlando, Florida, and virtually. David Churchward is the conference's Executive Chair. He offers advice and shares what attendees can expect at the upcoming conference.

WHAT ARE THE TOP THREE REASONS YOU WOULD TELL SOMEONE THEY SHOULD ATTEND THIS CONFERENCE?

Access to knowledge, networking, and innovation. The ISPE mission of "connecting pharmaceutical knowledge" is front and center during the annual meeting. It truly is a rare opportunity to meet with more than 2,000 peers from across the pharmaceutical industry, service partners, and regulators to share the knowledge that will take our industry forward. I am also proud that in addition to seeking solutions to future challenges, we always retain a committed line of sight to the patients that we serve.

ANY ADVICE FOR SOMEONE TO MAKE THE MOST OUT OF THE CONFERENCE?

The educational opportunities are extensive—seek out something new. We can all become more effective as professionals by learning about part of our industry that might not be in our current sphere of expertise.

Help others maximize their opportunity. I really encourage engagement between people at all stages of their career and areas of responsibility. This year we will have another great cohort of students, young professionals, and Emerging Leaders attending. We can all benefit in spaces where inquisitive thought meets experience.

Last but not least, maximize your networking opportunities! ISPE offers us a huge opportunity to broaden our knowledge and experience not just from educational events and publications, but also from the relationships we build. The long-term benefits that we can gain from the knowledge and experience in our network are incredible.

THE CONFERENCE HAS A THEME OF 'WORKFORCE OF THE FUTURE' THROUGHOUT. WHAT MAKES THIS SUCH A COMPELLING SUBJECT?

We cannot hold back the tide of technology and scientific discovery that will be disruptive to current drug development, manufacturing, and healthcare delivery. The treatments and technologies that our industry will develop over the foreseeable future is likely to significantly change the skills that our greatest asset—our workforce—requires.

If we are to meet the future needs of patients, we need a workforce ready for the future. This means ensuring that we continue to develop the skills and education of our current workforce and attracting professionals and students with new skills from other disciplines who may previously not have considered pharma in their career path.

WHAT ARE YOU MOST LOOKING FORWARD TO?

Firstly, the incredible diversity of educational material produced by our membership during workshops, presentations, and panel discussions. Beyond the conference agenda, I also look forward to the discussions and relationship building that benefit us far beyond the boundaries of the event.

WHY DID YOU ACCEPT THE INVITATION TO BE EXECUTIVE CONFERENCE CHAIR?

I was delighted to accept the invitation to be the Executive Conference Chair and have the chance to work with Conference Chair Ciby Abraham's fantastic team, the organizing committee, and ISPE staff to deliver the 2024 program.

The role of Executive Chair has given me the opportunity to share my view of our industry's strategic needs and shape the conference themes to help our industry meet future technological, regulatory, and healthcare challenges. In particular, I appreciate the team's willingness to align future workforce needs through the conference technical tracks, workshops, and Hackathon event, as I believe this to be critical for our future success in delivering for patients.

WHY DO YOU ENJOY BEING A MEMBER OF ISPE?

The education events, guidance documents, networking, and connection with global regulators that ISPE has offered me over the past 20 years have been a key element of my professional growth—and beyond that, I have formed many friendships among our members.

I find ISPE to be an inspiring community of individuals who, together, are working to solve some of the world's biggest healthcare challenges. Being a member of ISPE, and volunteering in working groups, Communities of Practice, Affiliates, and Chapters is both professionally and personally rewarding to help achieve this mission.

About the author

David Churchward joined AstraZeneca's global quality team in January 2024. In his current role, he leads the AstraZeneca global audit and GMP compliance functions. David's previous roles include two years leading the global sterility assurance team in Lonza's cell and gene therapy division and 17 years with UK Medicines and Healthcare Regulatory Agency as a GMP inspector. David has extensive experience of international regulatory harmonisation and previously served as a member of the PIC/S Executive Bureau and Committee of Officials and subcommittee for GMP Harmonisation, and delegate to the ICH Assembly. In addition to serving as Executive Chair for the Annual Meeting & Expo, he is a Director on the ISPE International Board and serves as Board Liaison to many ISPE Chapters and Affiliates. He joined ISPE in 2011.

Roche Named ISPE 2023 Company of the Year

By Marcy Sanford

The ISPE International Company of the Year award recognizes outstanding leadership and support provided by a company, as reflected by significant active participation in the Society's committees, Communities of Practice (CoPs), programs, and activities, as well as its support of employee participation in ISPE. The winner for 2023, Roche, was announced at the 2023 ISPE Annual Meeting & Expo in Las Vegas, Nevada.

Founded in 1896 in Basel, Switzerland, Roche is one of the world's largest biotechnology companies and a global leader in in-vitro diagnostics. "Roche, including their subsidiaries, was selected due to their strong commitment to employee participation and membership within ISPE," said Thomas Hartman, President and CEO, ISPE.

"Their engagement with ISPE spans across multiple areas within the Society," he said. "This includes involvement in ISPE conferences through program committees, speaker participation, Hackathon organization, plus they provide support for their staff to attend. ISPE is grateful for the contributions from Roche."

In addition to being the pharmaceutical company with the highest number of ISPE members, Roche employees have served as co-chair or chair of guidance document task teams—including the recently published *ISPE Baseline® Guide Vol 8: Pharma 4.0™* and the *ISPE Guide: Advanced Therapies Medicinal Products: Recombinant AAV Comparability and Lifecycle Management*—and served on the program committee for the 2023 ISPE Pharma 4.0™ and Annex 1 Conference.

> Long-term involvement in ISPE allows for continued development of technical skills and early involvement in new opportunities to adopt best practices.

Roche employees have served as judges for the ISPE Facility of the Year Awards and are members and leaders of numerous CoPs, including Advanced Pharmaceutical Ingredients (API), Sustainable Facilities, HVAC & Controlled Environments, and GAMP®. They are mentors and participants in ISPE communities such as Women in Pharma®, Emerging Leaders, and the Drug Shortages Initiative Team and have helped with ISPE activities like the annual ISPE Hackathon.

"Our contributions to ISPE Communities of Practice, Chapters, conferences, and global expectations have highlighted the impact we can have as professionals in our industry and our ability to shape the future together—from technical standards all the way to emerging spaces and new modalities," said Georg Singewald, Head of Roche Pharma Technical Operations Global MSAT, Engineering, and Sustainability.

"Equally as important, we have a lot to learn from our industry partners," Singewald adds. "Our long-term involvement in ISPE allows for continued development of our technical skills and early involvement in new opportunities to adopt best practices."

2024 ISPE ANNUAL MEETING & EXPO

13-16 October | Orlando, Florida, USA and Virtual

LEARN 40+ HOURS OF EDUCATION

100+ Speakers

220+ Exhibitors

5 In-Depth Workshops

FEATURED TOPICS INCLUDE:

- DIGITAL TRANSFORMATION
- REGULATORY, COMPLIANCE, AND QUALITY
- ADVANCED THERAPY MEDICINAL PRODUCTS (ATMPS)
- MANUFACTURING, QUALITY CONTROL, AND OPERATIONAL EXCELLENCE

LEARN MORE AND REGISTER AT **ISPE.ORG/AM24**

NETWORK

16+HOURS OF NETWORKING

- 2024 ISPE INTERNATIONAL EMERGING LEADER HACKATHON
- SUNDAY SOCIAL
- ISPE'S SELF-DEFENSE CLASS POWERED & LED BY WOMEN IN PHARMA®
- TUESDAY NIGHT CELEBRATION
- 15TH ANNUAL ISPE 5K RUN/WALK
- MEMBERSHIP MEETING AND AWARDS LUNCH
- WELCOME RECEPTION
- 2024 FOYA BANQUET AND AWARDS CELEBRATION
- ANNUAL ISPE FOUNDATION GOLF TOURNAMENT
- NETWORKING SOIREE POWERED & LED BY WOMEN IN PHARMA®

EXPERIENCE

- WORLD FAMOUS LOCATIONS – 100+ THEME PARKS, MUSEUMS AND ATTRACTIONS
- YEAR-ROUND TROPICAL CLIMATE – 85° AVERAGE TEMPERATURE IN OCTOBER
- NATURAL ATTRACTIONS – 2,000+ LAKES, SPRINGS, RIVERS, AND BEACHES
- LEGENDARY GOLF – 175+ COURSES

ISPE®

Introducing the 2024 ISPE FOYA Submission Finalists

Each year, ISPE recognizes innovation in pharmaceutical facilities with the Facility of the Year Awards (FOYA). The 2024 FOYA submission finalists were announced at the 2024 ISPE Aseptic Conference in Vienna, Austria. Finalists for the 2024 awards highlight the continued progress and innovation at play in pharmaceutical manufacturing worldwide and across modalities. From projects tailored to the delivery of novel therapeutics to facilities focused on pushing the limits of speed and efficiency, one common thread is the focus on delivering life-changing therapies to patients in need.

FOYA is the premier global awards program recognizing innovation and creativity in manufacturing facilities that serves the regulated healthcare industry. The award-winning projects selected by the FOYA program demonstrate excellence in facility design, construction, and operations, setting the standard for pharmaceutical facilities of the future. Winners are recognized across the categories of Innovation, Operations, Supply Chain, Pharma 4.0™, and Social Impact.

"The announcement of ISPE's FOYA submission finalists is step one to recognizing and celebrating innovation in pharmaceutical manufacturing plant design and qualification," said Thomas Hartman, President and CEO, ISPE. "These facilities, and the people that bring them to life, transform patient lives. Our ultimate priority is to foster novel technologies and processes, accelerating the availability of transformational medicines to patient populations."

2024 ISPE FOYA SUBMISSION FINALISTS

Beam Therapeutics

Project: Beam Cell and Gene Therapy Facility

Location: Research Triangle Park, North Carolina, US

Mission: Beam is a value-driven organization committed to its people, cutting-edge science, and a vision of providing lifelong cures to patients suffering from serious diseases. The cell and gene therapy facility is a significant part of this vision and is instrumental in Beam's commitment to establishing a leading, fully integrated platform for precision genetic medicines.

Bristol Myers Squibb

Project: Devens Cell Therapy Facility

Location: Devens, Massachusetts, US

Mission: The mission of the Devens cell therapy facility is to design, build, and start a world-class facility that will deliver innovative medicines that help patients prevail over serious diseases.

Chugai Pharma Manufacturing Co., Ltd.

Project: UK4

Location: Tokyo, Japan

Mission: With the UK4 Project facilities, Chugai aims to rapidly start first-in-human trials in the initial stage of clinical development to achieve early proof of concept in its antibody and other bio-drug projects. The facility will help Chugai expand supply capacity and enhance speed and flexibility. This will accelerate the development

of ever-evolving antibody drugs to deliver innovations to patients worldwide. The accelerated development of new products will address unmet patient needs for effective treatments. In addition to patient needs, the UK4 facility was also constructed to contribute to sustainability through environmental goals.

Eli Lilly Kinsale Limited

Project: IE2b

Location: Kinsale, Ireland

Mission: With the IE2b project, Eli Lilly set out to develop and deliver a first-of-its-kind hybrid peptide manufacturing facility. IE2b was built to support the commercial supply of large-volume, life-changing synthetic peptide molecules. This was done with a combination of traditional solid-phase peptide synthesis technology, new liquid-phase peptide synthesis concepts, continuous processing technology, and digital plant solutions.

INCOG BioPharma Services

Project: First to Flex

Location: Fishers, Indiana, US

Mission: INCOG set out to build a customer-driven contract development and manufacturing organization (CDMO) focused on providing customers with unparalleled service and products with the highest quality standards.

Novartis Pharmaceutical Manufacturing GmbH

Project: BioFuture Plant1

Location: Langkampfen, Austria

Mission: A groundbreaking concept brought to life: the innovation in manufacturing drug substances for biologics known as BioFuture Plant1 represents a revolutionary leap forward. BioFuture stands for "Biomanufacturing of the Future." It is one of the world's most advanced facilities dedicated to producing therapeutic proteins through continuous and automated process technologies. The adaptable design of the BioFuture facility supports the manufacturing of a diverse range of molecules across a broad product portfolio. Accelerating time to market ensures that lifesaving and life-changing medications are available to more patients sooner. With reduced CO_2 emissions, BioFuture is also environmentally friendly.

OrchidPharma LTD

Project: Sterile API Manufacturing Facility (Phase 27)

Location: Tamilnadu, India

Mission: OrchidPharma's mission is to complete the development of the sterile API manufacturing facility (phase 27) on time, cost-effectively, and in a safe environment, resulting in the production of 50 tons of sterile injectables per year.

Pfizer Asia Pacific Manufacturing Ltd

Project: Pfizer API Facility Extension

Location: Tuas, Singapore

Mission: This project was aimed at accelerating supply through the Pfizer API Facility Extension.

Takeda Austria GmbH

Project: beePFS - Prefilled Syringe Filling

Location: Linz, Austria

Mission: The goal of the beePFS project is to implement a prefilled syringe filling line in Linz for Takeda products. Classified as a "super warp speed" project, it was intended to significantly reduce the time required to achieve process performance qualification in 24 months.

Ultragenyx

Project: Vector Gene Therapy Manufacturing Facility

Location: Bedford, Massachusetts, US

Mission: This project focused on advancing and expediting gene therapy production for rare and ultra-rare diseases with an in-house GMP manufacturing facility (both drug substance and drug product). This will ensure a reliable supply of products for clinical and commercial use.

United Therapeutics Corporation

Project: Lightyear

Location: Research Triangle Park, North Carolina, US

Mission: In anticipation of the expected US FDA approval of Tyvaso DPI—a new formulation and inhalation device for inhaled treprostinil and the only dry powder inhaler approved for use in pulmonary arterial hypertension and pulmonary hypertension associated with interstitial lung disease—United Therapeutics identified the urgent need to expand their warehousing and logistics capabilities to support their growing operations. Not only would this new warehouse and logistics center provide the needed space for continued growth, but it would also deliver critical resiliency for facility and logistical operations. In addition to expanding treatment options and further fortifying the supply chain, the project was carried out with as minimal an impact on the environment as possible.

Wheeler Bio

Project: The Ziggurat

Location: Oklahoma City, Oklahoma, US

Mission: To accelerate the path from discovery to investigational new drug filing, Wheeler Bio, a new CDMO established in Oklahoma City, set out to build a GMP facility for early clinical phase biologic services. The facility is designed with a risk-based approach, using open ballroom and single-use manufacturing. It is digitally connected and uses a local workforce to sustain the future biomanufacturing ecosystem. Wheeler Bio's facility and business model allow for a low-cost and accelerated model for translating innovation into clinical impact.

Zydus Pharmaceuticals Ltd.

Project: Oral Solid Dosage Manufacturing Facility

Location: Gujarat, India

Mission: Adhering to Zydus's promise of being "dedicated to life" in all its dimensions, this project's mission is centered on an unwavering commitment to excellence and passion for innovation. It will support implementation of advanced technologies and sustained quality culture, providing affordable and quality medicines globally.

ABOUT THE ISPE FOYA PROGRAM

Established in 2005, the ISPE FOYA program recognizes state-of-the-art projects using new, innovative technologies to improve product quality, reduce the cost of producing high-quality medicines, and demonstrate advances in project delivery. The FOYA program provides a platform for the pharmaceutical science and manufacturing industry to showcase its accomplishments in facility design, construction, and operation while sharing the development of new technology applications and cutting-edge approaches. Visit ISPE.org/FOYA for more information.

CoP
LEADER
PROFILES

SUSTAINABLE FACILITIES, HVAC & CONTROLLED ENVIRONMENTS COMMUNITY OF PRACTICE CHAIR

ALLEN B. KOESTER, PE, PMP

Growing up on a farm, Allen Koester thought he would design farm equipment after earning his degree in mechanical engineering. Instead, he landed a job as a consultant working in the heavy metals and aluminum industry, then when the industry took a downturn, he began working on a project at Bristol Myers Squibb. "They were doing energy studies and sustainability-type work before it was even considered sustainability. I got the opportunity to work on all kinds of projects—installing processing equipment and building processing rooms. During that time, I joined ISPE, took the ISPE HVAC [Heating, Ventilation, and Air Conditioning] class, and used ISPE guidance documents to learn more about the pharmaceutical industry."

Allen served as a consultant for Bristol Myers Squibb for several years and then the company offered him the opportunity to work solely for them. "I was able to be involved with several blockbuster projects. One of the most interesting was a project where the product was just out of the lab. I worked with process engineers to bring in new process equipment for a potent compound, and I had the opportunity to work with them to set up the tablet processing and then the full-scale manufacturing facility. We gutted the building and built a whole new manufacturing facility in that structure, and I was able to work on that from conception all the way through qualification. We worked on the project for three years before the product hit the market. I was able to wear many hats and managed the project from buying the equipment to overseeing the design and managing all the construction and validation work and obtaining approval from FDA."

Now as Senior Vice President/Senior Project Manager at Salas O'Brien, Allen works on capital projects and manages the design and execution of multidiscipline capital projects. Thanks to his broad experience in pharmaceutical processing equipment design, installation, and qualification, Allen can advise a wide variety of clients on how to best bring their projects to fruition. His expertise and innovation in tackling complex challenges are instrumental in helping his clients reach their efficiency and sustainability goals. "I feel like it is my nature to be a problem-solver, to learn and then to share what I learn."

In addition to being chair of the Sustainable Facilities, HVAC & Controlled Environments CoP Steering Committee, Allen is a member of the team working on revision of the *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning* (*HVAC*) and has served as a board member for the Great Lakes Chapter. "Early in my career, I used ISPE to absorb knowledge about the industry through Baseline Guides, the HVAC class, and other utilities guidance documents. It helped me to learn common practices and best design good practices. I still follow Engage to see what questions people are asking and to see responses from experts in the field. I am honored to be able to share the knowledge I've learned with others and think it is fundamental to continue learning."

— Marcy Sanford, ISPE Publications Coordinator

CRITICAL UTILITIES COMMUNITY OF PRACTICE CHAIR

ROD FREEMAN

Rod Freeman started his career in the pharmaceutical industry as an analytical chemist. "Getting a degree in chemical engineering, I thought I'd work at a refinery or a chemical plant. I was aware of the pharmaceutical industry but hadn't given it much thought. Once I started in the industry, I was really interested in it. In that role, I was supporting instrument validation and method validation, and once I got the word 'validation' on my resume, there was always work. Over the years, I worked in facilities maintenance and validation before moving into quality."

Now as Associate Director of Quality Engineering at Kite Pharma, Rod is responsible for commissioning, qualification, validation, and risk management for facilities, utilities, and equipment for a multi-viral vector manufacturing facility. He leads a commissioning, qualification, and validation team to generate site validation master plans, user requirement specification, risk assessments, and qualification schedule and protocols. "I oversee the jobs I used to do. I think it is beneficial that I worked as an engineer for years in all those disciplines. I have a better understanding of what it takes to do the job and of the impact differing changes or incidents can have in quality systems."

"When I joined Kite Pharma, I was part of the team that basically built the plant I'm now at. We built the facility, qualified all the assets, brought it online and received FDA and European approval. I've worked on a lot of good projects, but bringing this from seeing the foundations poured to FDA approval was a great journey."

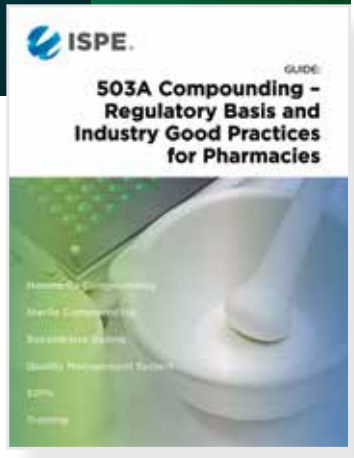
"I've always enjoyed working in the pharmaceutical industry because we help people, we improve and extend the lives of people everywhere. The therapies that I've gotten to be part of, especially where I'm at now, it makes a significant improvement in people's lives. We create viral vectors that are used in downstream manufacturing process. Right now, our chimeric antigen receptor T cell (CAR T) therapy is used primarily to treat leukemia and other types of blood cancers, but we are trying to expand our therapies into other therapeutic areas outside of cancer. I feel fortunate that at this point in my career, I get to be part of a new type of therapeutic class that I think will have a lot of growth in the decades to come. It is exciting to see what is possible."

In addition to being chair of the Critical Utilities Community of Practice Steering Committee, Rod has been instrumental in the development of many ISPE guidance documents. He is co-chair of the team working on the revision of *ISPE Good Practice Guide: Ozone Sanitization of Pharmaceutical Water Systems* and was on the authoring teams for the original *ISPE Good Practice Guide: Good Engineering Practice, ISPE Good Practice Guide: Process Gases, Second Edition, ISPE Baseline Guide® Vol. 4: Water and Steam Systems, Third Edition,* and *ISPE Good Practice Guide: Approaches to Commissioning and Qualification of Pharmaceutical Water and Steam Systems, Second Edition.* He has also been active in ISPE's San Diego Chapter.

— Marcy Sanford, ISPE Publications Coordinator

New Guide for Compounding Pharmacies

By Marcy Sanford



In April 2024, ISPE published the *ISPE Guide: 503A Compounding - Regulatory Basis and Industry Good Practices for Pharmacies,* adding to the growing body of knowledge ISPE is producing for the pharmaceutical compounding industry. Written by industry experts and reviewed by practitioners in the area, the guide provides an overview of relevant US Food and Drug Administration (FDA) regulations and guidance for conducting safe compounding. It also outlines the authority of state boards of pharmacy and their coordination of oversight with the FDA.

A significant portion of this guide addresses all relevant United States Pharmacopeia (USP) chapters that relate to the operation of 503A pharmacies. The differences in USP General Chapter <795> Pharmaceutical Compounding - Nonsterile Preparations and USP General Chapter <797> Pharmaceutical Compounding - Sterile Preparations are discussed throughout this ISPE guide. This is to aid 503A compounders in understanding the requirements and accessing appropriate information.

Compounding requirements for 503A pharmacies focus on the quality management system (QMS) and its application throughout the compounding process, including materials, facilities and equipment, environmental controls, storage, shipping, and transport. Readers will find the information on personnel knowledge and training requirements valuable. To aid pharmacies in maintaining compliance with federal and state regulations, several lists of suggested standard operating procedures based on the type of compounding conducted are included.

A survey of compounding pharmacies and regulators conducted by ISPE in early 2022 identified the need for guidance regarding pharmaceutical compounding FDA regulations and recommendations and USP criteria. The *ISPE Guide: 503A Compounding - Regulatory Basis and Industry Good Practices for Pharmacies* and *ISPE Guide: 503B Compounding - Regulatory Basis and Industry Good Practices for Outsourcing Facilities,* which was published in August 2023, are the result of ISPE's response to that survey.

The *ISPE Guide: 503B Compounding – Regulatory Basis and Industry Good Practices for Outsourcing Facilities* combines FDA regulations and recommendations with pharmaceutical industry standards, providing a go-to document for 503B facilities of all sizes. Various aspects of the compounding process are covered: the importance of current GMPs, establishing a quality system (including qualifying suppliers and vendors), receipt of raw materials/active ingredients, and the shipping of finished drug products.

The guide also provides recommendations for facility and equipment design, drawing from aseptic manufacturing practices and scaled to meet the needs of 503B facilities. In addition, it presents industry best practices for aseptic manufacturing, emphasizing personnel training and qualification.

Additionally, the ISPE 503B Guide addresses microbiological and analytical testing, including verifying the suitability of compendial methods and validating non-compendial methods. It covers beyond-use dating, offering essential insights into limited stability testing, and stability best practices. A dedicated chapter on preparing for regulatory inspections provides facilities with a valuable resource.

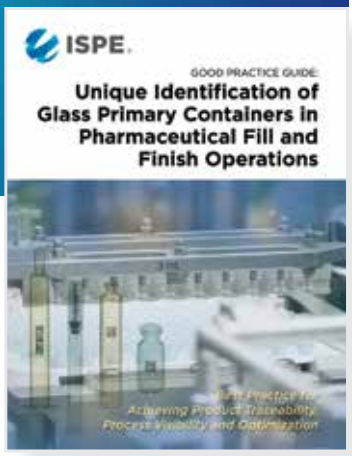
In 2023, ISPE also established the Pharmaceutical Compounding Community of Practice (CoP), which seeks to foster innovation to improve the practice of pharmaceutical compounding, and to disseminate ideas, knowledge, and best practices. This is done through the generation of ISPE content, including guidance documents, *Pharmaceutical Engineering*® magazine articles, webinars, blog posts, conference presentations, and training materials.

The new CoP provides a venue for industry and regulatory informal interactions to drive practical and effective design and operational practices. It also addresses regulatory expectations and provides solid scientific justification for practices accepted by industry and regulators alike.

ISPE members interested in being considered to participate on the recently established Steering Committee leading the ISPE Pharmaceutical Compounding CoP are urged to email ISPE at communities@ispe.org

A Guide to Unique Identification of Glass Primary Containers

By Marcy Sanford



The new *ISPE Good Practice Guide: Unique Identification of Glass Primary Containers in Pharmaceutical Fill and Finish Operations* involved a cross-functional team of industry experts and professionals from parenteral/injectable medicine manufacturing. The team included industry competitors who worked together to establish a common approach. They provided a balanced, industrywide perspective on the use of containers with unique identities.

Many current challenges facing the pharmaceutical industry revolve around increased product complexity, reduced batch sizes, and higher flexibility requirements. The challenges are coupled with increased requirements for product traceability, both internally and by regulatory bodies.

Additionally, as the industry moves toward a continuous manufacturing process model, it is more challenging to define the production stage at which something began to go wrong. Unique identifiers (UID) tags—radio frequency identification (RFID) or 2D barcodes—that are placed on the glass containers (e.g., vials, syringes, and cartridges) of sterile pharmaceutical products can help address these issues. This is because they enable traceability at the individual container level.

"A UID can help manufacturers pinpoint exactly where something went wrong with a batch production" said Guide Co-Lead Alessandro Pelizzi, Associate Manager, LifeBee. "With a UID, a manufacturer could more precisely pinpoint where the issue began and would only have to get rid of that portion of the batch. This could contribute to increased efficiency and eliminate waste, fight the drug shortage problem, improve the ESG [environmental, social, and governance] performance, and, of course, save money in the long run."

Members of ISPE's Supply Chain, Operations, and Packaging Excellence (SCOPE) Community of Practice (CoP) wanted to research the industry's knowledge of and interest in UIDs after the technology was developed by industry stakeholders. In February 2021, ISPE published a discussion paper written by the SCOPE CoP team. This paper included the team's research and asked readers to provide feedback on the issues and challenges that could occur if uniquely identified primary containers for parenteral products were implemented in manufacturing operations.

"We received a lot of feedback on the discussion paper from all across the industry, but one thing that became very apparent was that the industry needed some guidance on the best practices for implementing this technology," said Guide Co-Lead Tod Urquhart, Executive Industry Adviser, Eagas. "The team that wrote the guide included professionals from different parts of the pharmaceutical industry, including supply chain experts and companies who are beginning to implement this technology."

The *ISPE Good Practice Guide: Unique Identification of Glass Primary Containers in Pharmaceutical Fill and Finish Operations* describes processes for applying a UID on each primary parenteral container. The guide outlines best practices for developing, implementing, and managing a traceability project across one or more processes.

The unique identification of single glass containers described in this guide represents a technological advancement that can support the robustness of pharmaceutical manufacturing processes. It encompasses all types of glass primary containers made from tubular glass or molded glass for the containment of pharmaceutical liquids or lyophilized products.

"There are huge benefits to UIDs," said Urquhart. "As the container moves through each different process, data is being collected on each step of production. All of that information can give you a life history that can help with process optimization, analytics, and information to support regulatory compliance questions."

Topics covered in the guide include:

- UID methods and technologies for the different container types
- The UID structure
- Performance requirements for glass containers
- Barcode readability and verification
- RFID technologies
- Instructions for reading different formats
- Automated inspection processes
- Traceability in processes

This guide also discusses how to manage the container UID without affecting the package serialization required by the European Union (EU) and US Food and Drug Administration (FDA).

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

Experts Create Examples of C&Q Deliverables

By Commissioning and Qualification Community of Practice Steering Committee Members

In 2019, ISPE released the Second Edition of the *ISPE Baseline® Guide Vol 5: Commissioning and Qualification*. This guide mirrors the industry's evolution toward harmonizing with latest regulatory expectations, highlighting the significance of quality risk management and evidence-based decision-making while also achieving cost and time efficiency.

Diverging from conventional practices, the risk- and science-based commissioning and qualification (C&Q) approach involves generating documented evidence to ensure that systems are installed and operate to comply with established specifications. Spearheaded by the engineering team and quality and other process experts, this evidence is generated in accordance with the company's Good Engineering Practices. The format of these documentation sets is predetermined within C&Q plans, subject to the company's quality approval procedures.

The C&Q Baseline® Guide provides in-depth insights into implementing risk- and science-based C&Q approaches. To support this, a team of industry experts has crafted examples of C&Q deliverables spanning three distinct types of manufacturing systems: bioreactor unit operation, primary and secondary packaging operation, and utility systems. Although these examples may not universally apply, their aim is to provide examples of the output for these systems to enhance the understanding of the baseline guide approach.

It is important to note that these examples are not intended for direct adoption but rather to facilitate a deeper understanding of the C&Q Baseline® Guide. Therefore, it is recommended to engage with the guide before using these examples.

You can access the examples by scanning the QR code.

Meet the ISPE STAFF

Saana Tykkä

In each issue of *Pharmaceutical Engineering®*, we introduce a member of the ISPE staff who provides ISPE members with key information and services. Meet Saana Tykkä, Program Manager, Conferences & Digital Engagements (CDE) team, a dynamic force hailing from the Nordic city of Helsinki, Finland, and currently making waves in Columbia, South Carolina.

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

As a Program Manager on the CDE team, my days are a whirlwind of activity, collaborating with ISPE volunteers and our dedicated staff to orchestrate our Aseptic Conference and Annual Meeting & Expo. I also help produce our webinars. Each day brings a new challenge, from fine-tuning our call for proposals to ensuring seamless execution onsite. My role involves a blend of strategic planning, virtual collaboration, and on-the-ground coordination, ensuring that every aspect of our events exceeds expectations.

What do you love about your job?

What truly ignites my passion is the opportunity to work alongside our exceptional volunteers. Their unwavering dedication to ISPE and their industry expertise are truly inspiring. The collaborative spirit within the CDE team and our conference planning committee fuels my excitement as we craft each event. Witnessing months of planning culminate in a successful conference, with speakers, presentations, and networking opportunities seamlessly coming together, is immensely gratifying, even if it leaves me temporarily drained of energy.

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

After work, you'll find me indulging in my favorite pastimes. Whether I'm lost in the pages of a captivating book, exploring new destinations, or cherishing precious moments with my family, I thrive on variety. An avid fitness enthusiast, I frequently hit the gym or embark on refreshing runs or outdoor activities, accompanied by the playful antics of my two dogs.

The ISPE Foundation: Fueling Global Health Equity

This year, the ISPE Foundation made great strides in its mission of fueling global health equity by fostering access to knowledge and nurturing diverse talent.

The ISPE Foundation provides a pathway for the diverse and unique perspectives of all people to be heard within our industry through programs such as ISPE Foundation Diversity Internship Program, Technology without Borders, and Women in Pharma®.

This past International Women's Day, the ISPE Foundation celebrated by spotlighting multiple members of Women in Pharma, including the Chair for the Women in Pharma International Steering Committee, Vivien Santillan, who said, "Programs with a focus on personal and professional growth with social impact at their core will shape the future of the pharmaceutical industry."

The ISPE Foundation's Technology without Borders program has achieved notable progress, particularly with the successful completion of its inaugural cycle in Brazil. Recently, the ISPE Foundation recognized the program's achievements, which were made possible with a generous contribution from Gilead Sciences. The contribution helped expedite the availability of essential industry guidance documents and training in emerging economies. These resources are critical to regulatory bodies and industry professionals who would otherwise have limited or no access to the pharmaceutical industry's best practices and standards. The program's success in Brazil is evident, with over 125 Portuguese-speaking individuals benefiting from resources and training in their native language.

If you would like to strengthen your involvement with the ISPE Foundation, join them on 16 October for the Annual ISPE Foundation Golf Tournament at Celebration Golf Club in Orlando, Florida, following the 2024 ISPE Annual Meeting & Expo. Because proceeds from the event directly benefit the ISPE Foundation, this is an exceptional opportunity for your company to both demonstrate its philanthropic dedication and spend the day networking among industry leaders and professionals. If you are interested in playing or sponsoring the tournament, please contact Dave Dunham, Senior Director, Business Development (ddunham@ispe.org) for more details.

Please Join Us in Thanking ISPE's Corporate Partners

Through the ISPE Corporate Partnership program, these companies have committed to supporting and contributing to ISPE's mission within the pharmaceutical industry.

PLATINUM

GOLD

SILVER

ACCEPTABLE DISCOLORATION LEVELS on Pharmaceutical Weld Beads

By Ken Kimbrel, Brad Krantz, and Daryl L. Roll, PE

Welds used in biopharmaceutical manufacturing must meet critical criteria to maintain a defined level of purity and bioburden control. One highly debated area of concern is the level of discoloration allowable on the product contact surfaces in the welded condition and secondary finishing methods. This article addresses the studies commissioned by the American Society for Mechanical Engineers (ASME) to determine the allowed discoloration in the heat affected zone (HAZ) and weld bead.

Discoloration of stainless steel welds and HAZs are visible evidence of various thicknesses and compositions of oxides, hydroxides, and other surface contaminants formed during welding. If these levels of discoloration are significant enough, they have the potential to contaminate the drug product, reduce the corrosion resistance of the metal, and reduce the life cycle of the piping system.

Therefore, appropriate levels of discoloration of welds made in the construction of process equipment and piping systems, such as those used in the manufacture of biopharmaceuticals, are highly debated within the pharmaceutical industry.

Numerous independent studies to determine acceptability of weld and HAZ color have been performed. Although these studies have impacted, improved, and modified published information over the years within manufacturing standards, levels of weld color acceptability remained unanswered. In 2020, the ASME Bioprocessing Equipment (BPE) Subcommittee on Material Joining (MJ) commissioned studies to answer the question and end the debate on discoloration allowed in the HAZ of the weld and any color within the weld bead itself.

BACKGROUND

The ASME BPE Standard addressed weld discoloration by referencing the American Welding Society (AWS) D18.2 color chart [1] in the 2002–2009 editions. In 2004, an additional study was conducted by Ernie Benway and Sunniva Collins of Swagelok Company to identify acceptable discoloration levels on the weld bead and HAZ [2]. The test was conducted on type 316L stainless steel tubes using the ASTM G150 critical pitting temperature (CPT) test. At the time, the results of this study were considered proprietary information.

The summary of that report stated: "All samples were visually inspected under a microscope at 10X magnification. CPT results illustrate in both electropolished (EP) and mechanically polished (MP) conditions, that as the oxygen increases, the pitting resistance decreases as measured in 1M [sodium chloride] NaCl. Pitting occurred in most samples in the HAZ, both upstream and downstream of the weld bead" [2].

In 2010, another study was performed using representative discoloration levels in the HAZ and was published in *Pharmaceutical Engineering®* in November 2011 [3]. In this case, a modified ASTM G61 cyclic polarization test was used to determine the critical pitting potential of each sample. The study concluded:

> *"Even with color in the HAZs, enhancements such as passivation, electrochemical cleaning, or electropolishing when performed properly will further improve the corrosion resistance in that area of concern. The passivation process may not completely remove color from the HAZ but will improve the corrosion resistance to acceptable levels. Electrochemical cleaning and electropolishing will not only remove the color from the welds and HAZ, but also improve corrosion resistance to acceptable ranges without requiring welds be ground to remove metal and without further passivation processes. A color chart recognizing the effects of color for electropolished material should be developed and adopted for the pharmaceutical industry showing accurate acceptable levels of color" [3].*

Based on these 2004 and 2010 studies, the 2012 edition of the BPE Standard was published with color charts developed by the BPE MJ subcommittee with expanded discoloration levels more focused at lower concentrations of oxygen as needed in that industry, and the reference to AWS D18.2 [1] was dropped at that time. The new BPE color chart provided color photographs of welds on both MP and EP interior surfaces of 316L stainless steel tubing [4–5].

Each study had identical results on acceptable color by delineating when and where pitting started to initiate. These studies again centered on the acceptable levels of discoloration in the HAZ and not on the weld bead itself, thus the impetus for the wording on the initial ASME BPE color charts allowing "a light blue to straw color" in the HAZ with "none allowed" on the weld bead itself [2].

Since initial publication, the ASME BPE color charts have had some minor revisions to clarify the intended area of view of the weld bead and HAZ on the weld samples and to reflect changes in the acceptance criteria, as shown in the MJ tables, where no color is allowed on the weld bead.

The release of the raw data from the original corrosion tests performed in 2004 indicated that the testing did include the weld bead, as well as the HAZ. The MJ subcommittee's attention then shifted focus to the amount of allowable discoloration levels not only in the HAZ but also on the weld bead itself. Additional testing was commissioned by MJ representatives, which involved independent laboratories to verify the results of the previous corrosion testing. ASTM G61 cyclic polarization testing evaluates the impact on corrosion resistance caused by residual color from the welding process in the HAZ as well as specifically on the weld bead. A testing protocol was developed and approved by the members of the MJ Subcommittee Task Group.

TESTING PROTOCOL

The purpose of this study is to examine the corrosion resistance effects of weld discoloration on both the weld bead and the HAZ in sanitary process welds. Currently the BPE Standard and industry subject matter experts have stated that any residual color from the welding process (automatic orbital gas tungsten arc welding [GTAW]) that may be acceptable in the HAZ is not allowed on the weld bead. This study was designed to test sanitary weld samples with color in the HAZ as well as any corresponding color on the weld bead for any impact on corrosion resistance with color in the weld bead.

The testing method used is the ASTM G61 cyclic potentiodynamic polarization test, which determines the susceptibility to initiation of localized corrosion given by the potential at which the anodic current increases rapidly due to the initiation of pitting. The solution used in this test program will be identical to the solution used in previous BPE testing for evaluating heat tint. The test area on each specimen will be chosen to evaluate both the HAZ and weld bead areas.

This testing determines the critical pitting potential (CPP) and provides a detailed description of the location of the attack and whether it occurred in the HAZ or weld bead. The coupons of 316L (ASTM A269/A270) stainless steel tubing were welded with automatic welding equipment. Oxygen was introduced into the inside diameter (ID) and monitored with O_2 analyzers controlling the O_2 levels to match the colors previously documented and illustrated in the ASME BPE color chart.

Both EP and MP coupons were tested using the same protocol and test parameters meeting ASME BPE color chart colors #3 and #4. The inside of the test coupons remain in the as-welded condition. No post-weld treatment or passivation was performed. MJ reviewed the data and added changes to its acceptance criteria to accept corresponding color on the weld bead area as shown in the color charts of the BPE and data from this study. Parts or all the information obtained may be used for inclusion into the BPE Standard, Part MJ, subsequent nonmandatory appendices, and industry white papers.

Figure 1: Masked inside surface of EP (left) and MP (right) samples.

Table 1: Testing parameters for welding samples.

Initial Delay (open circuit monitoring):	1 hour
Initial Potential:	1-hour open circuit potential (Eoc)
Scan Rate:	0.167 millivolt per seconds (mV/s)
Maximum Potential:	1 Volt (V)
Final Potential:	1-hour Eoc

TESTING

The test samples were approximately a 1-inch segment, 2-inches long, cut from a 2-inch x 0.065-inch wall 316L stainless steel tube containing an orbital weld. The prepared pre-test samples are shown in Figure 1. The ID surface was designated as the test surface.

Each sample was prepared by spot welding a 1/16-inch-diameter wire to the backside outside diameter (OD). The wire connection, backside, and edges were masked with silicone paint (see Figure 1). The exposed ID surface was measured to be approximately 11 cm^2. A standard three electrode electrochemical cell as described in ASTM G61 was used with an appropriate verified counter electrode, reference electrode, and the prepared samples as the working electrodes. The solution was deaerated with nitrogen prior to and during the test periods, maintained at 25°C. The immersed electrodes were connected to a calibrated Gamry Instruments potentiostat. Each potentiostat was programmed to perform the ASTM G61 test with the parameters as listed in Table 1.

Figure 2: Scans: EP (red), MP (blue).

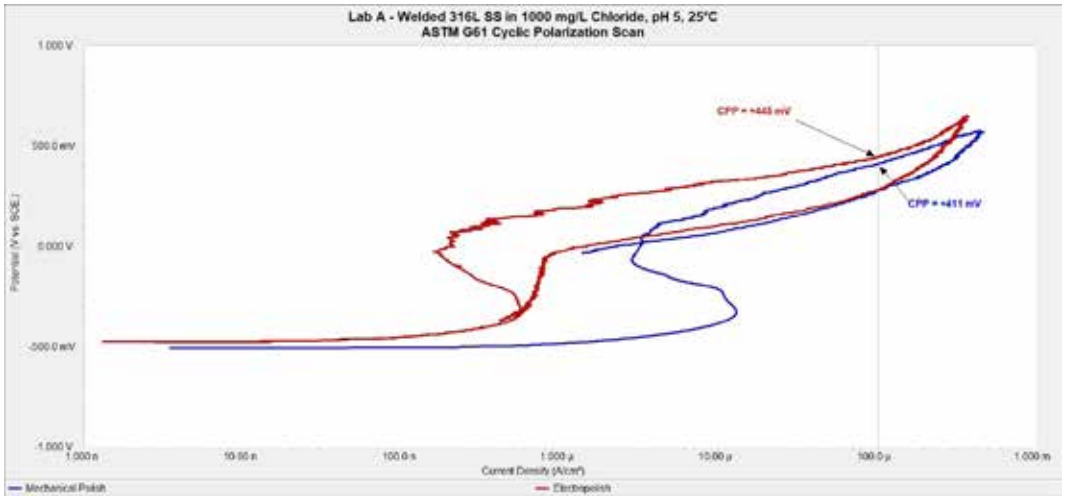


Table 2: The collected potential and current data were plotted using Gamry's Echem software.

Sample	CPP
MP	+411
EP	+445

The collected potential and current data were plotted using Gamry's Echem software. All specimens exhibited similar behavior. The CPP was determined as the potential at which the current density exceeds 100 µA/cm² (see Table 2).

Overlays of the plotted electrochemical data are presented in Figure 2.

Visual examination of the exposed test specimens confirmed the presence of pitting corrosion on each sample primarily in the HAZ of all samples. Little or no pitting occurred on the weld bead and non-HAZ tube area. Individual close-up images of the weld bead and HAZ areas are presented in Figure 3.

Figure 3: EP (left) and MP (right) sample after testing.

SUMMARY

The review of past available data provided results that showed a lower level of color present on the weld bead with a higher level of corrosion resistance based on the CPP data. The location and amount of pitting occurring on the weld bead was much less compared to the HAZ. The testing, earlier described, was then performed to confirm these historical results and suggest changes in the weld acceptance criteria in the MJ tables. This was to allow for color on the weld bead, as shown in the MJ color chart for the weld bead, to be acceptable as in the HAZ.

The need for this work was based on two previous studies that evaluated acceptable levels of weld discoloration. This study proved that the light color on the weld bead, as seen in the color charts and in this study, provided little or no pitting corrosion and should be within the acceptance criteria.

The following technical studies provided the basis for observations that some level of discoloration was present on weld beads that otherwise met the BPE weld acceptance criteria in MJ's tables for the HAZ. They also provided corrosion testing data that could confirm that pitting initiation occurred in the HAZ and not the weld bead itself with a very small amount of pitting occurring on the tubing base metal area outside the weld.

2004 Study (Released in 2020)

This study [2] evaluated the CPT of 316L stainless steel (MP and EP) welds made with varying levels of oxygen in the shielding

gas. The tests were performed in accordance with ASTM G150 using 1M NaCl as the electrolyte as in this and other BPE studies. The results showed that CPT values decreased with increasing oxygen content, with the EP samples performing better than the MP samples. Post-test visual examination revealed that pitting was primarily in the HAZ with significantly fewer or no pits in the weld bead or base metal.

This study tested 110 coupons within 18 groups comparing EP and MP 316L stainless steel at oxygen exposure limits of 10–500 ppm oxygen. These samples were tested for CPT in accordance with ASTM G150 using 1M NaCl solution and visually inspected for color and pit location.

Interestingly, the results showed that of the 14 samples at 50 ppm oxygen exposure welds, their CPT averaged 11.0°C for EP samples and 6.2°C for MP samples. The pit locations for the 50 ppm oxygen coupons and all other 96 samples showed the weld bead had the lowest number of pits identified in the entire weld area, while the HAZ area was significantly higher (10–50 times more than on the weld bead).

2011 Study

This study [3] determined the critical pitting potential (CPP) of 316L stainless steel (MP and EP) welds made with varying levels of oxygen. The purpose of this test program was to relate pitting corrosion resistance to weld discoloration and evaluate the effect post-weld surface treatments may have on corrosion resistance. The tests were performed in accordance with ASTM G61 and modified to use an alternate test solution: 1,000 ppm chloride as NaCl at a pH of 5.0.

The results showed decreasing resistance to pitting corrosion (lower CPP values) with increasing oxygen (discoloration). When performed properly, post weld surface treatments were determined to be effective at increasing the CPP values of discolored welds. The data also indicated that the CPP values of base metal and weld metal were higher than values obtained on the HAZ.

This article [3] contains data showing that welds made at or near 50 ppm oxygen exposure in the purge gas during welding compared to the AWS D 18.2 color chart at level #3. These welds produced test results that this level of weld color "will have no effect on the corrosion resistance recognized in the pharmaceutical industry for EP 316L stainless steel material" [3]. The study used 13 samples that were studied at weld conditions from 316L base material with welding shielding gas at 20, 50, and 80 ppm oxygen, with and without electropolishing and passivation treatments.

CONCLUSION

The referenced studies presented facts that were used to guide the current investigation. The current study was undertaken to confirm that the HAZ of a 316L stainless steel weld with discoloration was more susceptible to pitting corrosion than the weld bead with lower amounts of color or surrounding base metal when tested per ASTM G61 using the modified test solution. The results from this study confirm that the weld bead can have corresponding color and be acceptable. The HAZ is the more susceptible area of a discolored weld. This is because observed pitting was predominantly in the HAZ with little or no pitting in the weld bead or base metal.

The results from all four studies demonstrate that the weld HAZ is more prone to pitting corrosion than the weld bead or base metal. The criteria for color acceptance on the weld bead was correctly changed from "no color" to "acknowledged color" from the color charts on the weld bead as confirmed in this study.

Acknowledgements

Corrosion Testing Laboratories, Inc. and Astro Pak Corporation provided the required corrosion testing and financial support for this study, and Cotter Brothers Corporation provided the welding and sample coupons and financial support in the development of this study. We would also like to acknowledge the following MJ members for their work in the development of this paper and for serving as the editorial review group.

Ken Kimbrel – ASME BPE Past Chair / VNE Corporation Co-Author
Curtis Elkins – MJ member, Past Vice Chair / CSI Pharmacy
Daryl Roll – MJ contributor / AstroPak Corporation Co-Author
Randolph Cotter – MJ member, Past Chair/ Cotter Brothers
Jim Dvorscek – MJ member, Past Chair / Vessel and Weld Inspection Services, LLC
Ernie Benway – MJ contributing member / Ironwood Specialist Inc.
Jim Fritz – MJ member / JDF Metal Consulting
Cullen Weeks – MJ member / RGD Project Management, Inc.
William Daprile – MJ Member / Eli Lilly & Company

References

1. American Welding Society. "AWS D18.2 Guide to Weld Discoloration Levels on Inside of Austenitic Stainless Steel Tube." Published 1999.
2. Benway, E., and S. Collins. "Weld Discoloration Study." Swagelok Corporation. Published 2020.
3. Kimbrel, K. "Determining Acceptable Levels of Weld Discoloration on Mechanically Polished and Electropolished Stainless Steel Surfaces." *Pharmaceutical Engineering* 31, no. 6 (November/December 2011).
4. American Society of Mechanical Engineers. "ASME BPE-MP Discoloration Acceptance Criteria for Welds and Heat-Affected Zones on Mechanically Polished UNS S31603 Tubing." Published 2022.
5. American Society of Mechanical Engineers. "ASME BPE-EP Discoloration Acceptance Criteria for Welds and Heat-Affected Zones on Electropolished UNS S31603 Tubing." Published 2022.

About the authors

Ken Kimbrel is the Product Manager of Special Alloys for VNE Corporation. He has an extensive background in engineering and equipment manufacturing, and he is a NACE International certified corrosion technician. He is Past Chairman of the ASME BPE Standard. Ken attended Tulsa Community College. He joined ISPE in 2002.

Brad Krantz is Vice President of Laboratory Services at Corrosion Testing Laboratories, Inc. He is an Association for Materials Protection and Performance (AMPP)/NACE International certified materials selection/design specialist. Brad has over 30 years of experience in corrosion engineering, applying laboratory studies to solve corrosion- and materials-related issues. He is an active member in AMPP, ASM International, and ASTM International. He attended Iowa State University.

Daryl L. Roll, PE, is Technology Consultant at Astro Pak Corporation, providing technology support requirements for the sales and operations teams. Daryl serves as Astro Pak's primary senior technical advisor to clients and employees for corrosion, surface chemistry, and stainless steel passivation. He is a member of American Society of Mechanical Engineers: Bioprocessing Equipment, providing support to the subcommittees for surface finish, material joining, and metallic materials (member) requirements. He has been a contributor to many of the passivation, rouge, and surface chemistry task groups. His papers on passivation and rouge control have been published in *Pharmaceutical Engineering, IEEE Micro,* and *Chemical Engineering Journal.* Daryl holds a degree in chemistry and earth science from the California State University of Fullerton and a professional engineer's license from the state of California.

ARTIFICIAL INTELLIGENCE GOVERNANCE in GxP Environments

By Armand Mintanciyan, Rory Budihandojo, John English, HCCP, Orlando Lopez, Jose E. Matos, and Robert McDowall, PhD

Artificial intelligence (AI) is used by pharmaceutical and biotech companies, providing support from drug discovery through manufacturing. The nature of AI and concerns of bias, privacy, transparency, and security in a regulated industry necessitate a governance framework to ensure concerns are controlled using "guardrails." These guardrails ensure the quality, privacy, and security of data used in AI applications. This article provides a recommended approach to implementing guardrails through several policies and procedures and discusses AI governance, which defines data ownership, consent, and access policies and procedures.

This article provides points to consider for those implementing AI in a GxP environment. At a high level, these include governance for AI, as well as for machine learning operations (MLOps). MLOps is a set of practices that automate and simplify machine learning (ML) workflows and deployments [1]. This article also provides the relationship between AI and MLOps and why both are important in an AI implementation.

Definitions for AI, generative AI, ML, and deep learning (DL) can be found in ISO/IEC Standard 22989, "Information Technology — Artificial Intelligence — Artificial Intelligence Concepts and Terminology" [2]. Within this article, security and cybersecurity are used interchangeably, with the definition for cybersecurity found in the National Institute of Standards and Technology's Glossary [3].

AI USE: FROM DRUG DESIGN TO DISTRIBUTION

AI is used throughout drug discovery, drug product development, clinical development, manufacturing, and distribution. Within drug discovery, drug design (e.g., target protein structure prediction) and drug screening (e.g., bioactivity prediction, toxicity prediction, and physicochemical property prediction) are impacted areas benefiting from AI [4]. Note that drug design is out of regulatory scope; it would be best business practice to implement policies and procedures noted within this document. In drug product development, AI assists in deciding suitable excipients, monitors and modifies the development process, and ensures in-process specification compliance [4].

Clinical trial design and monitoring (e.g., subject enrollment/selection, patient drop out, and trial monitoring), manufacturing (e.g., automated manufacturing, personalized manufacturing, and correlating manufacturing errors to set parameters), and quality assurance/quality control (e.g., electronic lab notebooks) use AI to improve decision-making as well [4].

In post-marketing, AI could also be used to analyze data to predict a new indication or usage of the drug by using real-world data collected after the drug was marketed and/or in combination with the pre-marketing data. The drug's new indication or usage may extend the drug's patent expiration date.

AI-associated processes, such as data collection, processing, analysis, storage, and utilization of algorithms to derive decisions, would require guardrails to assure data quality and integrity so that the results are accurate, reliable, trustworthy, and explainable.

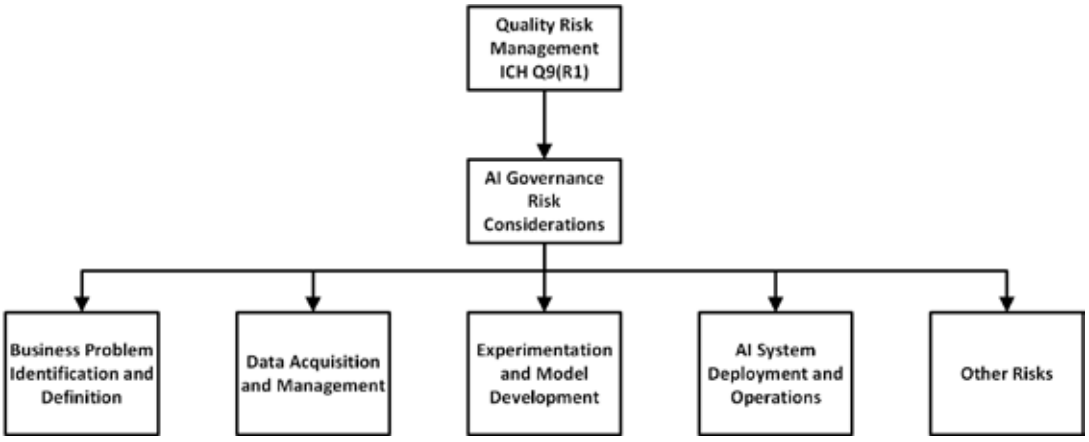
AI GOVERNANCE

AI governance is a system of laws, regulations, policies, controls, frameworks, standards (e.g., ISO/IEC Standard 42001, "Information Technology Artificial Intelligence — Management System"), practices, and processes at international, national, and organizational levels to manage, regulate, and optimize software application development, deployment, and usage within an organization. AI governance allows AI-applicable technology stakeholders to manage, regulate, optimize, implement, and oversee the use of AI technology [5]. It also helps manage associated risks to ensure AI aligns with stakeholders' objectives, is developed and used responsibly and ethically, and complies with applicable requirements [5].

AI governance could further set ethical principles by controlling how AI is developed, implemented, and used. Consistent, end-to-end AI governance would enhance internal capabilities through methodologies and tools that address critical ethical requirements such as accountability, fairness, privacy, transparency, and robustness.

The recommended approach for AI governance throughout this document could be seamlessly integrated with *ISPE GAMP® 5*

Figure 1: AI-specific risks as outlined in ICH Q9.



Guide: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition) [6]. It is recommended to implement operational processes, as defined in *GAMP® 5, Second Edition* Appendix O - Introduction to Operation Appendices (e.g., corrective and preventive action), and quality risk management processes.

Quality Risk Management

Quality risk management (QRM) processes as per "ICH Harmonised Tripartite Guideline Q9: Quality Risk Management" (e.g., risk assessment, risk control, and risk review) must be implemented [7]. However, the following risks specific to AI would need to be considered [8]:

The implementation and/or use of the policies and procedures noted throughout this article should be conducted considering a risk-based approach, with only a subset of the documents recommended being implemented for lower-risk systems. Overall risk should be determined by impact to patient, product, and data integrity.

A quality management system (QMS) in alignment with the Pharmaceutical Inspection Convention Pharmaceutical Inspection Co-Operation Scheme (PIC/S) "PIC/S Guide to Good Manufacturing Practice for Medicinal Products - Part I" [9] and Code of Federal Regulations - Part 820 - Subpart B - Quality System Requirements [10] is recommended to be in place. This is to provide the quality oversight needed to provide overall assurance to the output generated by the AI (i.e., ML, DL, or generative) systems used to aid in developing, manufacturing, or distributing a drug product.

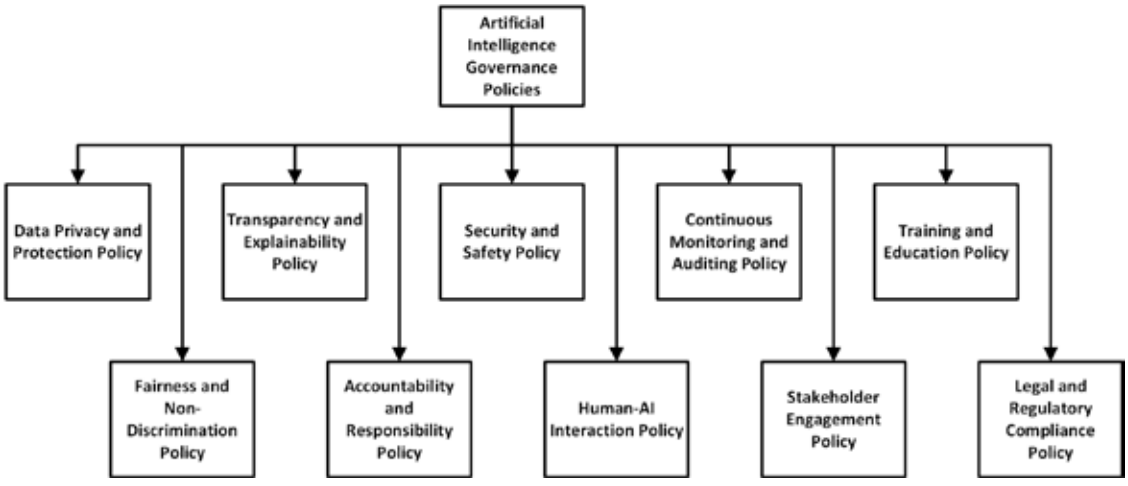
AI GOVERNANCE POLICIES

Creating policies for an AI governance framework is essential to ensure that AI systems are developed, deployed, and managed responsibly and ethically. It ensures the systems are tested and validated for GxP intended use and comply with data governance

Table 1: A categorical list of AI risks and topics for consideration.

Risk Area	Topics for Consideration
Business problem identification and definition	• Regulatory compliance risk • Missing ethics risk • Risk of unexpected consequences • Risk of missing risk rating and classification • Missing security and privacy requirements risk • Inadequate/improper business process design
Data acquisition and management	• Data set selection or bias risk • Data quality and missing data risk • Data labeling risk • Missing regulatory and compliance data check • Data privacy risk • Adversarial attack risk (cyber) • Data ownership and stewardship • Data standards and architecture
Experimentation and model development	• Lack of sensitivity and scenarios analysis risk • Model assumption, limitations, selection, transparency, fairness, evaluation, use, and impact risk • Missing lineage risk
AI system deployment and operations	• Human supervision risk • Technology integration and scalability risk • Model performance and behavior change risk • Fallback procedure risk • Adversarial attacks (cyber) • Cybersecurity
Other risks	• Bias and fairness • Lack of transparency and regulation • Security and ethical concerns • Data privacy • Dependence and reliability

Figure 2: AI governance policies.



and cybersecurity policies and regulations. The following are some key policies that organizations should consider implementing as part of their AI governance framework [11–13].

Data Privacy and Protection

Establish a policy for AI systems. Ensure compliance with data protection laws such as collecting, storing, and processing data used in the General Data Protection Regulation, California Consumer Privacy Act, and EU AI Act. Define obtaining informed consent, anonymizing data, and protecting sensitive information.

Fairness and Nondiscrimination

Develop a policy to prevent and mitigate bias and discrimination in AI systems. It includes conducting regular audits to identify and address sources of bias in data, algorithms, and models. Establish guidelines for fairness testing and validation.

Transparency and Explainability

Create a policy to ensure that AI systems are transparent and explainable. Provide documentation and explanations of AI models, decision-making processes, and outcomes. Make sure that stakeholders can understand and trust AI systems.

Accountability and Responsibility

Define clear roles and responsibilities for developing, deploying, and managing AI systems. Assign accountability for addressing issues such as bias, discrimination, and errors in AI systems. Establish procedures for reporting and addressing AI-related incidents.

Security and Safety

Implement a policy to ensure the security and safety of AI systems. Protect AI systems from unauthorized access, tampering, and attacks. Establish guidelines for secure coding practices, vulnerability assessments, and incident response.

Human–AI Interaction

Develop a policy for human–AI interaction, including guidelines for human oversight and intervention in AI systems. Define procedures for handling situations where AI systems provide incorrect or harmful recommendations.

Continuous Monitoring and Auditing

Create a policy for continuous monitoring and auditing of AI systems. Establish the tracking of the performance and impact of AI systems over time. Regularly review and update AI models to meet ethical and legal standards.

Stakeholder Engagement

Establish a policy for engaging with stakeholders, including employees, customers, regulators, and the public. Gather input and feedback on AI systems to ensure alignment with the values and needs of the community.

Training and Education

Implement a policy for training and education on AI ethics, best practices, and governance. Provide resources and support for employees and other stakeholders to build a culture of responsible AI.

Legal and Regulatory Compliance

Develop a policy to ensure AI systems comply with relevant laws and regulations. Establish conducting legal and regulatory assessments of AI systems.

AI GOVERNANCE FRAMEWORK PROCEDURES

Creating procedures for an AI governance framework is essential to operationalizing the policies established in the framework. This section includes essential procedures that organizations should consider implementing as part of their AI governance framework [11–13].

Data Management
Establish a procedure for collecting, storing, and processing GxP data used in AI systems. Define steps for data cleaning, validation, and transformation. Ensure that data is representative, unbiased, and of high quality.

Bias Detection and Mitigation
Develop a procedure for identifying and addressing bias in AI systems. Define steps for conducting fairness audits, analyzing sources of bias, and implementing bias mitigation techniques.

Model Development and Validation
Create a procedure for developing and validating AI models. Define feature selection, model training, hyperparameter tuning, and model evaluation steps. Ensure that models are robust, accurate, and generalizable.

Continuous training and continuous testing (or retesting) should be considered where the addition of data, fine-tuning of the algorithm(s), and/or retraining of the model occur. In addition, new patterns of bias should be investigated.

Transparency and Explainability
Establish a procedure for providing transparency and explainability in AI systems. Define steps for generating explanations, visualizations, and documentation of AI models and decision-making processes. The verification of AI-generated content would need to be considered by cross-referencing the information with credible sources; verifying facts, statistics, and claims against multiple trustworthy references; monitoring the AI's performance and reviewing its output regularly; and assessing the generated content for potential biases, errors, or inconsistencies [14].

Security and Safety
Implement a procedure for ensuring the security and safety of AI systems. Define steps for conducting vulnerability assessments, implementing secure coding practices, and responding to security incidents.

Human–AI Interaction
Develop a procedure for human–AI interaction, including human oversight and intervention in AI systems. Define steps for handling situations where AI systems provide incorrect or harmful recommendations.

Monitoring and Auditing
Create a procedure for continuous monitoring and auditing of AI systems. Define steps for tracking performance metrics, conducting impact assessments, and updating AI models.

Stakeholder Engagement
Establish a procedure for engaging with stakeholders, including employees, customers, regulators, and the public. Define steps for gathering input, addressing concerns, and incorporating feedback into AI systems.

Training and Education
Implement a procedure for providing training and education on AI ethics, best practices, and governance. Define steps for conducting training sessions, providing resources, and assessing knowledge and skills.

Incident Response
Develop a procedure for responding to AI-related incidents, such as bias, discrimination, and errors. Define steps for reporting incidents, conducting investigations, and implementing corrective actions.

Legal and Regulatory Compliance
Create a procedure for ensuring compliance with relevant laws and regulations. Define steps for conducting legal and regulatory assessments, obtaining approvals, and maintaining documentation. It's recommended to add a compliance issue escalation process (including responsibilities) to this procedure.

MLOps PROCEDURES
MLOps is a set of practices that unifies ML system development and operations (Ops). It aims to automate the end-to-end ML life cycle, ensuring faster experimentation, deployment, reproducibility, and monitoring. For a robust MLOps framework, several procedures should be established [15]. By establishing these procedures within an MLOps framework, organizations can streamline the ML life cycle, ensuring faster deployments, scalability, reproducibility, and maintainability of ML systems.

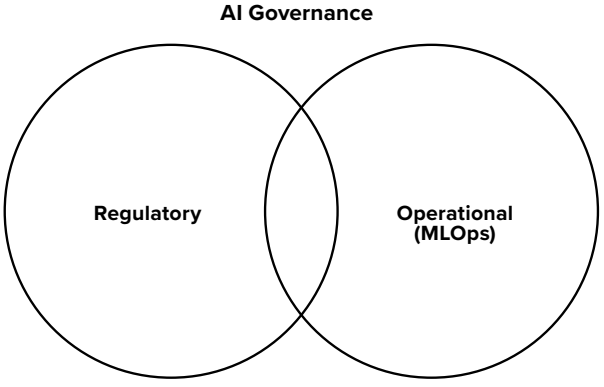
Version Control
Use version control systems for code, data, and model artifacts, and to ensure traceability of changes and facilitate collaboration among team members.

Data Management
This procedure should define protocols for data collection, storage, preprocessing, and validation; implement data versioning to track changes and ensure reproducibility; and monitor data for drifts or anomalies that might affect model performance.

Model Development and Validation
This procedure should establish coding and architecture standards for model development, implement automated testing for model validation, and use techniques like cross-validation to assess model performance. It should be used in addition to computer validation (e.g., *GAMP® 5, Second Edition* expectations).

Continuous Integration and Continuous Deployment (CI/CD)
This procedure should automate the integration of new code, data, or model changes. It should ensure automated testing at

Figure 3: The relationship between regulation and operations (MLOps) in AI governance.



each integration step and automate the deployment of validated models to production.

Model Monitoring and Logging

This procedure should monitor deployed models for performance degradation or drift and log model predictions, inputs, and anomalies for traceability and debugging.

Model Retraining and Fine-Tuning

This procedure should define criteria for when and how models should be retrained and automate the retraining process using updated data or when performance drops below a threshold.

Experiment Tracking and Management

This procedure should use tools to track and manage multiple experiments, hyperparameters, and results. It should also ensure reproducibility by logging experiment details and outcomes.

Infrastructure and Environment Management

This procedure should define protocols for provisioning, managing, and scaling infrastructure resources. It should also ensure consistency in development, testing, and production environments using containerization or virtualization.

Model Interpretability and Explainability

This procedure should implement tools and practices to interpret and explain model predictions and should ensure stakeholders understand model decisions, especially in critical applications.

Model Security and Compliance

This procedure should establish protocols for model security, including access controls and encryption, and ensure compliance with data privacy regulations and industry-specific standards.

Feedback Loop

This procedure should implement mechanisms to gather feedback from end-users or system interactions and then use feedback to improve models and address any issues or concerns.

Rollback and Disaster Recovery

This procedure should define protocols for rolling back deployments in case of failures or issues and ensure backup and recovery mechanisms for data, code, and models.

Collaboration and Communication

This procedure should facilitate collaboration among data scientists, ML engineers, DevOps, and other stakeholders. It should ensure clear communication channels for updates, issues, or changes in the MLOps pipeline.

MLOPS AND AI GOVERNANCE RELATIONSHIP

MLOps and AI governance are essential for responsible, effective AI development and deployment. They are closely related and complement each other but focus on different aspects of the AI life cycle. The following sections explain how they are related [16].

Relationship

MLOps focuses on the operational aspects of ML, including model development, deployment, monitoring, and maintenance. It aims to automate and streamline the ML life cycle, improve collaboration between teams, and ensure the reproducibility and scalability of models.

AI governance focuses on AI's ethical, legal, and social aspects, including fairness, transparency, accountability, and privacy. It aims to establish guidelines, policies, and procedures for the responsible and ethical development, deployment, and management of AI systems. This incorporates the regulatory expectation for thorough and reliable AI governance.

MLOps and AI governance overlap in model monitoring, validation, and documentation. MLOps provides the tools and practices for implementing these activities, whereas AI governance provides the principles and standards for guiding these activities. MLOps and AI governance emphasize the importance of stakeholder engagement, continuous improvement, and compliance with laws and regulations. They work together to ensure that AI systems are aligned with the values and needs of the community.

Implementation

Practices of AI governance and MLOps are considered together when developing the overall AI paradigm. This is to ensure governance is practical and implementable, and that complete and operational paradigms are capable of conforming to governance.

AI governance can be integrated into MLOps by incorporating ethical considerations into operational workflows. For example, MLOps can include bias detection and mitigation steps in model development pipelines, and model monitoring systems can track fairness and performance metrics.

Some examples (though not an exhaustive list) of procedural and technical controls, or guardrails, include:

- For US FDA–regulated drug companies: "21 CFR Part 11, Data Integrity and Compliance with Drug CGMP - Questions and Answers," *GAMP® 5, Second Edition*, and associated ISPE Good Practice Guides
- For EU-regulated drug companies: "EudraLex Volume 4 Annex 11"
- For UK-regulated drug companies: "Medicines & Healthcare Products Regulatory Agency (MHRA) 'GXP' Data Integrity Guidance and Definitions"

Benefits

MLOps and AI governance provide a comprehensive approach to AI development and deployment. MLOps ensures that AI systems are efficient, reliable, and scalable, whereas AI governance ensures that AI systems are ethical, transparent, and accountable. By combining MLOps and AI governance, organizations can achieve operational excellence and ethical responsibility in AI. It can lead to better AI outcomes, more significant AI impact, and higher AI trust.

MLOps and AI governance are closely related and complementary to the AI life cycle [17]. They work together to ensure that AI systems are operationally effective and ethically responsible. Organizations should integrate MLOps and AI governance to achieve the best AI development and deployment results.

CONCLUSION

Effective AI governance implementation requires collaboration across different departments and levels of an organization. It involves establishing a governance framework, defining roles and responsibilities, implementing technology solutions, and fostering an AI-driven culture. By adhering to AI governance principles, organizations can maximize the value of their AI assets while mitigating risks associated with poor AI quality. This includes escalation of GxP compliance issues that could impact quality attributes and data integrity principles and their resolution.

References

1. Amazon. "MLOps." Accessed 25 February 2024. https://aws.amazon.com/what-is/mlops/
2. ISO/IEC Standard 22989. "Information Technology — Artificial Intelligence — Artificial Intelligence Concepts and Terminology." July 2022. www.iso.org/standard/74296.html
3. National Institutes of Standards and Technology. "Glossary - Cybersecurity." Accessed February 2024. https://csrc.nist.gov/glossary/term/cybersecurity
4. Debleena, P., G. Sanapz, S. Shenoyz, D. Kalyane, K. Kalia, and R. Tekade. "Artificial Intelligence in Drug Discovery and Development." *Drug Discovery Today* 26, no. 1 (2021):82.
5. IAPP. "Key Terms for AI Governance." Updated November 2023. https://iapp.org/resources/article/key-terms-for-ai-governance/
6. International Society for Pharmaceutical Engineering. *GAMP® 5 Guide: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)*. North Bethesda, MD: International Society for Pharmaceutical Engineering, 2022.
7. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. "ICH Harmonised Tripartite Guideline Q9: Quality Risk Management." Published November 2005. https://database.ich.org/sites/default/files/Q9%20Guideline.pdf
8. Ping, D. *The Machine Learning Solutions Architect Handbook, 2nd Ed*. Birmingham, UK: Packt Publishing Ltd., 2022.
9. Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-Operation Scheme. "PIC/S Guide to Good Manufacturing Practice for Medicinal Products - Part I." Published August 2023. https://picscheme.org/docview/6606
10. US Food and Drug Administration. "CFR - Code of Federal Regulations Title 21, Part 820 - Subpart B - Quality System Requirements." October 1996. www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11
11. General Accounting Office. *Artificial Intelligence, an Accountability Framework for Federal Agencies and other Entities*. Accessed 1 December 2023. www.gao.gov/assets/gao-21-519sp.pdf
12. European Commission. *Laying Down Harmonised Rules on Artificial Intelligence (Artificial Intelligence Act) and Amending Certain Union Legislative Acts*. 21 April 2021. https://artificialintelligenceact.eu/the-act/
13. National Institute of Standards and Technology. *Artificial Intelligence Risk Management Framework (AI RMF 1.0)*. January 2023. https://nvlpubs.nist.gov/nistpubs/ai/NIST.AI.100-1.pdf
14. AIContentfy. "Quality Control: How to Verify AI Generated Content." 6 November 2023. https://aicontentfy.com/en/blog/quality-control-how-to-verify-ai-generated-content
15. Microsoft. "Machine Learning Operations (MLOps) Framework to Upscale Machine Learning Lifecycle with Azure Machine Learning." Accessed 13 December 2023. https://learn.microsoft.com/en-us/azure/architecture/ai-ml/guide/mlops-technical-paper/
16. Darnell, D. "MLOps and AI Governance, A Difference of Perspective." Dataiku. 21 June 2023. https://blog.dataiku.com/mlops-and-ai-governance-a-difference-of-perspective/
17. IBM. "AI Model Lifecycle Management: Overview." 9 November 2020. www.ibm.com/blog/ai-model-lifecycle-management-overview/

About the authors

Armand Mintanciyan is an independent consultant at Reliable Data, LLC, providing services to global pharmaceutical, biotech, and medical device companies. He has been involved with compliance, auditing, quality assurance, computer validation, and remediation of global enterprise information technology (IT) systems (e.g., enterprise resource planning, supply chain management, data analytics, Veeva [clinical, regulatory, quality], IT infrastructure, and process automation) for over 30 years. His areas of expertise are data integrity, data governance, risk management, quality management systems, and consent decree remediation. Armand holds a bachelor's degree in life sciences from the New York Institute of Technology. He joined ISPE in 1995.

Rory Budihandojo has over 40 years of industry experience in research and development, manufacturing, quality control, quality assurance, and IT. He was a co-founder and former chairman of GAMP Americas. He has various validation experience in GxP audits, remediation, and quality management system improvement. He is an expert in computer system validation (CSV) and data integrity. He joined ISPE in 1993.

John English, HCCP, is a Principal/Consultant in a private practice and has over 25 years of experience in review and validation of US FDA–regulated computer systems, both on-site and remotely. He is an expert in 21 CFR Part 11, data integrity, cloud and virtualization issues, analysis of FDA 483, and warning letters. John has served on the FDA-PDA Data Integrity Task Force and is a current member of GAMP Special Interest Group on AI and ML. He holds master's degrees from the University of Connecticut and Seton Hall University (SHU) and a certificate in US healthcare compliance from the SHU School of Law. He joined ISPE in 2002.

Orlando Lopez has worked for the past 30 years in the areas of worldwide pharmaceutical computer compliance, including US FDA and EU Annex 11 in the production and quality control systems relevant to the manufacture of medicinal products. He is a subject matter expert on CSV, e-records integrity, and worldwide computer compliance. His specialties are e-records integrity and computer trustworthiness. He joined ISPE in 1997.

Jose E. Matos has over 30 years of experience in biopharmaceutical, pharmaceutical, OTC manufacturing, global information technology (IT) system operations, engineering design firms, and chemical and petrochemical operations. His areas of expertise include instrumentation engineering, process control and automation engineering, QA e-Compliance, information technology (IT), industrial control system (ICS) cyber security, digital forensics, data recovery, and IT and cyber security compliance audits. He is a part-time university professor, teaching engineering and technology courses. He joined ISPE in 1993.

Robert (Bob) McDowall, PhD, is an analytical chemist with over 50 years of experience, including 15 years working for two pharmaceutical companies, 30 years as a consultant, and over 35 years in CSV. Bob writes the Questions of Quality column for *LCGC International* and the Focus on Quality column for *Spectroscopy*. He edited the first book on a laboratory information management system (LIMS) and is the 1997 LIMS Awardee from the LIMS Institute. He has written two books on validation of chromatography data systems and one on laboratory data integrity. He also contributed to the *ISPE GAMP® Guide: Records and Data Integrity* and four ISPE GAMP® Good Practice Guides. He is the co-author of the *USP <1058>: Analytical Instrument Qualification's* current draft and the European Compliance Academy's *Guide for an Integrated Lifecycle Approach to Analytical Instrument Qualification and System Validation*. He joined ISPE in 1998.

ROOM DIFFERENTIAL PRESSURES IN FACILITY DESIGN: FUNDAMENTALS

By Norman Goldschmidt, Nicholas R. Haycocks, and Ulla Thomsen

The expectations for room differential pressures to maintain air quality in pharmaceutical facility design are consistent and well defined from a regulatory perspective. However, there is no common approach to the design, monitoring, or alarming of area differential pressures. This article explores differential pressure concerns in aseptic manufacturing, or cleanroom classes B, C, and D.

BACKGROUND ON DIFFERENTIAL PRESSURE CONCERNS

The expectations for differential pressures are well defined by the US Food and Drug Administration (FDA) and EudraLex Annex 1 (see Table 1) [1, 2]. However, there is no common approach to the design, monitoring, or alarming of area differential pressures. This article explores the role of heating, ventilation, and air conditioning (HVAC) systems and the control of air-handling units (AHUs) in aseptic manufacturing. It also discusses differential pressure concerns, including pressure differential measurement, instrument selection and signal processing, alarm delays, door control, and power failure response.

Table 1: Relevant US and EU regulatory guidance on differential pressures.

Regulatory Body	Guidance
US FDA [1]	An essential part of contamination prevention is the adequate separation of areas of operation. To maintain air quality, it is important to achieve a proper airflow from areas of higher cleanliness to adjacent less clean areas. It is vital for rooms of higher air cleanliness to have a substantial positive pressure differential relative to adjacent rooms of lower air cleanliness. For example, a positive pressure differential of at least 10–15 Pascals (Pa) should be maintained between adjacent rooms of differing classification (with doors closed). When doors are open, outward airflow should be sufficient to minimize ingress of contamination, and it is critical that the time a door can remain ajar be strictly controlled. In some cases, the aseptic processing room and adjacent cleanrooms have the same classification. Maintaining a pressure differential (with doors closed) between the aseptic processing room and these adjacent rooms can provide beneficial separation. In any facility designed with an unclassified room adjacent to the aseptic processing room, a substantial overpressure (e.g., at least 12.5 Pa) from the aseptic processing room should be maintained at all times to prevent contamination. If this pressure differential drops below the minimum limit, it is important that the environmental quality of the aseptic processing room be restored and confirmed. The Agency recommends that pressure differentials between cleanrooms be monitored continuously throughout each shift and frequently recorded. All alarms should be documented and deviations from established limits should be investigated.
EudraLex Annex 1 [2]	4.14 Cleanrooms should be supplied with a filtered air supply that maintains a positive pressure and/or an airflow relative to the background environment of a lower grade under all operational conditions and should flush the area effectively. Adjacent rooms of different grades should have an air pressure difference of a minimum of 10 pascals (guidance value). Particular attention should be paid to the protection of the critical zone. The recommendations regarding air supplies and pressures may need to be modified where it is necessary to contain certain materials (e.g. pathogenic, highly toxic, or radioactive products or live viral or bacterial materials). The modification may include positively or negatively pressurized airlocks that prevent the hazardous material from contaminating surrounding areas. Decontamination of facilities (e.g. the cleanrooms and the heating, ventilation, and air conditioning (HVAC) systems) and the treatment of air leaving a clean area, may be necessary for some operations. Where containment requires air to flow into a critical zone, the source of the air should be from an area of the same or higher grade. 4.16 Indicators of air pressure differences should be fitted between cleanrooms and/or isolators and their background. Set points and the criticality of air pressure differences should be considered within the CCS [contamination control strategy]. Air pressure differences identified as critical should be continuously monitored and recorded. A warning system should be in place to instantly indicate and warn operators of any failure in the air supply or reduction of air pressure differences (below set limits for those identified as critical). The warning signal should not be overridden without assessment and a procedure should be available to outline the steps to be taken when a warning signal is given. Where alarm delays are set, these should be assessed and justified within the CCS. Other air pressure differences should be monitored and recorded at regular intervals.

Note that the regulators do not expect pressure differentials to be maintained if a door is opened. Also, the use of a threshold velocity to provide containment is not a common practice for facilities, although it is used for equipment (e.g., unidirectional airflow hoods).

HVAC SYSTEM DESIGN OPTIONS

HVAC system balance plays a critical role in maintaining cleanroom pressure differentials. The supply air volume to a room is calculated based on the air supply required to offset heat and/or humidity gains/losses, dilute particles (for a classified area), and provide pressurization.

There are many HVAC system design variations, with different ways of controlling the relationship between supply and return air volumes used to provide control of room pressurization. Six basic concepts, with some common variations, are described next:

- Fixed-balance system
- Fixed-offset system
- Tracking system
- Direct pressure control system
- Nested loops system
- Hybrid systems

There are many HVAC system design variations, with different ways of controlling the relationship between supply and return air volumes used to provide control of room pressurization.

Fixed-Balance System

In a fixed-balance (or hard-balance) HVAC system, the supply volume is manually set by the air balancer per the design drawings, and return/exhaust volume is then manually adjusted by the air balancer to achieve the desired pressurization. This system must be manually reverified periodically unless the critical pressures are continuously monitored. The system is stable, but it does not respond to unplanned variations in system conditions. One way of addressing this is to add mechanical variable air volume control boxes on the supply.

Fixed-Offset System

In a fixed-offset HVAC system, the supply volume is set electronically, and measured supply flow is maintained by the controller per the design drawings. The return/exhaust volume is set electronically, and measured return flow is maintained by the controller to settings established by the air balancer to achieve the desired pressurization. This system is stable and responds to variations in air-handling system operating conditions, but it does not respond to variations in pressurization in adjacent spaces. Therefore, it must be periodically recalibrated.

Tracking System

In a tracking HVAC system, the supply volume is set electronically, and measured supply flow is maintained by the controller per the design drawings. The return/exhaust volume is measured and adjusted by the controller to maintain an offset from supply volume set by the balancer to achieve the desired pressurization. This system is stable and responds to all variations in the air-handling system conditions. It does not respond to variations in pressurization in adjacent spaces. This system must be periodically recalibrated.

Direct Pressure Control System

In a direct pressure HVAC system, the supply volume is set electronically, and the measured supply flow is maintained by the controller per the design drawings. The return/exhaust volume is controlled directly to achieve desired pressurization. This system responds to variations in air-handling system operation and pressurization in adjacent spaces. It must be periodically recalibrated. The pressurization loop is inactive when the door is opened; if it were not, the system could become unstable when the door is closed. Note that the process can be reversed for negative pressure.

Nested Loops System

In a nested loops (e.g., cascade or master/submaster) HVAC system, the supply volume is set electronically, and the measured supply flow is maintained by the controller per the design drawings. The return/exhaust volume is measured and adjusted by the controller to maintain an offset from the supply, which is set by the balancer. Room pressurization is measured and offset is continually adjusted to achieve the desired pressurization.

This system is stable and responds to variations in air-handling system operation and pressurization in adjacent spaces. This system must be periodically recalibrated. The pressurization adjustment is inactive when the door is opened. Correct selection of the airflow volume measuring and the variable air volume (VAV) control equipment used is critically important. These ensure that flow devices operate in the optimum range to provide the necessary accuracy and control sensitivity.

Hybrid Systems

The five basic systems can be combined to create an almost infinite number of hybrid systems. For example, a system could be designed so that 95% of the return balance is fixed, but a classified corridor extract is connected to a variable exhaust fan to control corridor pressure (either actively or by manual adjustment). This is a very simple and robust system with cost-effective installation and maintenance. Another hybrid system combines a fixed-balance system with pressure-stabilizing dampers for critical rooms and VAV on noncritical rooms and corridors.

Figure 1: Typical example of room pressure control applied to a secondary AHU.

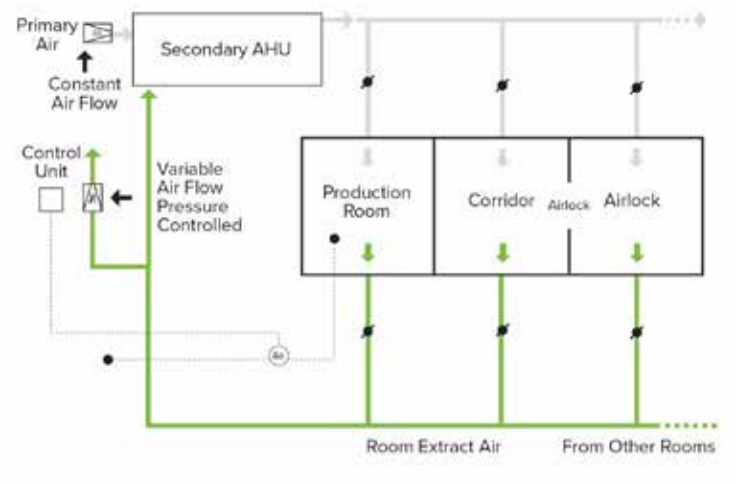
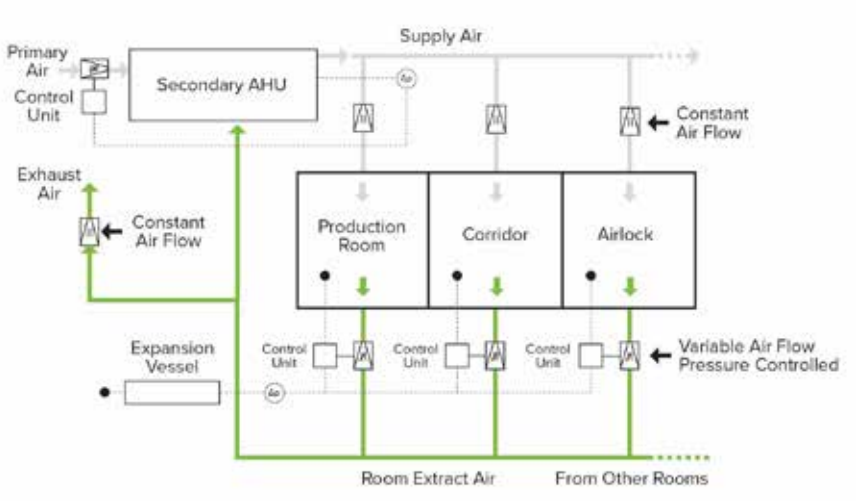


Figure 2: Typical example of secondary AHU control with room pressure controls.



AHU CONTROL

The control of AHUs has a direct impact on the performance of room pressurization controls. In primary/secondary systems (where outside air is provided by a dedicated unit), the control schemes outlined in the preceding section can be applied at the secondary AHU. See Figures 1 and 2 for examples of controls applied to secondary AHUs.

Flow controls should not be applied in series (i.e., room flow control should not be applied in series with AHU flow control). If flow controls are applied in series, the difference in measurement error between the two sets of readings can cause the systems to "fight" each other, with both elements continually hunting and driving a control response that influences the other. This effect is particularly pronounced if the two flow control loops are not programmed and tuned identically.

Providing room pressure controls at the AHU level and again at the room level is not a recommended practice; a simpler system will perform more reliably. AHU fans and primary air should be controlled on supply duct static pressure. If room pressure controls throttle (restrict) the amount of room extract that is returned to the AHU, this amount of air must be made up by primary air. Failing to do so will result in a cascading failure where loss of room pressure results in reduced airflow, which exacerbates the loss of room pressure, and so on.

PRESSURE DIFFERENTIAL MEASUREMENT

Pressure Cascade Specification

The regulatory objective for pressure differentials can be summarized as maintaining a differential of 10–15 Pa (across the airlock) between adjacent rooms with doors closed and maintaining the

Figure 3: Example of a pressure cascade.

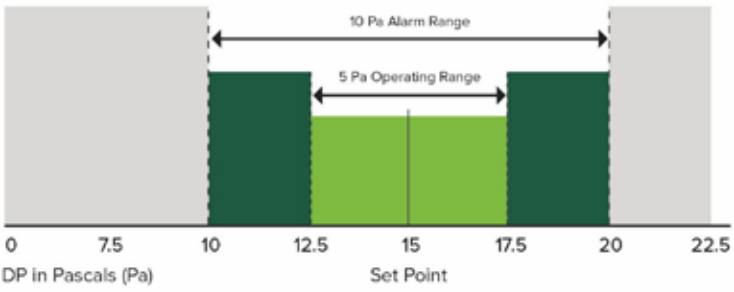
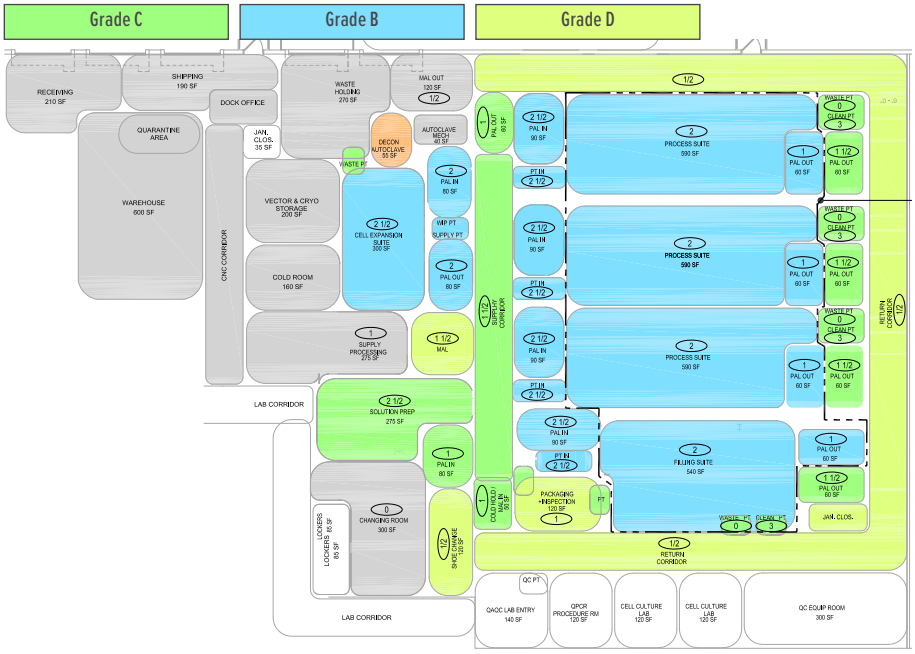


Figure 4: Example of an overall pressurization scheme.



Recommended Pressurization Scheme

Pressurization Steps	Pressure Range Pa				
	Low		Set Point	High	
	Alarm	Alert		Alert	Alarm
0	-5.00	-2.50	0.00	2.50	5.00
1/2	2.50	5.00	7.50	10.00	12.50
1	10.00	12.50	15.00	17.50	20.00
1 1/2	17.50	20.00	22.50	25.00	27.50
2	25.00	27.50	30.00	32.50	35.00
2 1/2	32.50	35.00	37.50	40.00	42.50
3	40.00	42.50	45.00	47.50	50.00
3 1/2	47.50	50.00	52.50	55.00	57.50
4	55.00	57.50	60.00	62.50	65.00
4 1/2	62.50	65.00	67.50	70.00	72.50
5	70.00	72.50	75.00	77.50	80.00

desired airflow direction between rooms with a door open. The *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning* (*HVAC*) [3] suggests that a 5-Pa differential between rooms of the same classification is a minimum to be maintained for product/process separation. This suggests that a differential less than 5 Pa is not robust.

A pharmaceutical plant consists of many production rooms with various cleanliness classifications that must maintain differential pressures to ensure no cross-contamination between the areas. Figure 3 shows an example of a pressure cascade. The target is to provide a positive differential pressure from the cleanliness classification A to D, and from Grade D spaces to the adjacent controlled, not-classified, or nonproduction areas.

A well-designed and commissioned HVAC system should be able to limit room pressure fluctuations within a range of ±2.5 Pa (the lighter green area in the middle of Figure 3); this is the operating range. If the room pressure deviates from the operating range, an alert (warning) should be issued to call for maintenance attention. If the room pressure deviates from the set point by 5 Pa or more for a predetermined period of time, an alarm should be activated (i.e., an action limit/alarm).

Figure 4 presents one possible operating pressure cascade between rooms with set points as well as alert and alarm points in half-step increments (nominally across each door of an airlock). Note that there is no requirement for an equal pressure drop across each door of the airlock. This cascade maintains 10 Pa between the upper and lower operating limits, from clean to the less-clean production rooms, even when both rooms are at the limits of their operating ranges (the lower-room-pressure room at the high end of the operating range and the higher-room-pressure room at the low

Figure 5A: An example of a simple differential pressure monitoring scheme, measuring room to room.

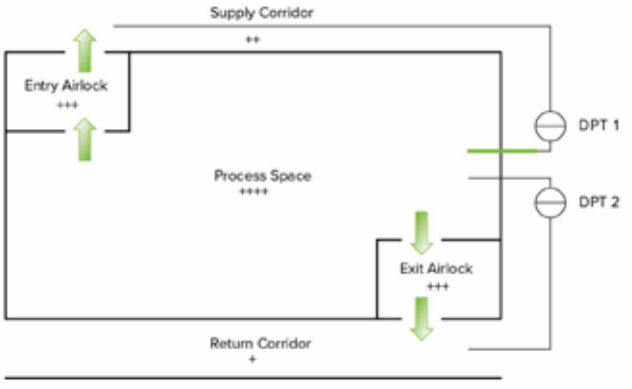
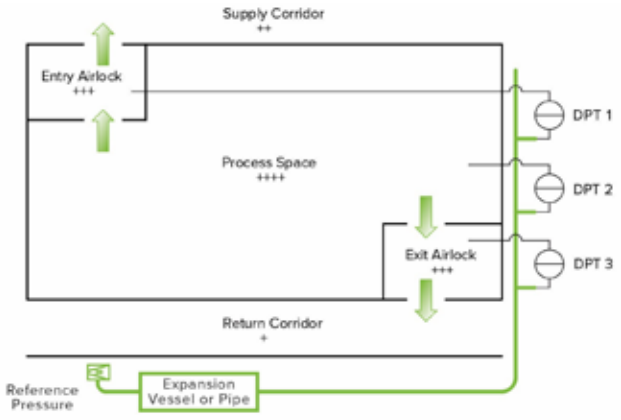


Figure 5B: An example of a simple differential pressure monitoring scheme, measuring from each room to a common reference location.



end of the operating range). This setup also results in manageable velocities across any opening between Grade B and Grade D rooms (e.g., a "mousehole" for filled vials moving by conveyor from filling to inspection), and it ensures that some difference is present even when the rooms are in alarm.

As an alternative to this approach, alerts and alarms may be generated based on calculated room-to-room pressure differentials between rooms of different classifications. In this case, the room-to-room (across the airlock, if any) pressure setpoint is normally around 15 Pa, with an alert at 12.5 Pa and the alarm at less than 10 Pa.

Airflows to Adjacent Rooms

To maintain room pressurization, air must be supplied to replace air flowing to adjacent rooms with lower pressurization. This "leakage" airflow goes through openings such as cracks around doors, piping penetrations, ceiling system cracks, and wall openings (e.g., "mouseholes" for vials moving from filling to inspection). These flows are important elements to account for in the HVAC system design.

To achieve design pressure differences, it is also important to maintain dropdown seals (where used) and door closers that are intended to ensure consistent operations. Often, door seals are not used. This is to simplify maintenance and to ensure that the leakage airflow is sufficient to be controlled.

"Controlled leakage" from higher- to lower-pressure rooms is a means to maintain stable room pressure. It also supports the FDA requirement for outward airflow in the open-door situation [1]. This is often done using the leakage through gaps around doors. Alternatively, when that leakage is insufficient to ensure a good outward flow with the door open, grilles, dampers, or pressure stabilizer dampers can be employed. In the latter approach, normal airflow is through the damper: When the door opens, the damper closes and the air flows through the door opening.

DIFFERENTIAL PRESSURE MEASUREMENT AND MONITORING SETUP

The differential pressure cascade within a classified area must be monitored to demonstrate that the pressure cascade is effective during manufacturing operations. When the differential pressure is across rooms with different classifications, monitoring of differential pressures across rooms with differing classifications is a GMP expectation [1].

The engineering system that supports maintenance of these differential pressures is a good engineering practice. There are two approaches: measuring room to room and measuring from each room to a common reference location.

Measuring from Room to Room

This approach is easy to implement and does not require any calculation in the automation system (see Figure 5A). With a very large facility, depending on the layout, instrument accuracy, and alarm settings, using this approach would not provide visibility of any undesirable differential pressures between different suites. This design option may use fewer differential pressure transmitters and allows direct measurement of the individual room pressures, which can simplify control.

Measuring from Each Room to a Common Reference Location

This approach is often used for monitoring and/or control of complex facilities (see Figure 5B). In this scheme, all rooms are connected back to a common reference area. The area for the reference pressure should be inside the building (pressure neutral instead of pressure controlled). The room-to-room differential pressure values can then be calculated, with alarms based on the calculated values, as previously outlined. This system's functionality is dependent upon the use of a stable reference point.

Measuring the Common Reference Pressure

A suggested design for measuring the common reference pressure is to:

1. Plumb the low-pressure ports on all differential pressure transmitters into a common manifold.
2. Connect the common manifold to an expansion vessel or large-diameter (3- to 4-inch) pipe. The expansion vessel or large-volume pipe manifold helps damp any transient air pressure fluctuations.
3. Locate the reference point within the building, outside of the controlled pressure space and away from other unstable influences, if possible.

Using reference points within the unventilated or continuously fixed, ventilated interstitial space is an excellent and relevant choice for a stable reference. Outdoor references are rarely stable enough for responsive room pressure control.

INSTRUMENT SELECTION

Avoid large instrument ranges that extend significantly outside the range required. Similarly, select ranges of accuracy within the operating ranges of ±0.25 Pa. In deviation handling, information about whether the pressure was low or negative is relevant. Therefore, consider including part of the negative scale in the instrument range. For example, for a differential pressure that should be 50 Pa, an instrument range of -10–100 Pa could be used. Instruments should be robust enough to take the pressure fluctuations experienced in use and during calibration.

INSTRUMENT SIGNAL PROCESSING

It is desirable to see the actual differential pressure, which implies a fast-responding instrument, but it is also important to ensure stable control. Often, the control signal is filtered due to the extremely low pressures associated with space pressurization of the order of 2.5–50 Pa (0.01- to 0.20-inch water gauge). Signals from space pressurization instruments are often unstable, especially at the low end of the device's range.

Use of rolling average values or time-weighted rolling average values can be useful to help provide stable control and limit the appearance of nuisance alarms. At a minimum, a short time delay should be used.

ALARM DELAYS

Room pressurization, while a regulatory expectation for classified spaces, is not necessarily a primary or process parameter. Rather, it is important as an indication of a space's ability to protect itself from airborne external contaminants. For this reason, loss of target room pressurization rarely needs to be reported immediately, as loss of pressurization is not necessarily indicative of a loss of clean conditions or incorrect airflow.

The delay prior to reporting pressurization alarms is commonly set to a few minutes (typically less than 10) and is supported with data on the duration of door opening needed to perform the process and study the impact of the maximum duration of pressure loss. These impact studies may include open-door particle counts, smoke studies of the ingress of air from lower-classification spaces to higher ones, recovery studies from upsets due to door opening, and similar qualification activities to ensure the maintenance of the desired classification when the door is open.

When establishing the alarm categorization, consider the potential impact of a reverse airflow (room differential pressure reversal or inversion). It is common to focus on internal differential pressure events; however, it is also important to consider external differential pressure events and the potential for ingress from outside spaces.

A best practice is to observe the time associated with loss of conditions due to an HVAC system failure to assure that the pressurization alarm delay is set to a safe value before conditions (pressure differentials, particle counts, temperature humidity etc.) are lost. This can be arrived at by simulation or by reviewing historical operational data.

DOOR CONTROL

As noted in Table 1, the US FDA has explicitly stated that room pressurization must be maintained during periods when the door is closed, and door control when any single door to an airlock is open must therefore be strictly enforced [1]. The difference in pressure

between adjacent rooms of different classifications separated by an airlock should not change even with door opening, as one door is always closed; however, short-term variation may be observed. Loss of pressure between differently classified spaces is indicative of an HVAC failure, not a door control failure.

Pressurization alarms are typically used to report changes in pressure due to door openings, not to report HVAC system failure. Depending on the system, they may also provide an alarm if the HVAC system fails. Because brief door openings are common, alarm delays are required to discriminate excessive door-open time from common and allowable door openings. It should be noted that door switches could also be used to determine the state of doors, monitor door-open times, and confirm closing.

The best practice is to observe the necessary door-open time associated with operations and ensure that the door-open alarm delay is set to a value greater than the maximum necessary door-open time. This setting can be determined by simulation or by observing operational data. It should be less than the time associated with loss of conditions.

POWER FAILURE RESPONSE

In areas where the power supply is unreliable and there is no standby generation, the environmental monitoring system should be on an uninterruptible power supply so that there is data to cover the duration of the event. If power loss is a risk, standby power (depending on the process and materials, consider an uninterruptible power supply [UPS]) should be provided to biosafety level 3 and biosafety level 4 equipment, Grade A unidirectional flow zones, isolators/restricted access barrier systems, and, ideally, Grade B areas.

The HVAC design should consider the power failure risk and controls—for example, one consideration could be the use of shutoff dampers to ensure that air movement is controlled. This aspect of the proposed HVAC design should be assessed during design qualification to ensure that it is robust. A risk assessment should be used to support the specific installation and determine the potential risks that could be caused through loss of differential pressure (part of the CCS).

Operational verification should include confirmation of system function and control loop tuning, as well as simulation of potential failure modes and system restarts. It should also address expected operational issues such as opening both doors to an airlock. Environmental qualification should include verification of the temperature, relative humidity, airborne particle levels, and airborne microbial cleanliness.

In practice, there is usually a loss of pressure for a short time during a line clearance and minor clean that may be within acceptable limits prior to returning the area to operation. This could span the time from when protection is not lost (seconds to a minute) to when protection is lost but conditions are maintained. A time should be established after which the line must be broken down and a 3x-clean initiated. A safety factor is always applied to any test results. For example, a study yielding good results for about 45 minutes may use a safety factor of 3 and set the 3x-clean requirement to 15 minutes.

If a power failure event is considered unlikely, a strategy should be defined in case the event does occur. For example, the strategy might involve taking additional environmental monitoring samples, recording personnel flow in the area during the event, and noting observations about outside conditions, which part of the higher-classified room was impacted by pressure inversion, and whether unidirectional flow countered any ingress.

CONCLUSION

Though regulators have clearly defined expectations for differential pressures, there are numerous ways to approach the design, monitoring, and alarming of differential pressures areas. This article discusses options for HVAC systems, the control of AHUs, and other aseptic manufacturing concerns for differential pressures to ensure best practice is used. The use of best practice will help prevent cleanroom contamination and reduce the risk of contamination.

References

1. US Food and Drug Administration. "Guidance for Industry. Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice." September 2004. Page 11, section C, Clean Area Separation. https://www.fda.gov/media/71026/download
2. European Commission. "EudraLex Volume 4: EU Guidelines for GMPs for Medicinal Products for Human and Veterinary Use. Annex 1: Manufacture of Sterile Medicine Products." Published 2022. https://ec.europa.eu/health/sites/default/files/files/gmp/2017_12_pc_annex1_consultation_document.pdf
3. International Society for Pharmaceutical Engineering. *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning.* North Bethesda, MD: International Society for Pharmaceutical Engineering, 2009.

About the authors

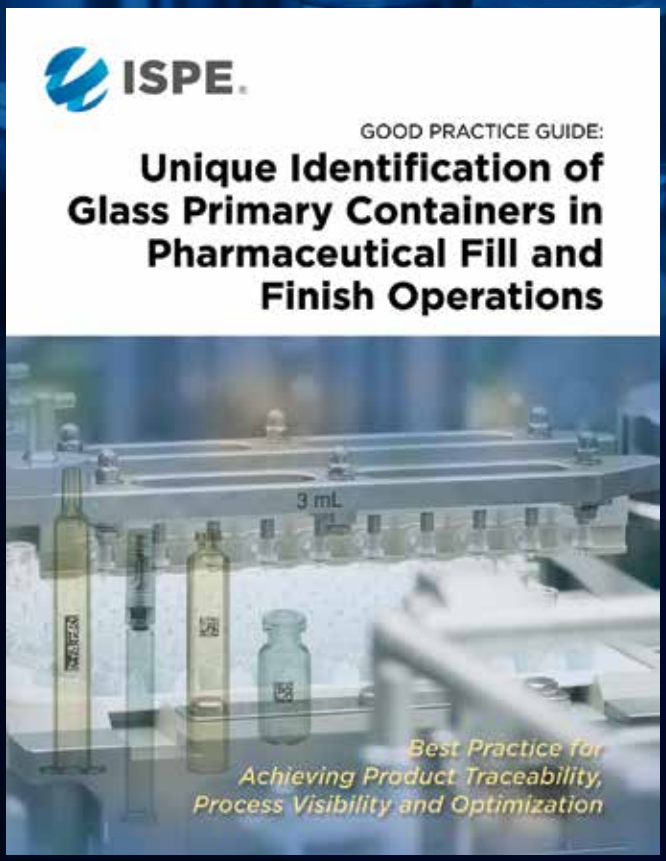
Norman Goldschmidt is the President of Genesis AEC, specializing in innovative, efficient designs for life science clients. His industry experience spans the many types of facilities and processes necessary to bring therapy to patients—from research and development through manufacturing. Norman has over 30 years of experience in conceiving, designing, and delivering processes and facilities. He served 20 years with Bristol-Myers Squibb, culminating as Executive Director, Global Engineering for Strategy and Design. Norman holds four patents for innovations in HVAC and pharmaceutical processing. He is also an internationally recognized expert in environmental control, cleanroom design, isolation technology, and compliance. He has authored the HVAC or environmental control sections of seven ISPE guides, is ISO author and convener, and teaches for ISPE, PDA, and regulatory agencies. He studied mechanical engineering at the University at Buffalo and engineering management at Empire State University. He joined ISPE in 1996.

Nicholas R. Haycocks was a Senior Specialist QA for Amgen Inc., supporting international distribution quality. In 2006, he joined Amgen's engineering department and moved to quality in 2009. He is a subject matter expert for critical utilities and has worked on projects in a commissioning and qualification role in many locations including China, Singapore, and Kenya. Nick is currently a member of the ISPE HVAC and Sustainability Community of Practice Committee and has been a team member for a number of ISPE Guidance Documents, including the *ISPE Baseline® Guide: Commissioning and Qualification,* the first edition of the *ISPE Good Practice Guide: Good Engineering Practice,* the *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning,* the first edition of the *ISPE Good Practice Guide: Controlled Temperature Chambers,* and the *ISPE Good Practice Guide: Approaches to Commissioning and Qualification of Pharmaceutical Water and Steam Systems.* He has been a member of ISPE since 2002.

Ulla Thompsen works as HVAC subject matter expert for Novo Nordisk. Her areas of work include design and compliance of aseptic filling facilities and HVAC for pharma in general. Ulla holds an MS in mechanical engineering. She has been a member of ISPE since 2007.

ISPE.

NEW ISPE Good Practice Guide



Are you seeking solutions to unique identifiers for primary parenteral containers? Created by a cross-section of industry experts in the parenteral/injectable medicine manufacturing industry, this good practice guide outlines best practices for developing, implementing, and managing traceability projects.

Learn more at: **ISPE.org/GuidanceDocuments**

DATA ANALYSIS OF Contamination Control Strategies for Production

By Jeffery Odum, CPIP, and David Raab

On 25 August 2023, the long-awaited revision to Annex 1 became effective, introducing significant regulatory changes, including the requirement of a documented contamination control strategy (CCS). During a workshop at the 2023 ISPE Annual Meeting & Expo, 11 teams of attendees were presented with a risk-based methodology to develop and evaluate CCS elements focused on extrinsic contamination events using the same data set for process and facility. This article presents a summary of the workshop results and a learnings analysis from the evaluation of the data as presented by the 11 teams.

UPDATED ANNEX 1 REQUIREMENTS

The updated Annex 1 introduced significant regulatory changes, including a greater emphasis on quality risk management, detailed requirements for barrier technology, and a widened regulatory scope to cover sterile products. One of the most significant changes was the requirement for a documented CCS that should be implemented across facilities.

The CCS should unify disparate contamination controls into a unified framework in alignment with US Food and Drug Administration (FDA) and Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) regulations and guidance documents issued by ISPE, the Parenteral Drug Association (PDA), and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

Current regulatory guidance around a formal CCS includes:

- EudraLex Vol. 4, Annex 1, section 2.3 [1]
- PIC/S Guidance for Good Manufacturing Practice, Part 1, section 3.6 [2]
- WHO, Annex 6 (Good Manufacturing Practices for Sterile Pharmaceutical Products), section 2.3 [3]

According to Annex 1, the CCS is referred to as a family of documents that unite, evaluate, and record the adequacy of tools used to assure the purity and quality of drug products [1]. The heightened focus on the CCS is centered on the physical mechanisms to control intrinsic and extrinsic contamination and emphasizes how the mechanisms work together and are managed as a group.

The Case Study

The case study was taken from a new viral vector manufacturing facility used for cell and gene therapy products. The facility was also designed for executing specific T cell therapy manufacturing operations for a targeted 240 patients per year. The T cell therapy operations were based on a worst-case 9-day expansion cycle, at a 24/7/365-day operating cycle. The viral vector operations per suite targeted finished product every 28 to 34 days, again at a 24/7/365-day operating cycle.

The process basis for the viral vector manufacturing is represented in the general block flow diagram (BFD) in Figure 1. For clarity, locations of each operation are shown for suite 4 only. These same operations occur in manufacturing suites 1–3 as well.

The general viral vector manufacturing area layout is shown in Figure 2. This layout corresponds to the BFD previously identified and includes the associated air classifications for each suite.

WORKSHOP OBJECTIVE

The Annex 1 revision's focus on a comprehensive CCS requires a holistic review of contamination sources, identification of risks and control points, and interaction of these elements between all facility attributes. To do this requires a process focused on prevention, remediation, and monitoring. It also requires the analysis of large amounts of data across several different disciplines and the participation of recognized subject matter experts in key areas such as manufacturing, quality control, microbiology, and engineering, as examples.

The workshop focused on introducing a set of tools that have proven successful in the analysis of the data that make up the root causes of many extrinsic contamination events. The attributers of these events are often heavily influenced by facility design, operational protocols, and the execution of standard procedures impacted by human intervention. Many of these attributes and

Figure 1: A viral vector BFD.

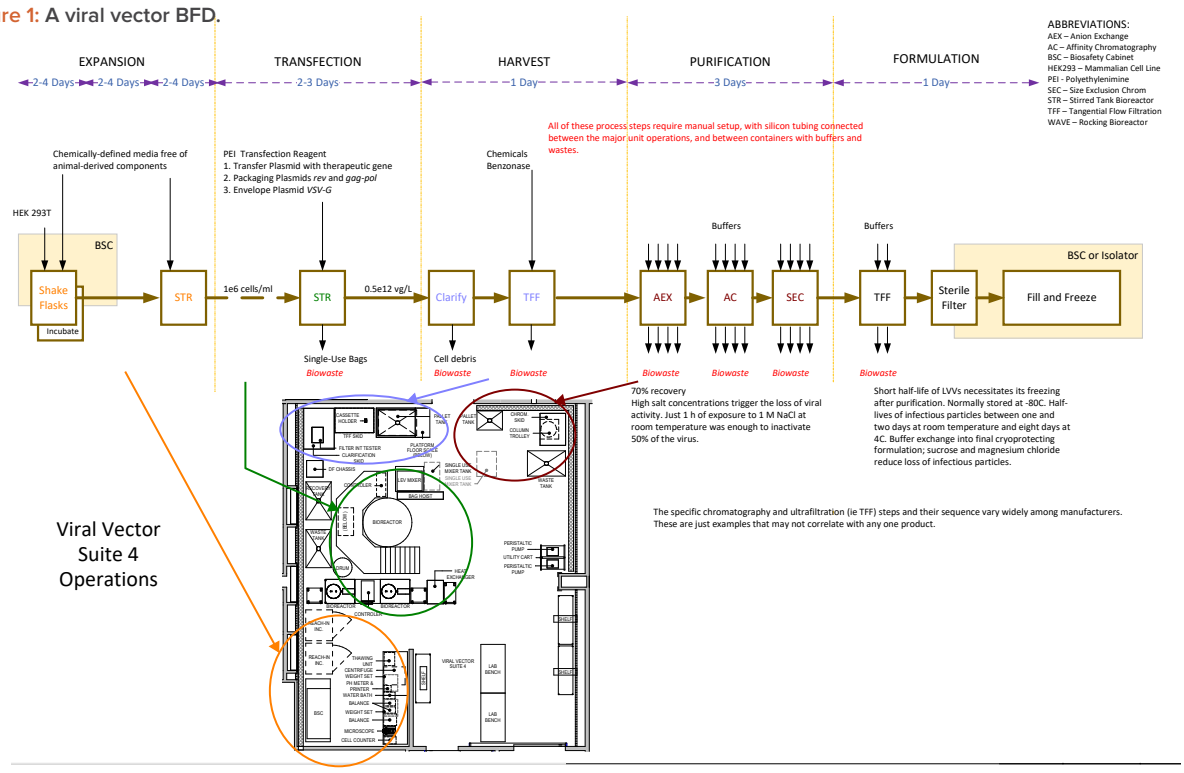


Figure 2: A viral vector manufacturing area layout with air classifications.

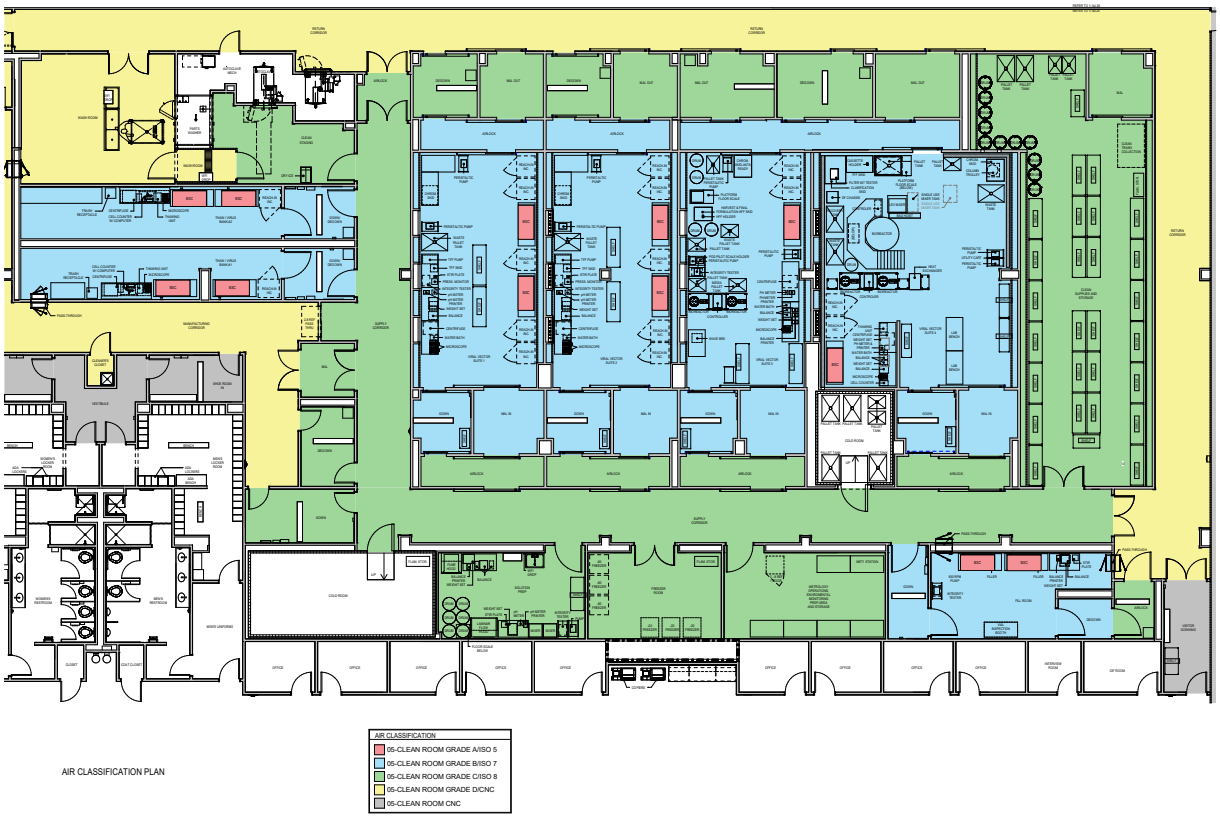
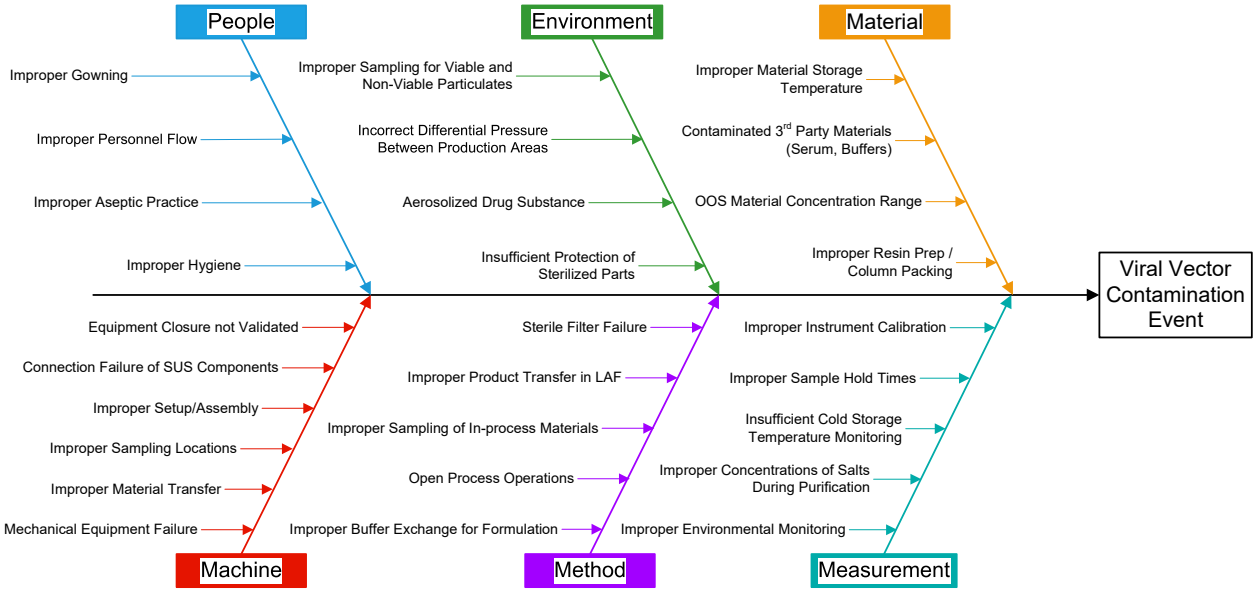


Figure 3: An Ishikawa diagram presenting possible causes of contamination of the viral vector intermediate.



protocols are common to the majority of manufacturing entities: gowning, environmental monitoring, cleaning, etc.

By establishing a defined roadmap for execution that implements these tools consistently, the resulting analysis of the data should produce a level of consistent results by the majority of those participating in the data analysis. But will that always be true?

EXECUTION APPROACH

Each workshop team was given a set of background documents to understand the case study. These documents included a personnel flow diagram, description of personnel flows, airflow/air classification diagram, description of environmental controls, and BFD of the viral vector manufacturing operation.

Teams were encouraged to ask questions to the facilitators where the material was not clear. However, because it would be impractical to ask a workshop team to read and comprehend a full set of design drawings, operating instructions, corrective and preventative action (CAPA) records, and other data associated with a functional facility, the teams were instructed to make assumptions where needed. For example, a team could assume certain safeguards, such as operator qualification requirements, were in place even if they were not explicitly mentioned in the case study materials.

Ishikawa Diagrams

When developing a CCS, whether for a new or existing process, it is critical to first identify process contamination hazards and understand the associated risk. There are many recognized methodologies and tools identified in ICH Q9 that can be applied to quality risk assessments, such as hazard analysis and critical control points; flowcharts; and failure modes, effects, and criticality analysis (FMECA) [4].

An Ishikawa diagram (also called a cause-and-effect or fishbone diagram) is a flowchart method for process mapping. Ishikawa diagrams provide an easily understood graphical representation of cause-and-effect relationships. Used in combination with brainstorming, they help identify potential causes for a particular effect of interest. Causes are often categorized to form the flowchart paths, or "ribs" of a fishbone. Categorization of paths helps with the brainstorming process to ensure that all relevant aspects of a process are considered.

In the case study, the viral vector produced can be considered an intermediate that is used in production of the T cell therapy drug product. The Ishikawa diagram of the case study lists the effect of interest as contamination of the viral vector intermediate. Contamination from many possible sources is considered, including viable particulate, nonviable particulate, leachable chemicals, and cross contamination with other intermediates or products.

Paths on the Ishikawa diagram used in the case study include the five m's typically considered for manufacturing processes (i.e., machine, method, measurement, material, manpower/people). A sixth path is included for environment, which is critical to controlling contamination in an aseptic pharmaceutical manufacturing process.

A full contamination risk assessment must consider all categories of contamination, but the case study was limited to the people and environment paths to allow for reasonably detailed analysis given the background materials and time provided. Possible causes of contamination were provided for these two paths, as shown in Figure 3. The other paths were not presented to the workshop participants but are shown here for clarity.

Table 1: FMECA criteria used for scoring.

Impact	Value	Failure Consequence / Impact Assessment Criteria
High	**5**	Failure of the function can directly lead to: - Any negative health effect that requires treatment to a patient - Inability to license or pass inspection, or regulatory action requiring cessation of operations
Medium-High	**4**	Failure of the function can directly lead to: - Delay to license, citations, or regulatory action requiring significant interruption of operations (serious citations, warning letter, etc.) - Observable negative health effect to a patient (not requiring treatment)
Medium	**3**	Failure of the function can directly lead to: - FDA inspection observation of objectionable conditions (Form 483 citation)
Medium-Low	**2**	Failure of the function can directly lead to: - Significant inquiry by inspector (citation is not certain)
Low	**1**	Failure of the function can directly lead to: - No inspection observations or adverse health effects to patients

Probability	Value	Probability of Occurence Assessment Criteria
High	**5**	The design or function is very complex, new, and not well-known, or this failure may be expected on a weekly or more frequent basis
Medium-High	**4**	The design or function is fairly complex, new, and less well-known, or this failure may be expected on a monthly or more frequent basis
Medium	**3**	The design or function is moderately complex, or this failure may be expected more than once in a year
Medium-Low	**2**	The design or function is reasonably standard, reasonably simple, or well-understood (characterized); this failure is expected annually up to five years
Low	**1**	The design or function is standard, simple, or well-known; this failure is expected no more often than once every five years

Detectability	Value	Probability of Non-Detection Assessment Criteria
Absolutely Uncertain	**5**	The failure cannot be detected immediately and the failure cannot reliably be detected during regularly scheduled tests (during each batch) prior to release
Remote	**4**	The failure cannot be detected immediately but may be detected during regularly scheduled testing (during each batch) prior to release
Moderate	**3**	The failure may be detected immediately but can reliably be detected during regularly scheduled testing (during each batch) prior to release
Highly Likely to Detect	**2**	The failure will likely be detected immediately and can reliably be detected during regularly scheduled testing (during each batch) prior to release
Almost Certain	**1**	The failure will be detected immediately

Workshop teams of four to six people were assigned to either analyze the people or environment path. Each team considered the provided list of contamination causes from the associated path and then chose one or more causes for which they would analyze the associated risk.

FMECA

Although the Ishikawa diagram is a powerful tool in identifying causes for contamination, it treats all causes equally and does not assess the differences in risk between the causes. For true risk analysis, the causes identified with the Ishikawa diagram can then

Table 2: An example scenario.

Fishbone	Scenario Information				Risk Assessment					Results	
Fishbone Rib	Fishbone Cause	Contamination Failure Mode	Extrinsic Contamination Type	Safeguards	Impact	Probability of Occurrence	Probability of Non-Detection	RPN	Risk Level	Recommend-ations	Justification or Notes
Environment	Incorrect differential pressure between production areas	Door propped open	- Cross-contamination - Viable particulate contamination - Non-viable particulate contamination	- Door interlocks - Operator training - Alarms - SOP control for process stoppage	5	3	2	30	Medium	Install more robust or redundant door sensor with lower delay for trigger	Ensure immediate detection with additional control

Figure 4: Risk ranges.

be used to feed a failure-driven risk assessment tool.

FMECA is a well-established and recognized technique already commonly used in the pharmaceutical industry for risk assessment. FMECA documents the effects of each failure mode and assesses the criticality of each failure scenario through a risk scoring system. Each scenario is scored in three categories:

- Impact: How severe is the consequence of the contamination event on the patient that receives contaminated product?
- Probability of occurrence: Given the safeguards credited as being in place, how likely is the contamination event to occur?
- Probability of non-detection: Can a contamination event be detected, and if so, how quickly?

FMECA scoring criteria can differ between organizations. For the workshop, a proven scoring system based on a 1–5 scale for each category was chosen (see Table 1 for details). This scoring system has been used by the workshop facilitators for risk assessments of many pharmaceutical facilities. One category that may be initially confusing is the probability of non-detection. Because there is an inverse relationship—where higher detectability of a contamination event is associated with a lower risk—for scoring purposes ,the direct relationship between non-detection and risk is considered instead.

The criteria used by the workshop participants includes FDA regulatory consequences, as this workshop was based in the US. However, the impact criteria can easily be adapted to EU, national, or international regulatory consequences for use outside the US.

The workshop teams were given Ishikawa diagram causes to use as a starting point, but, by design, the causes were not overly detailed. The teams were encouraged to develop more specific contamination-failure-mode scenarios around their selected causes. In an example scenario shown in Table 2, a team started with incorrect differential pressure between production areas as the cause and then considered a door propped open as a failure mode for the FMECA.

For each scenario, teams were instructed to identify any safeguards that either prevent or mitigate contamination. Teams later shared their recommendations with the other workshop participants. However, no critique was made during the workshop on the effectiveness or feasibility of the recommendations given by the teams.

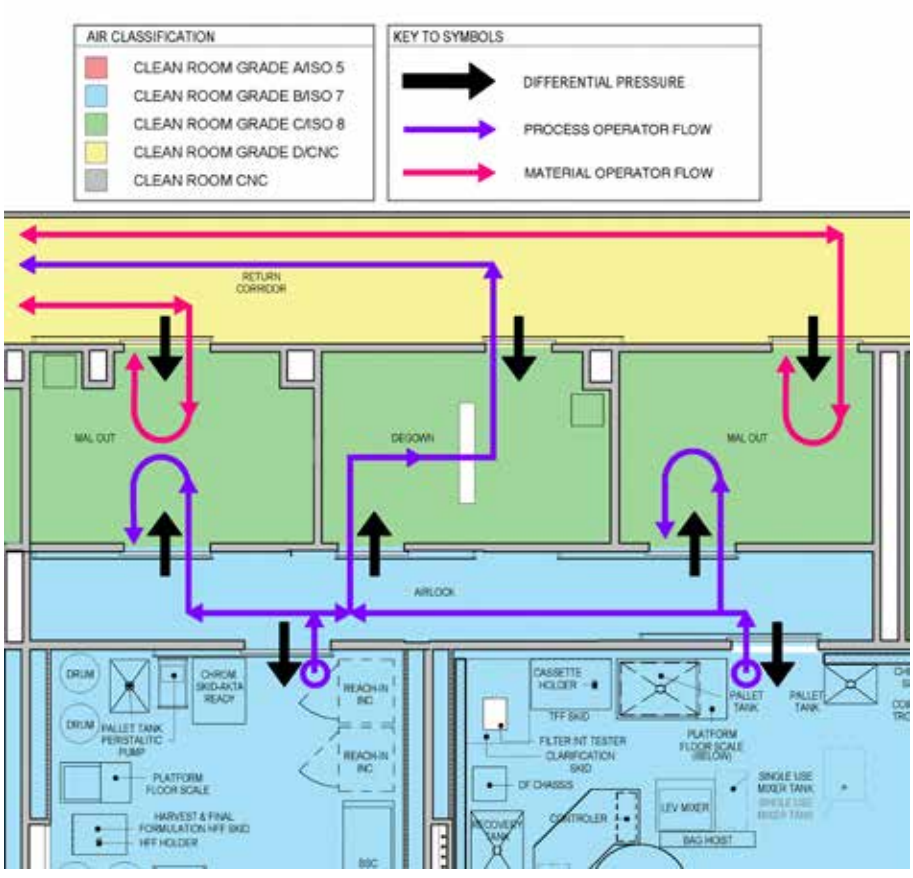
After fully detailing a contamination scenario and identifying safeguards, teams evaluated the risk associated with their scenarios based on the scoring criteria from Table 1. Scores for impact, probability of occurrence, and probability of non-detection are multiplied together to calculate a risk priority number (RPN). The RPN can be used to categorize contamination scenarios based on risk and prioritize recommendations for reducing risk. The RPN scale used in the workshop provides ranges for low, medium, and high risk levels, as shown in Figure 4.

The need for recommendations to reduce risk is based on the RPN and the associated risk level. Low-level risks were deemed acceptable without additional risk reduction; medium and high-level risks required the teams to consider a strategy for risk mitigation. Appropriate risk mitigation may include administrative controls, such as verification of a procedure by a second individual, or engineering controls, such as the recommended redundant door sensors from the example in Figure 4. Each team was given an hour to identify and evaluate their chosen risk scenarios using the described FMECA methodology.

KEY DATA SUMMARY

The 11 teams participating in the workshop were assigned arbitrarily based on table number to analyze either the people or environment Ishikawa diagram path. Six teams considered the environment path and four teams considered the people path, with one additional team choosing to analyze both. Although teams were guided by the causes of contamination, the causes were left open-ended so that the teams could create specific process and facility failure mode

Figure 5: Suites 3 and 4 exit airlock scheme.



scenarios to analyze. Major areas of focus for the teams included:

- Crossing of clean and dirty flow paths for equipment and personnel
- Gowning procedures and changes in gowning when moving between rooms
- Shared heating, ventilation, and air conditioning (HVAC) between production suites
- Intermittent environmental monitoring frequency
- Air classification grade transitions between rooms
- Sharing of airlocks between production suites
- Room pressurization schemes
- Control of doors between rooms
- General HVAC and power failures

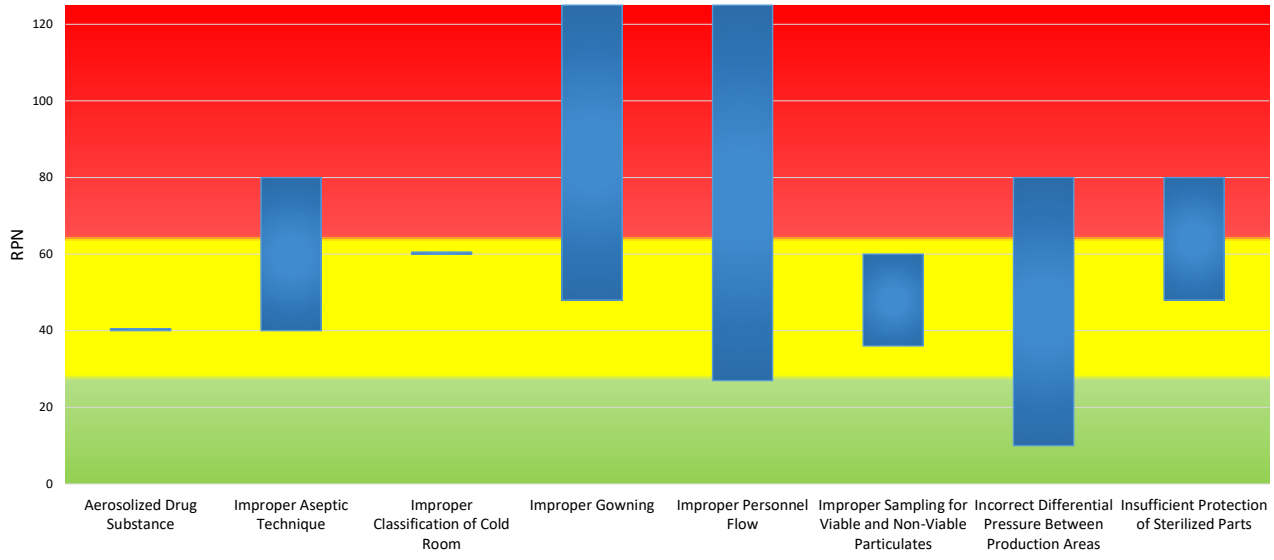
In looking for common themes among the identified contamination failure modes, a repeated area of focus was on the exit airlocks of the production suites. This includes both material airlock and personnel airlock transitions. Figure 5 shows an exit airlock scheme with a shared Grade B to Grade C airlock between production suites 3 and 4.

The design of this exit airlock area was considered to create an elevated risk by several of the teams. From an environmental standpoint, one team evaluated the risk of transfer of aerosolized material between the suites (cross contamination) as medium risk. Similarly, another team considered the risk of transfer of viable and nonviable particulate between material operators and process operators via the material airlock as a medium risk. Suggested remediations included adjusting the pressurization scheme to make the Grade C airlocks a bubble and the Grade B airlocks a sink and increasing the classification of the return corridor to Grade C.

The exit airlock personnel flow was also considered as an elevated risk by the teams. One team noted the possibility of a process operator fully entering a Grade C material airlock from the Grade B clean room to drop off samples and then returning to the Grade B clean room without any change in gowning. This situation, evaluated as a medium risk, could result in viable and nonviable particulate contamination. Another team noted that the material operator faces a similar situation where no change in gowning occurs upon moving between different grades. However, this team considered this to be a very high risk.

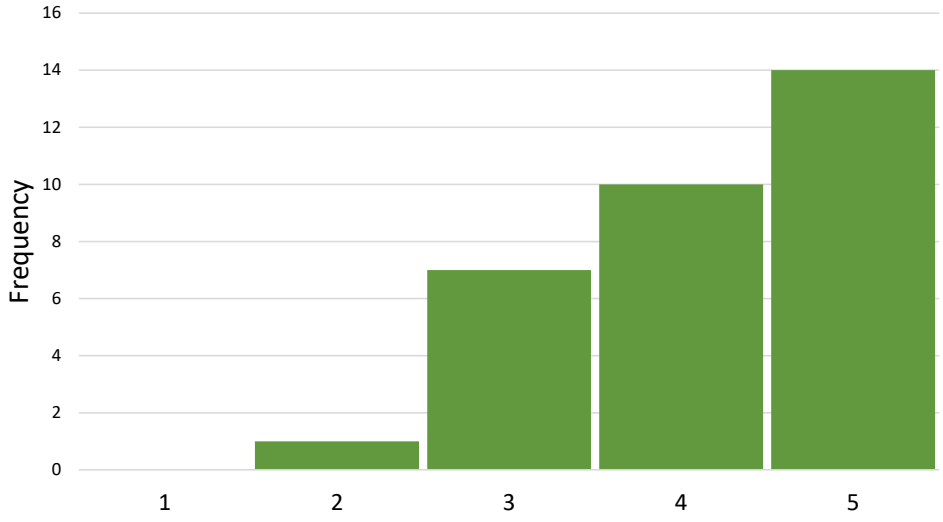
Possible remediations identified by the teams are the addition of exit signs and door interlocks to prevent reverse flow into clean rooms, as well as overgowning. Another team noted the possibility of operators from the two manufacturing suites (suites 3 and 4) comingling in the exit interlock and possibly entering a different

Figure 6: RPN ranges.



Risk level ranges are shown as background shading where green = low risk, yellow = medium risk, and red = high risk.

Figure 7: Assessed impact levels for contamination.



suite from which they left without any gowning change. Although this was considered a low risk given administrative controls, door interlocks with suite-specific access groups were recommended.

RESULTS

The bar chart in Figure 6 depicts the ranges of RPN scoring based on the cause. Although some causes are represented by a single scenario from one team, and therefore appear as a horizontal line on the chart, most were analyzed by more than one team. As evident from the chart, the same cause may have a range of risk associated with it. Ultimately, the assessed risk value and associated level depends on many factors, such as:

- Assessment team makeup, experience, and biases
- Assessment team expertise on understanding the impact of contamination on the substance or product
- Assumptions made at the time of the risk assessment

- Assessment team understanding and agreement on assessment criteria
- Level of granularity in defining failure modes

These factors almost certainly played a role in the results generated by the workshop teams. After reviewing the case study materials, some teams with experienced members pointed out what they considered to be facility design flaws to the facilitators. Other teams needed assistance to understand the materials provided. Some teams were more liberal with assumptions around functioning safeguards that may be in place at the facility, whereas others assumed the opposite. For example, one team assumed that HVAC air handlers would be shared between the production suites, which is not common in the experience of the workshop facilitators.

Another factor that affected the range of scoring was a team's perception of impact or severity of contamination. Although each team was presented with the same process and the same definitions for severity of a contamination event, the teams judged the severity of contamination differently. Figure 7 shows the distribution of severity for all contamination scenarios assessed by the teams.

In over 75% of the assessed scenarios, teams recognized the impact of a viral vector contamination event as being either high or medium high, corresponding to a negative health effect to a patient. However, the remainder of the assessed scenarios fall in the medium- or low-impact range, corresponding to an inspection finding but no impact to a patient.

In a real-world situation, other sources of variability may come into play as well, including:

- Methodology used for the risk assessment (FMECA, what-if, fault tree, etc.)
- Scoring system chosen for the risk assessment
- Design and operational information available at the time of the risk assessment

CONCLUSION

Data analysis is the foundation of a successful CCS effort. The vast amount of data to be analyzed includes both intrinsic- and extrinsic-focused information: protocols, standard operating procedures, environmental monitoring data, facility design requirements, and CAPA information. When initiating any risk-based analysis, it is important to identify and manage biases, realizing that there can be very diverse perspectives within a team of individuals from different backgrounds—such as manufacturing, quality, or engineering—and different levels of expertise.

Subjectivity can have a significant impact on the outcome of any risk-based assessment. An overreliance on participant experience or a focus on "rules of thumb" can introduce a bias into the process. It is also important to minimize favoritism to a particular technology or methodology when assessing data. To minimize the impact of this type of subjectivity in the development of a CCS, it is important to use a systematic and objective approach to risk, addressing both intrinsic and extrinsic contamination sources and properly analyzing the data.

The results of the workshop supported the need to mitigate subjectivity using a systemic and objective approach to data assessment. Teams performed a review of the same data set. Each made a series of assumptions based on their understanding of the information and accounted for uncertainties and variability in how they viewed risk. They documented their decision-making process and, through "spirited debate," challenged each risk element and made conclusions on the level of risk they deemed aligned with the data.

The complete elimination of subjectivity may not always be feasible. The goal is to manage and mitigate its influence as much as possible while reaching a robust strategy for controlling contamination events.

References

1. European Commission. "EudraLex, Volume 4: EU Guidelines for GMPs for Medicinal Products for Human and Veterinary Use. Annex 1: Manufacture of Sterile Medicinal Products." Published 25 August 2023. https://health.ec.europa.eu/document/download/e05af55b-38e9-42bf-8495-194bbf0b9262_en?filename=20220825_gmp-an1_en_0.pdf
2. Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-operation Scheme. "Guide to Good Manufacturing Practice for Medicinal Products - Part 1." Published 1 May 2021. https://picscheme.org/docview/6606
3. World Health Organization. "Annex 6: WHO Good Manufacturing Practices for Sterile Pharmaceutical Products." Published 2011. www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/production/trs961-annex6-gmp-sterile-pharmaceutical-products.pdf?sfvrsn=61682f0c_0
4. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. "ICH Harmonised Guideline Q9(R1): Quality Risk Management." Adopted January 2023. https://database.ich.org/sites/default/files/ICH_Q9%28R1%29_Guideline_Step4_2022_1219.pdf

About the authors

Jeffrey Odum, CPIP, is a recognized expert in biopharmaceutical manufacturing assets. He has authored over 60 published articles and four industry reference books on subjects related to biopharmaceutical manufacturing facility assets. He is a recognized speaker at international industry forums and conferences, presenting on topics relating to next-generation facility design, bioprocess manufacturing, project development, and GMP compliance. He is a member of the ISPE Technical Training faculty and is a Teaching Fellow in North Carolina State University's Biomanufacturing Training and Education Center graduate program in biomanufacturing. He has led training efforts in 15 countries in over 100 sessions, including training for global regulators from the US FDA, Health Canada, Thailand FDA, FDA-COFEPRIS, and the Chinese SFDA. He joined ISPE in 1994.

David Raab is a Senior Process Engineer at Genesis AEC, where he provides engineering design and consulting services to clients in life sciences manufacturing. At Genesis, David has co-authored procedures for CCS assessments and facilitated contamination risk assessments for several pharmaceutical manufacturers following the most recent EU Annex 1 revision. He was also a CCS workshop presenter at the 2023 ISPE annual meeting. David's background includes over 20 years of experience in process engineering design and manufacturing support across multiple industries. David holds a bachelor's degree from the Georgia Institute of Technology and a master's degree from Cornell University, both in chemical engineering. He joined ISPE in 2023.

INDEX

CLASSIFIEDS

ARCHITECTURE/ENGINEERING/ CONSTRUCTION

Fluor Corporation
100 Fluor Daniel Drive
Greenville, SC 29607
+1 864-281-4400
www.fluor.com

IPS-Integrated Project Services, LLC
721 Arbor Way
Suite 100
Blue Bell, PA 19422
+1 888-366-7660
www.ipsdb.com

CONSULTING

Arcadis
959 Concord Street
Suite 100
Framingham, MA 01701
+1 508-532-6760
www.dpsgroupglobal.com

ENGINEERING & DESIGN SERVICES

HIPP Design + Consulting
2301 Rexwoods Dr
Suite 200
Raleigh, NC 27607
+1 919-755-1033
www.hipp-usa.com

INFORMATION TECHNOLOGY

COPA-DATA
Karolingerstrasse 7b
Salzburg, Austria 5020
+43 662-43-1002-0
www.copadata.com

PROCESS EQUIPMENT

Aerre Inox S.r.l.
Via Gerola 4
26010 Fiesco (CR) – Italy
+39 0374 370828
www.aerreinox.it

Lisure Technology Co., Ltd
2559 US-130
East Windsor, NJ 08512
+86 512 62625790
www.lisure-us.com

PROCESSING & MANUFACTURING

MFG Tray Company (Molded Fiber Glass Tray)
6175 US Highway 6
Linesville, PA 16424
+1 814-683-4500
www.mfgtray.com

SOFTWARE SIMULATION & PROCESSING SYSTEMS

Intelligen, Inc.
2326 Morse Avenue
Scotch Plains, NJ 07076
+1 908-654-0088
www.intelligen.com

WATER TREATMENT & PURIFICATION

Elettracqua Srl
Via Adamoli 513
16165 Genoa, Italy
+39 010-8300014
www.elettracqua.com

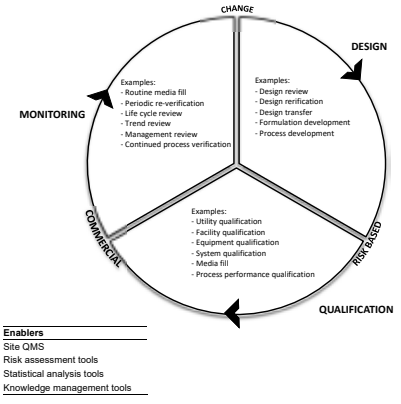
VALIDATION—MANUFACTURING

ValGenesis, Inc.
395 Oyster Point Boulevard
Suite 228
South San Francisco, CA 94080
+1 510-445-0505
www.valgenesis.com

VALIDATION—SERVICES (QUALIFICATION/COMMISSIONING)

Rees Scientific
1007 Whitehead Rd Ext
Trenton, NJ 08638
+1 609-530-1055
www.reesscientific.com

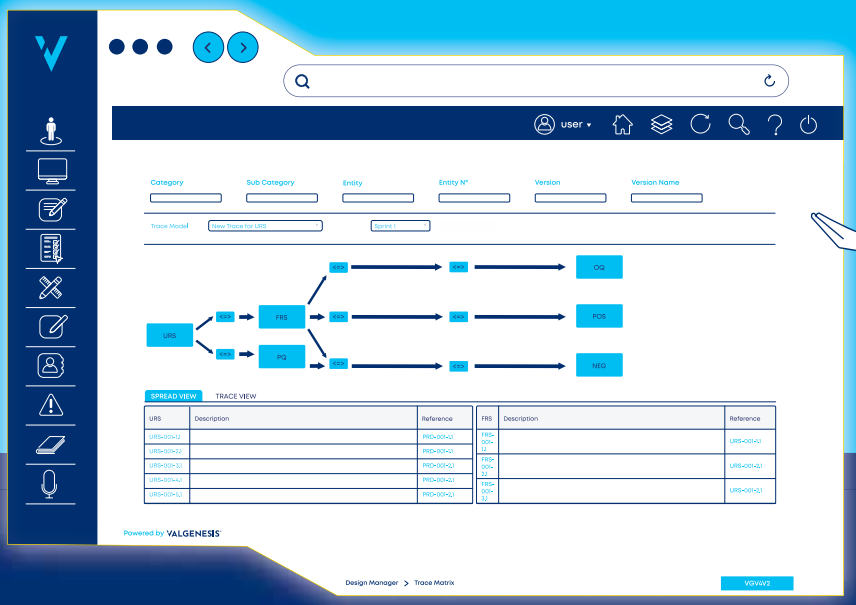
PLEASE SEE THE ADS FOR EACH OF OUR ADVERTISERS IN THIS ISSUE.



Correction to Pazhayattil et al. (2024)

In the article "Cell Culture Media Manufacturing Controls for Bio-Manufacturing" by Ajay Babu Pazhayattil, PhD, Sarah Jennings, and Catherine Spengler (*Pharmaceutical Engineering*, 2024, Vol. 44, No. 3, pp 49-55. https://ispe.org/pharmaceutical-engineering/may-june-2024) there was an error in Figure 3. The correct figure is pictured here.

Meet the Industry Standard Platform for Digital Validation



ValGenesis VLMS is the most complete validation system: a single digital source of truth, fully configurable, built for multisite scalability, designed for strict compliance and process optimization.

CSV and CSA: Apply a risk-based approach and reduce overtesting for shorter cycle times.

CQV: Ensure the facilities, equipment, and systems used throughout manufacturing fit their intended use.

Process: Eliminate silos with seamless connectivity across process, data, and knowledge management.

Equipment: Guarantee the accuracy and auditability of your equipment and instruments.

VALGENESIS®

Learn more about ValGenesis VLMS

valgenesis.com

ARCADIS

Delivering sustainable success *at the speed of science*

Personalized services with local expertise delivered on a global scale.

Architectural and engineering design
Commissioning, qualification, and validation
Construction management
Technical services
Strategic consulting
Managed services

Learn more at arcadis.com

DPS Group is now proudly a part of Arcadis.